Trends in Ecology & Evolution

CellPress

Review

Recombination Rate Evolution and the Origin of Species

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A recipe for dissolving incipient species into a continuum of phenotypes is to recombine their genetic material. Therefore, students of speciation have become increasingly interested in the mechanisms by which recombination between locally adapted lineages is reduced. Evidence abounds that chromosomal rearrangements, via their suppression of recombination during meiosis in hybrids, play a major role in adaptation and speciation. By contrast, genic modifiers of recombination rates have been largely ignored in studies of speciation. We show how both types of reduction in recombination rates facilitate divergence in the face of gene flow, including the early stages of adaptive divergence, the persistence of species after secondary contact, and reinforcement.

Introduction

In the absence of geographic barriers between populations, sexual reproduction is considered the greatest obstacle to the origin of new species [1]. While divergent natural selection creates distinct populations, sexual reproduction, through the homogenizing effects of genetic recombination, dissolves them. Cognizance of this antagonism has prompted many evolutionary biologists to deem that speciation within freely (sympatric) or between partially (parapatric) interbreeding populations is improbable [2]. However, recent theoretical and empirical results suggest that speciation in the face of gene flow should be feasible, and is perhaps common in nature [3–5]. Unfortunately, owing to our incomplete understanding of the genetics of speciation, the plausibility of key assumptions underpinning theoretical models of the process remain controversial. In the few instances where we do have some limited understanding (e.g., *Drosophila* and *Rhagoletis* fruit flies [6,7], *Ficedula* flycatchers [8,9], *Heliconius* butterflies [10], *Mimulus* monkeyflowers [11], and *Helianthus* sunflowers [12]), the genetics of speciation with gene flow appears to revolve around a key process: reduction of recombination between the genes that are responsible for reproductive isolation and those contributing to local adaptation [13,14].

Recombination generates new genetic combinations every generation, making it a rapid source of genetic variability upon which natural selection can operate [15]. However, recombination also breaks apart favorable combinations of alleles, potentially reducing the average fitness of a population [16,17]. This two-sided evolutionary effect of recombination is at the heart of both the evolution of sex [18] and the formation of new species when there is gene flow [19]. More specifically, the conditions that impede the evolution of sex and recombination are largely the same as those that facilitate speciation with gene flow. Alas, this connection is infrequently made, and therefore biological connections between the two processes have been often overlooked (but see [13,20]).

To visualize this connection, consider a situation where chromosomes carrying alleles *ABCD* or *abcd* confer high fitness, but chromosomes carrying any other combination of alleles produce

Trends

An often-overlooked connection between the evolution of sexual recombination and the origin of new species with gene flow suggests that the conditions for speciation with gene flow may be less restrictive than previously anticipated.

Evolutionary scenarios for which mathematical models predict selection for reduced recombination can provide insights into how ecological speciation and reinforcement can proceed.

Recent advances in our understanding of the molecular mechanisms of recombination in eukaryotes have provided first insights into how recombination rates can be modified within and between species.

In addition to the well-established role of chromosomal inversions during speciation, more subtle changes in recombination rates through modifier genes influencing the frequencies and distributions of crossover across the genome might also be important.

A better understanding of genomic patterns of differentiation during speciation could be gained by taking into account that recombination rates can themselves evolve.

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low fitness. Now assume a population with only *ABCD* and *abcd* chromosomes, in other words strong **linkage disequilibrium** (LD, see Glossary). Recombination would then reduce mean population fitness, and mutations that reduce recombination can be favored if they are linked to the *ABCD* loci [17]. During speciation with gene flow, a similar situation arises: if alternative combinations of alleles are favored in two populations (*abcd* and *ABCD*, respectively), then gene flow and recombination between them will generate new genotypic combinations of low fitness, reducing levels of LD in each population. Therefore, we expect that modifiers that prevent or reduce recombination would also be favored during speciation. Such **recombination modifiers** would preserve the original genotypes and maintain high fitness in the population via the increase and maintenance of high levels of LD within populations [18]. On the other hand, speciation with gene flow is dependent on divergent natural selection, and rates of adaptation can be greater in sexual than asexual populations [18]. Therefore, it is important to keep in mind that, during speciation driven by natural selection, sex and recombination can be favored within populations, but not between diverging lineages.

We review here important aspects of the fundamental link between the origin of sex and the origin of new species. We start by describing the various forms in which LD arises within a population and produces selection on recombination rates. Next, we review the various mechanisms that could evolve to change recombination rates, including structural (e.g., **chromosomal rearrangements**) and allelic modifiers of recombination. We then show how selection on recombination rates is expected to play out in various stages of speciation. We finish by outlining some of the consequences of recombination rate evolution for our understanding of divergence and adaptation.

The Why and How of Recombination Rate Evolution

Natural Selection on Recombination Rates

Recombination reduces LD within a population but normally does not alter allele frequencies. Therefore, for recombination rates to be under natural selection, LD must be present in a population and altering levels of LD must have fitness consequences. LD can be generated by several evolutionary forces, three of which are illustrated in Figure 1. Perhaps most importantly in the context of speciation, LD within a population will be induced by migration between two populations with different allele frequencies at two or more loci [21]. For instance, positive LD will build up when there is divergent selection in the two populations but polymorphism is maintained through migration (Figure 1A). This is most clearly seen in the extreme case where alleles *a* and *b* are fixed in one population and *A* and *B* in the other, such that one round of migration creates populations with both the *AB* and *ab* genotypes but no *Ab* or *aB* genotypes.

Second, LD is generated by natural selection in single populations when there is **epistasis** [22]: negative epistasis produces negative LD and positive epistasis produces positive LD (Figure 1B). This is intuitive because natural selection will produce an overabundance of intermediate genotypes (*Ab* and *aB*) when they are fitter than expected based on the average of the extreme genotypes *ab* and *AB* (negative LD), and vice versa (positive LD). Third, LD can arise as a result of random genetic drift or mutation. Over time and across many loci, drift and mutation *per se* will generate both positive and negative LD in equal amounts. However, when selection also acts on these loci, this distribution becomes biased towards negative LD through a mechanism known as the **Hill–Robertson effect**. According to this, genetic variation characterized by positive LD (e.g., only *ab* and *AB* genotypes present) will be eliminated more rapidly than genetic variation characterized by negative LD (e.g., only *Ab* and *aB*). This is because the former implies greater variance in fitness and hence more efficient natural selection. As a consequence, negative LD will predominate in the population (Figure 1C) [23]. Finally, LD can also be created by several other factors, including assortative mating and sexually antagonistic selection [19,24].

Glossary

Chromosomal rearrangement: a structural modification within or between chromosomes that affects the spatial location of genetic material.

Ecological speciation: the development of reproductive isolation between populations as a result of adaptation to different environments. It can take place in the face of gene flow.

Epistasis: non-independent effects of alleles at different loci. In particular, epistasis in fitness between two loci with alleles *A/a* and *B/b* can be defined in haploid organisms as $E = w_{ab}w_{AB} - w_{Ab}w_{aB}$, where w is the fitness of the respective genotype. Negative epistasis implies that the double mutant *AB* has a lower fitness than expected from the fitness effects of the two mutations *A* and *B* on the wild-type backgrounds *b* and *a*, respectively. Conversely, positive epistasis implies that *AB* has a higher fitness than expected from the individual effects of *A* and *B*.

Fitness trade-offs: alleles improving fitness in one environment reduce fitness in the other environment.

Hill–Robertson effect: negative LD arising from the interplay between random genetic drift and selection acting on several linked loci. Can produce selection for increased recombination rates.

Linkage disequilibrium (LD): non-random associations of alleles at different loci *in* a population. With two loci with alleles *A/a* and *B/b*, LD can be expressed as $D = p_{ab}p_{AB} - p_{Ab}p_{aB}$, where p is the frequency of the respective genotype in the haploid phase. Negative LD thus indicates an overabundance of the *Ab* and *aB* genotypes, whereas positive LD indicates an overabundance of the *ab* and *AB* genotypes. Note that labeling of genotypes and thus the sign of *D* is often arbitrary, but in the case of natural selection acting on both loci the convention is to assign genotype labels *AB* and *ab* to the genotypes with the highest and lowest fitness, respectively, whereas the *Ab* and *aB* genotypes have intermediate fitness.

Recombination hotspots: regions of the genome where crossovers occur at high frequency.

Recombination modifier: a gene that affects the rate of crossovers between other genes. A modifier

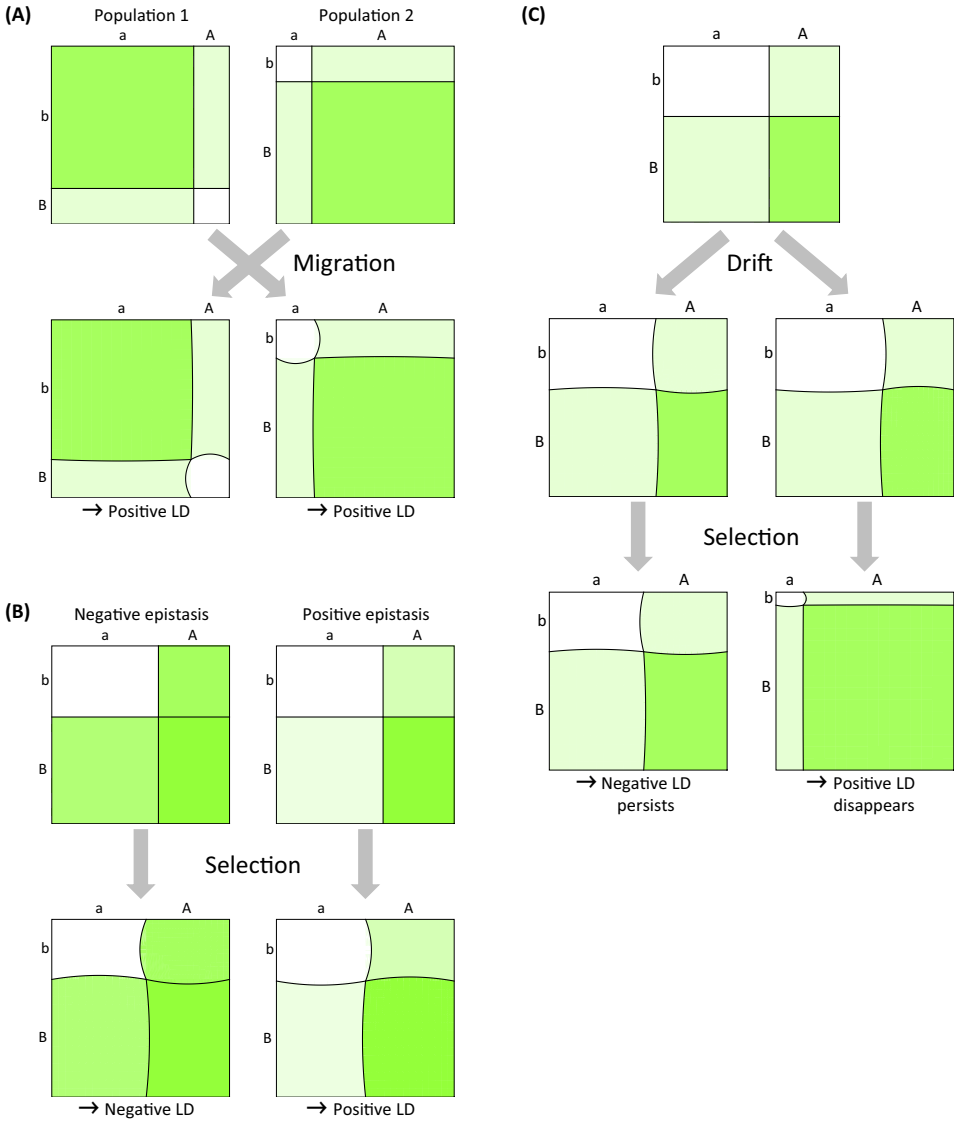

Figure 1. The Evolution of Linkage Disequilibrium (LD) in a Population. Illustration of three different ways in which LD can be created in a population: panel (A) migration, panel (B) epistasis, and panel (C) the Hill–Robertson effect. In all plots, two biallelic loci A and B are considered, and the two axes give the frequencies of alleles *a*/*A* and *b*/*B* at these loci, respectively. The four areas in the plots then give the proportion of the four possible haploid genotypes (*ab*, *Ab*, *aB* and *AB*), with fitness indicated by increasing intensity of green.

Provided that one or several evolutionary forces create LD in a population, will recombination be favored or disfavored by natural selection? Positive LD implies an overabundance of individuals with either very high or very low fitness compared to individuals with intermediate fitness values. This high variance in fitness means that natural selection will be very efficient, and thus there will be indirect selection against recombination to maintain the positive LD. More precisely, a modifier allele reducing recombination can spread by preserving and hitchhiking along with genotypes carrying multiple beneficial mutations, provided that linkage between the modifier and the selected loci is sufficiently strong. Conversely, negative LD implies a low variance in fitness and therefore impedes natural selection, such that recombination modifiers increasing recombination rates can be favored.

allele can increase or decrease in frequency by hitchhiking with the gene combinations it creates, thereby changing recombination rates within the population.

Reinforcement: the strengthening of reproductive isolation by natural selection in response to maladaptive hybridization. Reinforcement aids the completion of speciation.

Underdominance: individuals heterozygous at a given locus are at a selective disadvantage compared to homozygous individuals.

Based on this effect alone, divergent selection in two populations connected by migration as well as positive epistasis are predicted to produce selection against recombination, whereas negative epistasis and the Hill–Robertson effect would create selection for recombination. However, recombination also has the effect of breaking up co-adapted gene combinations, with immediate and potentially strong fitness effects. As a consequence, when there is strong negative epistasis, strong selection against recombination can outweigh selection for recombination resulting from indirect effects on facilitating adaptation. For in-depth treatments of the principles of selection on recombination rates, see [15,18,25,26].

Mechanisms To Change Recombination Rates

So far, we have discussed selection on recombination without specifying how genetic variation in recombination rates can arise. We will now focus on the two main mechanistic ways in which recombination rates between a pair of loci can change: through changing the rate at which crossovers occur between linked loci, or though genomic rearrangements that alter their physical location. An overview of different mechanisms affecting recombination that involves one or both of these principles is given in Table 1.

Most mathematical models for the evolution of recombination employ the modifier approach introduced by Nei [27]. Here, alleles at a modifier locus produce different recombination rates between other loci that might be under direct natural selection. Assuming such recombination modifiers is justified in that there is ample evidence for heritable variation in crossover rates within populations (e.g., [28]). Humans provide one of the most striking examples because **recombination hotspot** positions differ considerably between individuals of African versus European ancestry [29]. Similarly, recombination rates and patterns often vary considerably between

Table 1. Mechanisms Affecting Recombination and their Consequences on Fitness in a Single Individual

Mechanism	Effects		
	Change in Crossover Frequency	Change in Linkage Relationships	Pleiotropic Fitness Effects
Modifier alleles	Yes Acting locally (on linked or unlinked sites) or globally	No	Possible Possibly underdominant effects [65,66]
Gene transpositions	No	Yes Leads, by definition, to a new gene order along a chromosome, or movement to a new chromosome	Possible Might insert into another gene and disrupt it; changes in expression level are also possible
Inversions	Yes Particularly near breakpoints	Yes Between a gene within and a gene flanking the inversion	Possible Underdominant effects due to aneuploidy in gametes; fitness effects due to altered gene expression [67]
Translocations (including chromosome fusions)	Yes Particularly near breakpoints, and apparent linkage between different chromosomes	Yes Free recombination between translocated region and donor chromosome; linkage between translocated region and recipient chromosome	Yes Underdominant effects due to aneuploidy in gametes; changes in expression level are also possible [67]

closely related species, indicating fast evolution (reviewed in [30]). However, it is less clear how common locally-acting recombination modifiers of the type assumed in the population genetics models are relative to other 'modifiers' that are more firmly established empirically but exhibit more complex dynamics (Box 1).

In addition to changes in crossover frequencies between different loci, recombination rates will also change as a result of chromosomal rearrangements that produce new linkage relationships. The most important mechanism in the context of speciation is chromosomal inversions, which

Box 1. Recombination Modifiers: Theory vs. Data

In population genetic models, a recombination modifier is a gene that affects the rate of crossovers between genes (Figure IA) [27]. By hitchhiking along with the gene combinations it creates, a modifier allele can spread and thereby change recombination rates within the population. Since its inception in the 1960s, the modifier approach has afforded deep insights into how we should expect recombination rates to evolve under a wide range of conditions.

Recently, there have also been major advances in our understanding of the molecular mechanisms of recombination in eukaryotes. Recombination is initiated by an induced double strand break (DSB) during meiotic prophase. Using the homologous chromosome, the DSB is then repaired, resulting in either crossover or non-crossover events. DSBs are not randomly distributed in the genome but are often concentrated in recombination hotspots, 1–2 kb genomic regions characterized by strongly elevated crossover frequencies. In humans, more than 25 000 hotspots have been identified and 40% of these are enriched for a degenerate 13 bp sequence motif [68]. In both humans and mice, the location of most DSBs is determined by PRDM9, a histone methyltransferase that binds to sequence motifs within hotspots and recruits other proteins involved in recombination initiation [69–71].

Prdm9 evolves rapidly [72,73] and exhibits high within-population diversity in its DNA-binding region, giving rise to a large number of protein variants that bind to different sequence motifs [74]. *Prdm9* can thus be regarded as a major recombination modifier gene. However, *Prdm9* is distinct from classic recombination modifiers because different alleles that determine presence or absence of a recombination hotspot between two genes will likely also have pleiotropic effects on many other hotspots, and because *Prdm9* is not linked to most pairs of loci whose recombination it affects (Figure IB). Intriguingly, *Prdm9* is also known to cause hybrid sterility in mammals [65,66]. All of this indicates that *Prmd9* evolution is governed by principles other than those envisaged in recombination modifier models.

DSB-inducing sequence motifs within recombination hotspots could also themselves be viewed as a type of modifier allele that operates as a responder to different *Prdm9* alleles. Thus, mutations within those motifs that disrupt recognition by *PRDM9* could be favoured by natural selection because they locally suppress recombination. However, although they act locally they are again not expected to behave like classic modifiers. This is because DSBs are repaired using the homologous chromosome so that recombination hotspots are subject to erosion through gene conversion which would lead to spread of the 'colder allele' even in the absence of selection (see Figure IC). The persistence of hotspots in the face of these self-destructive dynamics is referred to as the 'recombination hotspot paradox' [75]. Overall, the emerging picture of recombination regulation in mammals indicates a need to refine existing population genetic models to account for the complexities of real-world recombination modifiers.

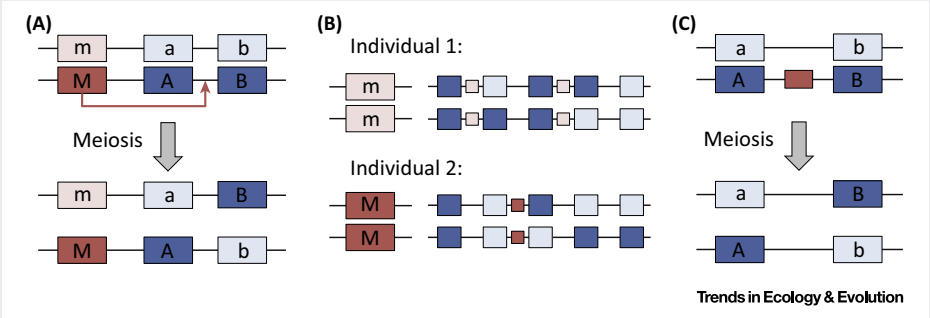

Figure I. Illustration of Different Types of Recombination Modifier Genes. (A) The classic theoretical approach, in which a modifier allele (*M*) affects recombination rates between two other linked genes (**A** and **B**) that are usually assumed to be under natural selection. (B) Simplistic view of how global recombination modifier genes such as *PRDM9* might act. Here, different individuals in the population carrying different modifier alleles create different recombination hotspots or coldspots (small squares) between a number of loci that are not necessarily linked to the modifier locus. (C) A local recombination modifier that is a sequence motif inducing crossover events (recombination hotspot); in the process of the actual crossover this hotspot gets deleted due to gene conversion.

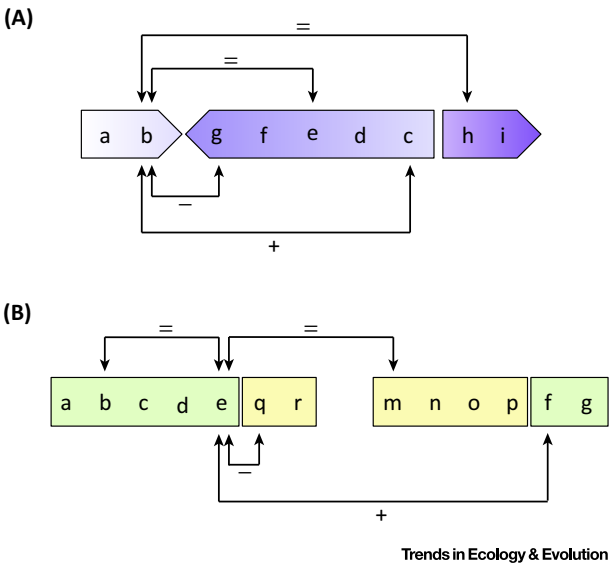

Figure 2. The Effect of Chromosomal Rearrangement on Linkage. (A) A chromosomal inversion (inverted purple box g–c) increases recombination rates between some loci that were previously tightly linked (b,c and g,h) and reduces recombination rates between other loci that were less tightly linked before the inversion occurred (b,g and c,h). (B) Translocations (mixture of chromosome blocks of different colors) also produce large-scale changes in linkage relationships, as denoted by arrows. Note that these changes in recombination rate arise in homokaryotypes; by contrast, in heterokaryotypes, additional factors influence the patterns of recombination (Table 1).

can affect recombination rates in several ways [13,14,31,32]. At the most basic level, by changing gene order an inversion increases recombination rates between some loci that were previously tightly linked and reduces recombination rates between other loci that were less tightly linked before the inversion occurred (Figure 2A). Moreover, crossover events in individuals that are heterozygous for the inversion will be suppressed in the region flanking the breakpoints of the inversion (sometimes extending several megabases away from the breakpoint), further reducing recombination rates between genes in the vicinity of the breakpoints [33–36]. Finally, in heterozygous individuals, crossover events can lead to unbalanced meiotic products (i.e., deletions and duplications). As a consequence, no recombinant offspring might be recovered because they are inviable or because recombinant meiotic products fail to develop into gametes. These effects are the basis for **underdominant** selection against inversions occurring in the heterozygous state.

Translocations and chromosome fusions are similar to inversions in that they also produce large-scale changes in linkage relationships (Figure 2B) but, in the heterozygous state, often result in unbalanced meiotic products, and are therefore selected against when rare (e.g., [37]). Finally, recombination rates can change on a more limited scale through transpositions of short DNA segments (e.g., containing only individual genes). For example, such transpositions can arise as a result of active transposable elements. Unless transpositions disrupt functional genes or strongly affect gene expression, they will generally not to be expected to be under strong negative selection. Transpositions will generally result in strongly increased recombination rates between genes that were formerly tightly linked.

The Evolution of Recombination Rates During Speciation

Adaptive Divergence and Ecological Speciation

How are recombination rates expected to evolve during speciation when there is ongoing gene flow between populations? Although this is a complex and underexplored question, some light can be shed through previous theoretical results. Consider a scenario of **ecological speciation** where two parapatric populations adapt to different environmental conditions. Assuming that **fitness trade-offs** between alleles contribute to adaptation, selection against recombination is expected. This is because selection for locally adapted alleles at different loci will be more efficient when these alleles remain together than when they recombine with non-adaptive migrant alleles. Selection against recombination in this scenario has been explored quantitatively

Box 2. Differences between Inversions and Modifiers

An inversion can be viewed as a special modifier gene that is completely linked to the genes it affects. Unlike allelic modifiers, inversions suppress recombination only in heterozygotes, and can have collateral effects on gene expression and elimination of gene function. Other differences between inversions and modifiers (e.g., underdominance, number of genes affected, pleiotropic fitness effects) are likely to be important as well, but might be more specific to particular inversions or modifiers. All else being equal, inversions should spread more readily than allelic modifiers through the local adaptation mechanism. This is because inversions are completely 'linked' to the loci they capture, and also because they do not suppress recombination rates within the diverging populations (i.e., between inversion homozygotes). By contrast, allelic modifiers may only be loosely linked to the loci whose recombination rates they affect. Modifiers are also expected to suppress recombination within each population, which might be costly. Unfortunately, variation for inversion versus modifier polymorphism remains largely unexplored. Although chromosomal inversions suppress recombination locally, they may do it over larger regions of the genome than local allelic modifiers. This may eventually increase the likelihood of speciation by facilitating the accumulation of genetic incompatibilities.

Finally, inversions also have global effects on recombination across the genome. For instance, in *Drosophila* crosses carrying an inversion, recombination rates decrease near breakpoints, but they increase elsewhere in the genome. This phenomenon is known as the Schultz effect, and is common across taxa [76,77]. An additional role of inversions during speciation could be that they facilitate adaptation within populations by increasing recombination rates outside inversions. This is potentially beneficial when the genetic architecture of adaptation is polygenic and relies on many loci scattered across the genome. Whether allelic modifiers of recombination also create interchromosomal effects on recombination rates remains to be explored.

in several recombination modifier models [26,38,39]. The same principle can also been applied to selection for inversions [20], chromosome fusions [40], and transpositions [41]. All else being equal, such chromosomal rearrangements should spread more easily than modifier alleles because rearrangements are completely linked to the loci under selection and recombination is suppressed only in heterozygotes (Box 2).

It is important to note that selection against recombination is not inevitable. For example, negative epistasis between loci can produce selection for modifier alleles that increase recombination rates even in the face of gene flow of locally maladapted alleles [26]. Similarly, and perhaps of more general importance, random genetic drift can also produce selection for recombination that alleviates Hill–Robertson interference among selected mutations at different loci. The Hill–Robertson effect has previously been shown to produce strong selection for recombination in both unstructured and subdivided populations [42,43]. It is conceivable that selection against recombination caused by differential adaptation with gene flow could be overcome by selection for recombination due to the Hill–Robertson effect, but this possibility remains to be investigated.

Secondary Contact and Intrinsic Reproductive Isolation

These considerations also apply to scenarios where previously allopatric populations come into secondary contact. As populations diverge in allopatry, they might accumulate genetic differences that would fail to work in a hybrid. One example comes from the evolution of interacting mutations that function in each population but fail to properly interact in the alternative genetic background of the diverging population (Dobzhansky–Muller model, see [1] for a review). For instance, the ancestral interaction *aabb* might evolve into *AAbb* in one descendant population and into *aaBB* in a second one. Although each allelic interaction is functional in each population, the hybrid combination *AaBb* might be defective because the functionality of *A* and *B* together has never been tested. Provided the hybrids are not completely inviable or sterile, this genetic disassembly in hybrids creates strong negative epistasis for fitness and thereby strong selection for the evolution of modifiers that reduce recombination, or for the ancestral genotypes and thus the breakdown of reproductive barriers. These modifiers of recombination could then spread to the two populations and partially favor the completion of speciation [44].

One potential case where reductions in recombination might have evolved in response to negative epistasis occurs in *Drosophila pseudoobscura* and *D. persimilis*. These fruit flies

co-occur and hybridize [45] in the northwestern region of North America, while *D. pseudoobscura* expands its range into southern forests of the USA and Mexico. Genetic experiments have found that genes contributing to postzygotic isolation localize exclusively to chromosomal inversions that separate the two hybridizing species [46]. In their hybrids, these inversions lock into place the untested *A* to *B* interaction we mentioned above. Therefore, these inversions preserve the evolved configurations, *AAbb* and *aaBB*, that function properly within each species and prevent the dissolution of the Dobzhansky–Muller incompatibilities that would occur in the presence of recombination [6]. This might provide evidence for selection against recombination as outlined above. Unfortunately, the alternative possibility that the inversions had been present already before secondary contact cannot be currently rejected. Moreover, in their sympatric range, *D. pseudoobscura* females strongly discriminate against heterospecific males (prezygotic isolation) compared to those females found in the southern allopatric ranges [47]. Thus, mating discrimination and reductions in recombination might evolve concurrently, a matter that we turn our attention to below.

Interaction with other Modes of Reinforcement

Overall, reduction in recombination rates after secondary contact helps to maintain the integrity of co-adapted gene clusters. Adopting a broad definition of **reinforcement** as an increase in reproductive isolation by natural selection in response to maladaptive gene flow, this reduction in recombination rates can be viewed as a mechanism of reinforcement (see also Table 1 in [44]). This is because, even though reduced recombination does not prevent the formation of hybrids, it does reduce the production of offspring with different parental gene combinations and thus enhances population differentiation. Other mechanisms of reinforcement include reductions in dispersal ([48], pp. 127–131, [49]), increased mate preference for conspecifics [50], and the evolution of alternative mating systems (e.g., selfing or asexual reproduction [51]). These mechanisms reduce genetic exchange between incipient species but act at different stages of the life cycle of the organism (dispersal, syngamy and meiosis, respectively; see also [44]). Some degree of competition between the different mechanisms of reinforcement can be expected, with a hierarchy that reflects the order of the different life stages. As an extreme example, consider the case where complete suppression of dispersal between two locally adapted populations has evolved. In this case, selection for reduced recombination rates (and for assortative mating) in response to maladapted migration will come to a full stop. The reverse however is not necessarily true: even when complete suppression of recombination between a set of loci has evolved, there might still be ongoing selection for reduced dispersal rates or assortative mating through selection against migrants, heterozygotes, or recombination at other loci.

An interesting interaction is predicted to occur between modifiers for assortative mating and recombination. In the classic model by Felsenstein [19], assortative mating can evolve as a consequence of selection against recombinants between two locally adapted genotypes. The higher the recombination rate between the two loci under selection, the easier it is for the assortative mating alleles to become associated with the locally adapted genotypes. As a consequence, modifiers that reduce recombination between the two loci under selection impede the evolution of assortative mating [52], illustrating the competition between assortative mating and recombination reinforcement. Conversely, recombination between the assortative mating locus and the loci under selection constrains speciation, and modifiers suppressing recombination are favored [52].

In general, the different mechanisms of reproductive isolation generated by reinforcement could evolve at the same time; which one is most dominant would depend on available genetic variation, biological constraints, and pleiotropic effects of the respective modifiers. Of course, recombination reinforcement alone is unable to bring about complete reproductive isolation

because of inherent limitations to genome-wide reductions in recombination. However, species can behave as gene clusters where a subset of genes controls species identity despite some levels of gene flow between groups. Under this species concept (Genotypic Clusters [53]), or in a Biological Species concept where we relaxed the criterion of complete reproductive isolation to describe the culmination of the speciation process [1], recombination reinforcement can aid in the formation and persistence of well-defined species.

Some Consequences of Altered Recombination Rates

The spread of modifier alleles during speciation with gene flow also affects the genetic architecture of speciation. A recombination modifier will spread if it is linked to alleles conferring local adaptation, or by facilitating reinforcement. We expect that regions of low recombination will tend to harbor genes for various forms of reproductive isolation, as well as modifiers of recombination, during the early stages of speciation or secondary contact. A chromosomal inversion can also play this role and, therefore, inversions are predicted to be disproportionally associated with these stages of speciation [6]. Furthermore, these regions might be partially responsible for genomic patterns of species differentiation. Although other genomic regions of low recombination (such as centromeres, Y chromosomes, and mtDNA genomes) could potentially be conducive to adaptive differentiation, it is not clear how important these regions are for ecological speciation with gene flow given their low gene density (but note that these regions could be important in other modes of speciation [54–57]).

Natural selection reduces genetic diversity around favored alleles within populations, while increasing the divergence of these regions between populations [58]. As a consequence, genomic divergence between populations is expected to be heterogeneous [59,60]. Gene flow intensifies these patterns by homogenizing neutrally-evolving but not divergently selected loci and their surrounding regions [61–63]. The extent to which gene flow can homogenize regions around selected loci is a function of the strength of selection, the frequency of hybridization, and the recombination rates experienced in hybrid meiosis [64]. If selection is strong, a selected locus can create large swaths of loci with strong genetic differentiation between populations, often known as islands of genomic divergence [59,63].

Measures such as the fixation index, FST, are often used to explore patterns of heterogeneous genomic divergence during speciation with gene flow, where clusters of loci with high FST values should indicate the presence of islands of genomic divergence [60]. Unfortunately, FST is sensitive to low levels of heterozygosity, which are likely to arise from selection acting on regions of reduced recombination [59,64]. Therefore, variance in FST might reflect the interplay between natural selection and gene flow, but also selective sweeps, or the action of background selection, in regions of reduced recombination occurring in local populations that do not exchange genes. However, as we have argued here, these regions of reduced recombination can in fact be a consequence of divergent selection during speciation with gene flow. In general, it is challenging to argue in favor of speciation with gene flow from patterns of heterogeneous genomic divergence alone, at least in studies where recombination rate variation within species is not considered (but see [35]).

Concluding Remarks

We have revisited the strong and natural link between the evolution of sex and the origin of new species. As populations adapt to new conditions while still exchanging genes with other populations, and also during secondary contact, recombination rates might evolve in response to maladaptive gene exchange. Generally, recombination is expected to be selected against, resulting in the evolution of coadapted gene complexes, favoring the evolution of various forms of reproductive isolation and thereby helping to advance the speciation process. It is important to

Outstanding Questions

Migration–selection balance favors the suppression of recombination. However, in finite populations, there may also be selection for increased recombination as this alleviates the Hill–Roberson effect. Can the Hill–Robertson effect cancel out selection for suppressed recombination, thereby hampering divergence? This may have relevance for the question of how population size impacts on the likelihood of speciation.

Migration between adapted populations may favor reductions in recombination between locally adaptive loci. Will these regions become islands of speciation?

Are chromosomal inversions more effective than genic modifiers of recombination rates in favoring the speciation process?

How much genetic variation for recombination rates at different genomic scales is there within and between species, and what is the genetic basis for this variation?

There are multiple forms of reinforcing selection. How do these interact, and what are the conditions under which the evolution of suppressed recombination fails to facilitate speciation with gene flow?

What are the consequences of the evolution of suppressed recombination for our understanding of genomic patterns of differentiation between populations?

stress, however, that there can also be conditions where increased rates of recombination are favored. Moreover, there are multiple scenarios where recombination rate evolution is not expected to play a role during speciation. For instance, strong selection could prevent gene flow almost instantaneously between parapatric populations, and modifiers other than those affecting recombination (especially dispersal and assortative mating) could predominate as mechanisms of reinforcement. These scenarios shorten the window of time in which recombination rates can evolve in response to gene flow between populations adapting to contrasting environments.

Chromosomal inversions should play a major role during speciation with gene flow. However, we have argued that our focus should also encompass allelic modifiers of recombination that might create more subtle patterns of recombination rate variation across the genome. Genetic mapping exercises within species are likely to reveal the genetic basis of recombination rate variation, and whether different mechanisms operate across the tree of life. Finally, we have suggested that the genetic architectures arising from the interplay between selection and gene flow are likely to produce islands of genomic divergence in regions of reduced recombination, thus complicating interpretations of patterns of genomic divergence between populations. Studies that scrutinize both genetic differentiation across space and variation in recombination rates within species are therefore necessary to gain a better understanding of the causes of genomic variation in nature. More generally, we expect that frequent dialogue between students of recombination rate evolution and those of speciation will lead to better-integrated theories for the origin and maintenance of genetic and phenotypic variability in nature.

Acknowledgments

We thank Mohamed Noor, Maddie E. James, and three anonymous reviewers for constructive comments on previous versions of this manuscript. D.O-B. and J.E. are funded by the Australian Research Council (Discovery Project Grant DP140103774). The work of L.H.R. on speciation is supported by a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada.

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