Experimental tests on the evolution of sex and recombination and their adaptive significance

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Abstract

Sex and recombination generate genetic variation and facilitate adaptation by reducing selective interference, but they can also disrupt genotype combinations maintained by selection. We here synthesize recent experimental evolution studies on the adaptive consequences of sex and recombination in constant environments, emphasizing insights gained from population genomic data. We discuss evidence showing how meiotic segregation (sex) and crossovers (recombination) disrupt negative disequilibrium between alleles within and between loci and enhance selection efficacy. While sexual reproduction can facilitate adaptation when compared to asexual reproduction, the benefits of higher and variable rates of sex and recombination under facultative sexual reproduction or facultative outcrossing are less clear, especially when overdominance and epistatic interactions cause segregation and recombination loads. We further discuss the challenges of measuring interference between selected alleles, particularly under polygenic adaptation and segregation of multiple modifiers of recombination, and propose directions for future research. Our discussion underscores the nuanced role of sex and recombination in adaptation, shaped by a balance between increased genetic variation and the disruption of co-adapted genotype combinations.

Keywords: recombination, sex, crossover, segregation, meiosis, selective interference, epistasis, experimental evolution, population genomics

Introduction

Sexual reproduction in eukaryotes has long been recognized for its role in generating genetic variation, fueling adaptation by mixing and shuffling different genotypes despite its many potential physiological and ecological costs [1, 2]. In prokaryotes and viruses, genetic mixing and shuffling also occur, and may be of adaptive significance, though the underlying replication processes are not necessarily associated with reproduction [3–5]. With sexual reproduction, genetic variation is generated during "sex" through the meiotic segregation of homologous chromosomes as well as through "recombination" and the meiotic crossover between non-sister chromatids (and gene conversion between sister chromatids, which we will ignore) [6]. The capacity to drive adaptation may well explain the prevalence of sexual reproduction in eukaryotes but it has been difficult to demonstrate because the realized or effective rates of sex and recombination depend on population-specific factors such as propensity for sexual reproduction [7], the presence of meiotic drive elements in the genome [8], the distribution of structural variants and crossover modifiers along chromosomes [9, 10], patterns of population subdivision and migration between habitats [11, 12], or the mode of reproduction (self-fertilization or outcrossing) and the degree of inbreeding among relatives [7, 13].

Understanding the evolution of recombination has been the primary focus in efforts to explain the widespread occurrence of sexual reproduction [14, 15]. Much of the reasoning emphasizes the ability of recombination to alleviate selective interference by breaking up associations between deleterious and beneficial alleles at different loci, known as negative linkage disequilibrium (LD) [14, 16–19]. The disruption of negative LD increases the variance in fitness within a population, thereby enhancing the effectiveness of natural selection and phenotypic responses [20, 21]. Sex through segregation is also important in determining adaptation, as it can increase the fitness variance and selection efficacy by breaking within-locus negative associations in heterozygotes [22–24].

In explaining the evolution of sex and recombination, comparisons are often made between sexually and asexually reproducing populations, which are perhaps only relevant for the emergence of sex and recombination when adaptation occurs from a limited supply of new mutations, or to answer the question of whether sexual populations are able to resist the invasion of asexual mutants [4, 5]. These comparative arguments imply the existence of group selection between sexual and asexual lineages, which does not hold when individuals with variable sex and recombination rates must compete and mate with each other [2]. In fact, genetic modifiers increasing sex or recombination rates might facilitate adaptation in the long-term because of an increase in fitness variance while not always being favored by individual selection on the short-term because, for instance, of disruption of co-adapted genotype combinations [21, 24–27].

Evolution experiments have been a favorite approach to test for the adaptive significance of sex and recombination [15, 28–30]. Our goal here is to highlight a few evolution experiments from the past decades, particularly those that have placed population genomic observations at the center of the debate (see also [31–33]). Time-series analysis of population genomic diversity is now possible, and several experiments have attempted to measure the genetic basis of adaptation under different degrees of sex

and recombination. Further, observations from natural populations indicate that the recombination rate genomic "landscape" is highly heterogeneous and heritable due to individual differences in the distribution of crossover position and number along the chromosomes [12, 34, 35], posing the problem of which evolutionary forces explain this recombination landscape heterogeneity and heritability. We focus on evolution experiments conducted in constant environments, though the evolution of sex and recombination in fluctuating environments is a significant topic in its own right [36–41]. We briefly review the main theoretical predictions for the evolution of sex and recombination and then discuss four related questions: Does sexual reproduction facilitate adaptation when compared to asexual reproduction? How does adaptation depend on the realized frequency or effectiveness of sex and recombination? Can selection explain the evolution of sex and recombination? What is the evidence for selective interference?

Theoretical background

Sex and recombination alter genotype frequencies when there is a departure from Hardy-Weinberg equilibrium within loci and gametic linkage equilibrium between loci [20, 21, 42]. Such disequilibrium are expected to be common in finite populations, as new mutations arise in complete linkage with the genetic background in which they occur [16, 17], and in a heterozygous state if the individual is diploid [22]. disequilibrium can also occur due to selection favoring or purging specific allelic combinations, or because finite populations can not contain all possible allelic combinations at many loci [14, 19, 21, 23]. Complicating factors such as population subdivision, inbreeding or self-fertilization can generate an excess of homozygosity by bringing together related genotypes increasing effective segregation but decreasing effective recombination [13, 43].

Selection can lead to within and between loci disequilibrium, particularly when the fitness effects of alleles are not independent, that is, when there is dominance and epistasis for fitness [20, 21, 42]. With negative epistasis, as when deleterious alleles at different loci act synergistically and beneficial alleles act antagonistically, selection leads to negative linkage disequilibrium and an excess of genotypes containing deleterious and beneficial alleles. By breaking negative linkage disequilibrium, recombination increases the frequency of genotypes with multiple deleterious alleles and of genotypes with multiple beneficial alleles, thereby increasing the genetic variance in fitness and the efficiency of selection [20, 21]. Breaking linkage disequilibrium generated by epistasis can however also reduce offspring fitness [27], due to the production of genotypes with multiple deleterious alleles, and a balance between short-term and long-term effects of epistasis will dictate the evolution of recombination [27]. Similarly, when beneficial alleles are (partially) dominant, or deleterious alleles (partially) recessive, sex through segregation will increase fitness variance by producing more homozygotes. This, however, will come at the expense of a fitness loss in offspring heterozygotes as they are fitter than the average of their homozygous parents [42].

Negative disequilibrium can also arise from the interaction of genetic drift and selection, a phenomenon known as the Hill-Robertson effect [19, 44, 45], and which occurs independently of dominance or epistasis for fitness. In any finite population, stochastic fluctuations in genotype frequencies generate both positive and negative

disequilibrium. However, selection eliminates positive disequilibrium as the most advantageous genotypes, which combine beneficial alleles, sweep to fixation, while the worst genotypes, combining deleterious alleles, are purged from the population. Negative disequilibrium will thus persist for longer due to selective interference between beneficial alleles located in different genotypes and increased sex and recombination rates can then be favored as they reduce this interference and allow beneficial alleles to spread more effectively [19, 44, 45]. Similarly, in asexual populations, clones carrying different beneficial mutations interfere with each other, constraining adaptation [16, 17], and further, the population as a whole may face Muller's ratchet as clones with less deleterious alleles cannot be recreated without genetic mixing and shuffling [18]. Analogous mechanisms within locus generate an excess of heterozygotes in finite asexual populations are also expected and when selection purges homozygous deleterious genotypes [22, 23].

Sexual reproduction facilitates adaptation

Most experimental evolution studies on the adaptive significance of sex and recombination have compared sexual with asexual populations, and almost exclusively using microorganisms such as the budding yeast (*Saccharomyces cerevisiae*) and the green alga *Chlamydomonas reinhardtii* (see Table 1 for a list of key experiments that are here discussed). A few studies accounted for the possibility that the environmental manipulation necessary to induce sexual reproduction in these organisms (usually starvation or density), rather than sex and recombination themselves, might have influenced adaptive outcomes. This was done by ensuring that the asexual population could undergo the same environmental manipulation without triggering sexual reproduction by maintaining a single mating type [46], or through genetic engineering of meiosis [47, 48].

Sexual reproduction typically increases fitness variation and accelerates adaptation to new environments when compared to asexual reproduction. The advantage over asexual reproduction is particularly evident in harsh, novel environments, and less pronounced in benign conditions to which populations were presumably already well-adapted. For instance, in benign environments, one study found greater adaptation in sexual than asexual populations [49], another observed no effect [48], and a third reported a loss of fitness due to sexual reproduction [50]. These mixed results can be attributed to weaker selection in benign or domesticated environments, or the segregation of predominantly deleterious alleles once adaptation has been achieved, which might have led to a smaller benefit of sex and recombination [51]. However, the two explanations are not mutually exclusive, as shown in a yeast study where an increase in mutation rates reduces adaptation in asexual populations under stressful conditions but not in more permissive environments [48].

In many studies, experimental populations were maintained as haploids, with diploidy only occurring transiently during a few sexual cycles [46, 52–55]. In these scenarios, the adaptive significance of sexual reproduction can be attributed to the effects of recombination, as the effects of sex and segregation in the maintenance of heterozygosity can be neglected because selection of diploids is minimal. Sexual reproduction has also been observed to facilitate adaptation in diploid yeast populations,

but in these cases the effects of sex and recombination are challenging to disentangle. Segregation is expected to confer an advantage to sexuals over asexuals by reducing deleterious load [56] or generating homozygotes for beneficial alleles, while asexual populations will be hindered by maintaining heterozygosity [22]. One study in yeast populations showed less adaptation in sexual populations compared to asexual populations under diploidy than haploidy [55]. Comparing ploidy treatments is however complicated by typical higher mean fitness and lower fitness variance in diploids, regardless of sex and recombination, presumably due to the masking of recessive deleterious alleles. The reduced advantage of sexual reproduction in diploids over haploids can also be explained by overdominant alleles providing a heterozygote advantage in asexual populations [26]. Indeed, such overdominant alleles are known to segregate in some yeast experimental populations [57].

Worth mentioning in the context of evolution of asexual reproduction and horizontal gene transfer, experiments with the RNA bacteriophage Φ6 allowing multiple virions to infect the same cell [58, 59], or with *Escherichia coli* allowing for F-plasmid conjugation between cells [60], have shown that adaptation is facilitated when compared to treatments where there was no opportunity for genetic mixing and shuffling between virions or cells. Interestingly, a particular beneficial mutation, monitored over time, was found to spread significantly faster within conjugating *E. coli* populations compared to non-conjugating populations [60], a result consistent with important clonal selective interference and impaired adaptation under asexuality cf. [32, 33].

More comprehensive results were found with population genomics data from budding yeast experiments with asexual populations [54, 61]. In them, adaptation typically involves the spread of single clones, each carrying one or a few beneficial alleles along with other neutral or even deleterious ones. In contrast, sexual populations display more independent allele frequency changes across the genome, suggesting that selective interference is alleviated and that selection can act independently across different loci [54]. As expected, deleterious mutations often hitchhike with beneficial ones in asexual populations, impairing adaptation, while recombination in sexual populations facilitates adaptation by separating beneficial alleles from deleterious hitchhikers. Intriguingly, one yeast evolution experiment with sexual populations found that selection consistently occurred at fewer than ten loci across replicates [62], raising questions about how sexual reproduction and variable sex and recombination rates determine the polygenicity of adaptation [63], a topic that we will return to in the next section.

The benefits of sex and recombination should increase when many selected alleles interfere with each other [64, 65]. Consistent with this idea, conjugating *E. coli* and sexual yeast experimental populations mentioned above show stronger adaptive responses in higher mutation treatments compared to their asexual counterparts [48, 60, 66]. Moreover, small-size bottlenecks reducing overall genetic diversity reduce the benefit of sexual reproduction over asexual reproduction in the green alga *C. reinhardtii* [52]. Bottlenecks can, however, also increase selective interference [29, 44, 45, 67, 68], as supported by increased benefits of genetic mixing and shuffling in the RNA bacteriophage Φ6 [59].

Organism	Ploidy	Focus of the study	Sexual reproduction	Genetic variation	Key findings	Ref.
Saccharomyces cerevisiae	Diploid	Adaptation sex/asex	One round of sex every 25 or 50 generations.	New mutations with or without genetic mutator	Use of the *spo11/spo13* genetic system enable identical environmental conditions between asexual and sexual populations. Sex has no effect in a benign environment (30°C) but increases adaptation to a harsh environment (37°C). Increasing mutations by deleting the MSH2 gene reduces adaptation of the asexual populations but not the sexual populations.	[47, 48]
	Haploid	Adaptation sex/asex	One round of sex every 90 generations	New mutations	In haploid-specific populations, sex increases adaptation to peptone dextrose medium by disrupting association between beneficial and deleterious mutations, altering their frequency dynamic.	[54]
	Haploid or diploid	Adaptation with varying sex and recombination	One round of sex every 40 or 120 generations.	Standing genetic variation	Sex prevents the loss of fitness variance and increases adaptation to peptone dextrose medium from standing generation. No difference is observed between rare sex and frequent sex.	[55]
Chlamydomonas reinhardtii	Haploid	Adaptation sex/asex	Single episode of 8 successive rounds of sexual reproduction	New mutations	Sex increases adaptation to sodium bicarbonate. This effect is reduced in populations that have undergone a small-size bottleneck.	[52]
	Haploid	Initial round of sexual reproduction	Adaptation with varying sex and recombination	Standing genetic variation	Following an initial fitness drop, sexual populations show a higher fitness variance and faster adaptation to varying substrate, compared to asexual populations.	[69]
	Haploid	Adaptation with varying sex and recombination	1 to 3 episodes of sexual reproduction among 150 generations	Standing genetic variation	Following an initial fitness drop, sexual populations show a greater adaptation to varying substrate, especially for a higher number of sexual episodes.	[53]
	Haploid	Extinction with varying sex	1 round of facultative or environmentally-induced obligate sexual reproduction every 4-12 generations.	Varying standing genetic variation	Sexual reproduction and genetic diversity delay the extinction of population in a gradually harsher environment (salt). This effect is more pronounced at higher rate of sex (rounds of obligate vs facultative sex).	[46]
Drosophila melanogaster	Diploid	Evolution of recombination	Obligate, outcrossing	Standing genetic variation	Increased recombination evolves in response to artificial selection on a few traits, sometimes in both directions. Increased recombination occurs in a large portion of the genome but not in all genomic intervals.	[70, 71]
	Diploid	Evolution of recombination	Obligate, outcrossing	Standing genetic variation	Increased recombination evolves when artificial directional selection is applied to bristle number (both directions), but decreased recombination evolves when artificial stabilizing selection is applied on the same trait.	[72]
Brachionus calyciflorus	Diploid (female) or diploid (male)	Evolution of facultative sexual reproduction	Facultative	Standing genetic variation	Rates of sex transiently increase during adaptation to varying algal food sources and NaCl. Sex is associated with an increase of fitness variance and a decrease in its mean.	[73]
Caenorhabditis elegans	Diploid	Consequence and evolution of outcrossing rates	Obligate, varying partial outcrossing.	Mutagen-induced mutations	Outcrossing facilitates recovery from deleterious mutation load and adaptation to varying environments. Increased outcrossing evolves in these environments.	[74]
	Diploid	Evolution of a recombination modifier	Obligate, predominant outcrossing	Standing genetic variation	The *rec-1* mutant smoothing the recombination landscape of *C. elegans* without inducing any obvious direct fitness cost impairs genome-wide adaptation but is favored through local indirect selection.	[63]

Table 1 Key experimental findings on the evolution of sex and recombination and adaptation.

High and variable sex and recombination rates not always facilitate adaptation

The experimental studies outlined so far provide crucial insights into the prevalence of sexual reproduction over asexual reproduction. However, their relevance to an understanding of how different rates of sex and recombination influence adaptation is limited. Rates of sex and recombination are generally low in microbial experimental evolution. For example, budding yeast populations typically undergo one round of sexual reproduction every 25 to 120 generations, with six crossovers per chromosome per round being expected [75], yielding much less than one crossover per chromosome per generation on average. Clearly, many other eukaryotes have higher and more variable rates of sex and recombination and so the question becomes how this variation is maintained.

It is often suggested that "a little sex goes a long way" cf. [76]. This is usually meant as a "little segregation and recombination is sufficient for adaptation" because even rare segregation or recombination events can generate new genotype combinations that will be efficiently selected [22, 77]. In addition, several models have suggested that selective interference is stronger, and the long-term advantage of sex and recombination in enhancing selection efficacy greater, when fitness is highly polygenic and many selected alleles are tightly linked [64, 65]. Therefore, high rates of recombination may only enhance adaptation from standing genetic variation and many loci are under selection [78, 79].

Adaptation from standing genetic variation is usually studied by crossing different wild isolates or lab inbred lines to create genetically diverse "multiparental" populations [46, 53, 55]. In yeast populations derived from two parental isolates, sexual reproduction enhances adaptation compared to asexual reproduction, but the level of adaptation is similar whether sexual cycles occur every 40 or 120 generations [55]. In *C. reinhardtii*, populations derived from 16 parental isolates, but not those derived from two parental isolates, frequent rounds of (environmentally-induced) obligate sexual reproduction delay extinction in a gradually deteriorating environment compared to facultative sexual reproduction [46]. In another experiment with *C. reinhardtii*, populations derived from 12 to 15 isolates and evolved for more than 150 generations showed that increasing the number of sexual cycles from one to two improved adaptation, but further increasing to three cycles had no additional benefit [53]. Thus, neither higher levels of standing genetic variation always lead to more extensive adaptation nor more frequent sexual reproduction always facilitate adaptation.

The question of whether natural populations harbor enough selected alleles to generate the selective interference necessary to explain obligate sexual reproduction or high recombination rates remains unresolved [14]. The number of independently selected alleles likely depends on the population's history, including factors like population size and ancestral effective rates of sex and recombination, which differ widely among organisms [80]. As a result, the choice of the organism can influence experimental outcomes, with microorganisms that seldom undergo sex and recombination in nature perhaps not being the best models. Additionally, the methods used to establish experimental populations affect observed adaptive responses. Populations derived from crosses between a few distant isolates can generate standing genetic variation but if

these isolates vary in their initial adaptation to the experimental environment, positive linkage disequilibrium and genotype-by-environment interactions may significantly bias and limit further adaptation [43]. This issue can be alleviated by maintaining multiparental populations in domestication environments for many generations to disrupt linkage disequilibrium before starting the experiment (if domestication is not of interest in itself) [81, 82].

The lack of clear evidence for enhanced adaptation under frequent sexual reproduction may result from an unknown balance between the benefits of increased selection efficiency in the long-term and the fitness costs of segregation or recombination in offspring generations. Populations with standing genetic variation are particularly prone to these recombination loads due to the disruption of beneficial epistatic genotype combinations [83, 84], or to segregation loads due to disrupting of beneficial pseudo- or true-overdominant alleles [26, 85–88], favored by prior selection. Several experiments support this idea. For example, recombinant lines of *Drosophila spp.* derived from wild populations exhibit reduced fitness compared to lines with male derived chromosomes (as males are achiasmatic) or recombination-suppressing chromosomal inversions [89, 90]. Recombination loads may also explain the observations of fitness loss following a round of sexual reproduction in haploid populations of *C. reinhardtii* with standing genetic variation from wild progenitors [50, 53, 69]. In another example, we have recently shown that in the nematode *Caenorhabditis elegans*, a modifier of crossover position increasing recombination rates in chromosomal centers, presumably containing linked epistatic loci [88, 91, 92], reduce the fitness of a domesticated multiparental population [63]. Reduced fitness is also observed in sexually produced offspring compared to asexually produced offspring in field-derived populations of the monogonont rotifer *Brachionus calyciflorus* [73, 93]. In this later case, however, and because of diploidy, the reduced fitness may be attributed to either a recombination load or to a segregation load. Segregation and recombination loads can cause an immediate fitness drop, which may be offset by enhanced selection efficacy over time [53, 69, 90], but they can also hinder long-term adaptation by preventing beneficial epistatic combinations or overdominant alleles from contributing to adaptation. The conclusion seems to be that there is a limit beyond which additional sex and recombination becomes disadvantageous [26, 84, 94].

Facultative sex and outcrossing are under selection

Experimental studies showing a benefit to sexual reproduction offer valuable insights into the prevalence of sexual reproduction over phylogenetic time or when sexual populations face competition from invading asexual mutants. However, their relevance in the evolution of varying rates of facultative sexual reproduction within a population is limited as increased rates of sexual reproduction can be selected against despite facilitating adaptation [23, 42]. Furthermore, one complicating issue in some evolution experiments is that sexual reproduction itself may evolve because of selection on phenotypes that accompany sexual reproduction and which are not related with sex and recombination during meiosis. Examples are provided by facultatively sexual organisms showing phenotypic differences between sexual and asexual individuals, such as

the production of eggs with variable resistance to stress, females or males, or individuals with different ploidy levels. In monogonont rotifers, for instance, diploid females produce haploid male offspring during sexual reproduction [73, 95]. Moreover, changes in rates of sexual reproduction often result from plastic responses to stress or environmental cues rather than the evolution of sexual reproduction per se [7, 95, 96]. The plasticity to engage in sexual reproduction can also evolve. In *C. reinhardtii* populations, for instance, increased propensity for spontaneous sexual reproduction evolve when individuals produced through sexual reproduction are selected when there is only a single mating type in the population [97].

In a comprehensive study with the rotifer *B. calyciflorus*, an increase in female sexual reproduction was observed during adaptation. This increase was linked to a rise in fitness variance and a decline in the average fitness of sexually produced offspring compared to asexually produced offspring [73]. Because *B. calyciflorus* females are diploid, changes in the offspring fitness distributions align well with the disruption of negative linkage disequilibrium under negative epistasis [27], or with the production of homozygous individuals and the exposure of deleterious recessive alleles to selection [23, 24]. The evolution towards higher levels of sexual reproduction was nonetheless moderate and temporary. Once adaptation occurred, a reversal was seen, with evolution to lower levels. This shift may be explained because the benefits of sexual reproduction are low in already-adapted populations or because of a transgenerational effect on the propensity for sexual reproduction. In a sister species, transgenerational effects have been shown to reduce the propensity for sexual reproduction in lineages undergoing more sexual cycles [95].

Experimental evidence for the evolution of phenotypes associated with sexual reproduction is also illustrated with experiments in *Caenorhabditis elegans*, a species that undergoes obligate sexual reproduction but facultative outcrossing. In this nematode, hermaphrodites can either self-fertilize or outcross by mating with males. Self-fertilization increases homozygosity, and as a consequence reduces effective recombination rates, potentially exposing deleterious recessives to selection but also increasing the fitness variance due to overdominant loci [86, 88, 98]. In experiments with partially self-fertilizing populations, outcrossing rates temporarily increase following exposure to a mutagen [74, 99, 100]. However, this increase remains modest even under environmental conditions where (genetically-engineered) obligately outcrossing populations exhibit higher fitness than partially outcrossing populations [74]. This underscores that, as beneficial genotypes produced by outcrossing are unlikely to remain associated with outcrossing individuals for long, and the evolution of outcrossing may be limited despite its potential long-term benefits in maintaining genetic variation. The evolution of outcrossing in these experiments should be driven by a short-term fitness advantage provided by the masking of recessive deleterious alleles in heterozygotes.

The evolution of predominant but partial outcrossing has also been observed in multiparental *C. elegans* populations with standing genetic variation that ancestrally relied on self-fertilization [88, 101]. In these studies, the evolution of outcrossing rates is attributed to the evolution of enhanced male performance [101]. However, it is

because of self-fertilization that an excess of heterozygosity across the genome is maintained. In partial outcrossing populations, selection purges deleterious recessive alleles, as more homozygotes are produced because of self-fertilization, in turn allowing for the expression and the maintenance of overdominant loci, or associative overdominance between linked deleterious recessives, as heterozygotes are produced because of outcrossing [87, 88].

Selection for recombination can be independent of polygenic adaptation

Early experimental studies addressing the evolution of recombination measured the selective response on traits in *Drosophila melanogaster* lines with or without chromosomal inversions suppressing recombination across varying portions of autosomes (reviewed in [28, 30]). These studies showed that recombination increases the efficacy of selection by expanding the fitness variance of the population. However, to be favored because of facilitating adaptation through increased fitness variance, a genetic modifier of recombination, such as a modifier of crossover position or number, has to be indirectly selected alongside the genotype combinations it creates. A recombination modifier is under indirect selection when it enhances the efficacy of selection within its local genomic neighborhood, allowing it to hitchhike with proximate genotypes but not with more distant genotypes [67, 102]. This is illustrated in Figure 1, where simulations of the distance between a modifier of crossover position and the many loci being selected will determine the strength of indirect selection on the modifier itself (Figure 1A,C,D). The sign of indirect selection will obviously depend on weather the modifier is located in a genomic interval where it increases or decreases recombination rates among selected loci (Figure 1B,C,E). In these illustrative simulations, and regardless of its genomic position, the recombinogenic effects of the modifier of crossover position on selected alleles remains constant as there is no impact the extent of adaptation. Indirect selection of a recombination modifier, driven by its local effects on nearby loci, and polygenic adaptation, driven by the efficacy of selection at a genome-wide level, are therefore independent whenever recombination rate landscapes are heterogeneous.

The evolution of recombination rates in response to strong artificial directional selection on other traits has been quantified in many different species (reviewed in [29, 103]; see also [71, 72]), including domesticated species [104, 105]. These studies generally reveal the evolution of increased recombination rates at particular genomic regions. Increased recombination rates also tend to evolve when the same trait is selected in different directions [70–72], indicating that pleiotropy (where an allele affects both the selected trait and recombination rates), or spurious initial associations between the modifier and selected loci, are not significant. Rather, these experiments suggest that modifiers increasing recombination rates are indirectly selected because they allow for more efficient selection on the genetic variation underlying the targeted trait. Other supporting evidence for indirect selection on recombination modifiers comes from *D. melanogaster* experiments where artificial stabilizing selection caused the evolution of reduced recombination rates [72]. Under stabilizing selection, reduced recombination rates are favored by indirect selection because recombination among

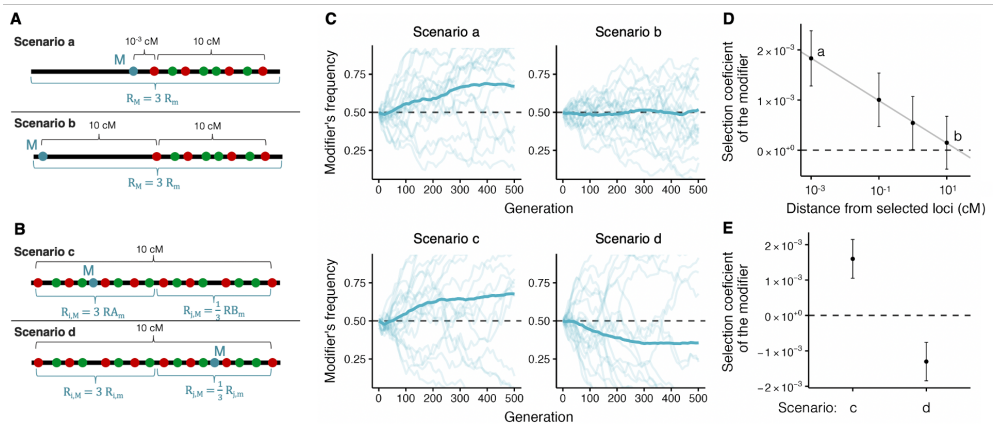

Fig. 1 Indirect selection on a recombination modifier is driven by its local genomic effects. We performed simulations of indirect selection on a modifier of crossover position and number along a chromosome. The ancestral population of 10^3 diploid individuals was generated with burn-in of 10^3 generations with one selected mutation ($s = e^{0.005}$) introduced per generation per 10^4 loci genome. After burn-in, a neutral recombination modifier was introduced in 500 randomly sampled genomes. Other protocol details can be found in the simulation methods section. We modeled the recombination effect of the modifier under four different scenarios. **A**. In scenarios a and b, individuals homozygous for the modifier allele (M) have a chromosomal map length (R_M) increased by 3-fold compared to the ancestral map length (R_m; we assume the modifier allele is co-dominant). Scenario a and b only differ by the position of the modifier relative to the selected alleles. We only represent one homologous chromosome. Red and green circles illustrate deleterious or beneficial alleles. **B** In scenarios c and d, the co-dominant modifier allele increases the map length in a first interval, i, and reduces it in an adjacent interval, j, by a factor 3. The modifier is located in interval i in scenario c and interval j in scenario d. **C.** The modifier frequency is tracked for 500 generations. Thin lines show the trajectories for 40 simulation runs per scenario, thick lines show the average of 500 simulations runs. **D.** Indirect selection coefficient (binomial generalized liner model: $modifier.freq \sim generation$) as a function of the distance between the modifier and the selected loci, for scenarios a,b, and in two additional intermediate scenarios (dots = mean; error-bars = 95% CI). The indirect selection coefficient of the modifier decreases linearly, on a log scale, as the function of its genetic distance from the selected loci. **E.** Indirect selection coefficient for scenario c,d is positive when the modifier is located in interval i, where it increases recombination, and negative when it located in interval j, where it decreases recombination. Overall, the indirect selection strength and sign on recombination modifiers depend their genomic proximity to selected loci.

the best genotypes at optimal trait values necessarily generates lesser fit genotypes [106, 107]. A population under stabilizing selection suffers from a recombination load because of epistasis among selected loci.

For indirect selection to result in the evolution of recombination, selected loci need to be in close genomic proximity to recombination modifiers (Figure 1). This is not unlike in many artificial selection experiments because recombination rates typically increase across large portions of the genome, and selected traits, such as stress resistance, are known to be highly polygenic [108]. The segregation of multiple segregating recombination modifiers, as commonly observed in natural populations [35], will further increase the likelihood that at least one modifier is found near selected alleles. Moreover, at the extreme selection pressures applied in these experiments (e.g.,

only 30 individuals out of 300 contributing to the next generation in [70]) could allow a modifier to be indirectly selection with more distant selected loci [67].

Another experimental approach to study indirect selection and the evolution of recombination is to track the evolution of a known modifier modifier of crossovers. This what we did with the multiparental poopulation of *C. elegans* mentioned in the previous section [63]. We genetically engineered the recombination landscape of *C. elegans*, which typically show large central chromosomal regions with much lower recombination rates relative to flanking regions, to homogenize recombination rates along the chromosomes [109]. Specifically, *rec-1* loss-of-function mutants generally redistribute crossover positions to central chromosomal regions, without directly affecting fitness [63, 109]. Because most genetic diversity is located in intervals where the *rec-1* mutant allele reduces recombination rates, it diminishes the genome-wide efficacy of selection and impairs adaptation to a new environment. Nonetheless, the *rec-1* mutant is favored because it increases recombination rates in its genomic neighborhood, thereby enhancing the local efficacy of selection [63]. Consistent with the Hill-Robertson effect, stronger indirect selection on the recombination modifier *rec-1* is observed at smaller population sizes, supporting the idea that indirect selection on recombination modifiers depends on selected loci in their genomic proximity, while being independent of genome-wide polygenic adaptation.

Detecting selective interference under variable recombination rates

Detecting selective interference from population genomic data that is now typically collected from evolution experiments is a considerable challenge. One needs to identify selected loci, and estimate whether there is negative linkage disequilibrium between them, which is not trivial if not impossible when adaptation is polygenic and there is an astronomical number of genotype combinations to test, each with relatively small effects [81, 110, 111]. Most studies use markers, such as single-nucleotide variants, that themselves must be in linkage with selected alleles to be informative. Only a few rare studies have provided examples of disruption of negative linkage disequilibrium between a small number of selected alleles e.g. [54]. Instead, averaged genome-wide estimates have been used to detect a recombination signal on marker allele frequency dynamics.

One way to estimate linkage between selected loci is by measuring the correlation between marker allele frequency dynamics [54, 63]. For instance, in the *C. elegans* experiments with the *rec-1* recombination landscapes mentioned before, adaptation was associated with higher correlations of allele frequency change in genomic regions with reduced recombination [63]. However, this measure does not indicate the sign of linkage disequilibrium and whether selected alleles are linked with other selected alleles, or neutral ones. The temporal covariance of allele frequency change is another metric that can be used to detect selective interference [112]. In this case, it is assumed that (mostly neutral) marker allele frequency changes result from the genetic background in which the selected alleles are found. Using time series data is a given marker allele frequency change within a period is less correlated with a frequency change at later periods when the marker is swapped between different genetic backgrounds by

recombination [112]. While this method has faced some criticism [113], experimental *D. melanogaster* populations show the expected reduction in temporal covariance between more distant time intervals [114]. Similar observations were reported in evolution experiments with the marine copepod *Acartia tonsa* [115]. In the *D. melanogaster* studies, there was a slight excess of negative temporal covariance, showing that marker alleles reverse their trajectories, which could be due to breaking negative linkage disequilibrium or epistasis.

Selective interference can also be measured as parallel genomic diversity responses among replicate populations evolving from shared standing genetic variation [55]. The intuition here is that recombination increases parallelism by enhancing selection efficacy, and thus, the same selected alleles will be found across replicates. For instance, [55] calculated the standard deviation of allele frequency between replicate experimental populations across generations as a measure of parallelism, having found that it is higher in sexually reproducing yeast populations than in asexual populations. Yet, recombination can also reduce parallelism when calculated as the correlation of allele frequency change between replicate populations [114]. In this case, parallelism is high in the first few generations of the experiments but quickly decays as ancestral haplotypes recombine and the fitness of particular genetic backgrounds determine marker frequency trajectories.

We illustrate with simulations this dual effect of recombination on parallelism of genomic responses among replicate population undergoing similar experimental evolution. We simulated adaptation from standing genetic variation under different recombination rate treatments and varying proportions of selected alleles (Figure 2). Results show that the relationship between recombination and parallelism among replicate simulations is not monotonic. Only under conditions of low recombination rates and a high proportion of selected alleles does parallelism increase with recombination. Conversely, increased recombination may decrease parallelism, despite facilitating adaptation, when selective interference is weaker. Thus, while high parallelism with recombination can be a sign of (strong) selective interference, low parallelism does not necessarily indicate its absence. Overall, new metrics are needed to better quantify the impact of variable recombination rates on the populations genomics of polygenic adaptation and interference between selected loci.

Future directions

The problems of the evolution of sex and recombination and their adaptive significance can be subdivided into a set of questions addressing different aspects of genetic mixing and shuffling between genotypes. It is now experimentally well established that sexual reproduction can facilitate adaptation by breaking disequilibrium between selected alleles. These observations generally provide an explanation for the prevalence of sexual reproduction over asexual reproduction in eukaryotes. However, evidence for the adaptive significance of high and variable sex and recombination rates is much weaker. While fitness is generally highly polygenic, it is still unclear whether there is a sufficient number of interfering alleles that segregate in natural populations to confer an advantage to high rates of sex and recombination. This uncertainty is compounded

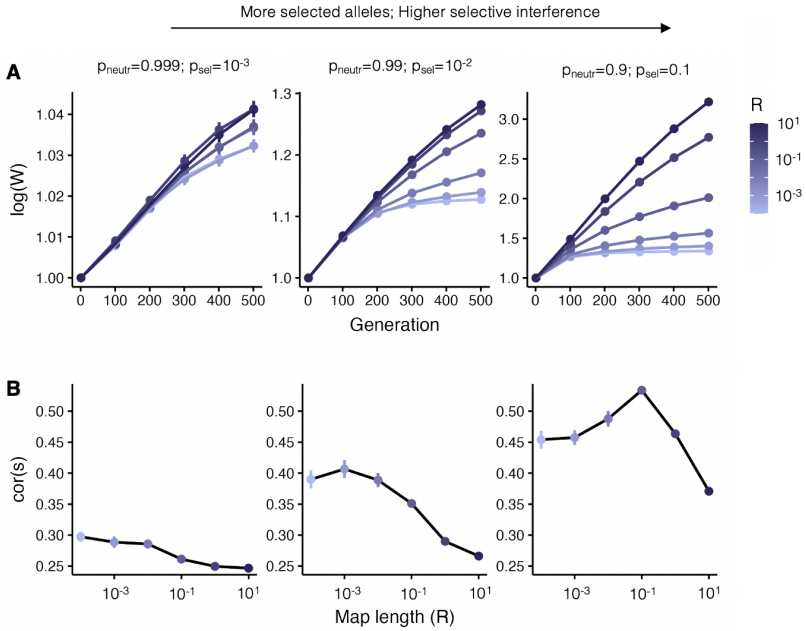

Fig. 2 Recombination can enhance or diminish replicate parallelism. The standing genetic variation of the ancestral population was generated as in Figure 1 (R=50 cM, 10^5 loci, average of one mutation per genome per generation). Both neutral alleles ($s = 0$) and selected alleles ($s = e^{0.005}$) were simulated with varying proportions indicated above the panels (p_{neutr} and p_{sel}, respectively). The higher the proportion of selected alleles, the higher the expected number of them segregating and interfering with each other. Adaptation from the standing genetic variation was simulated during 500 generations with varying map lengths (R; in cM). **A.** Adaptation is faster and more extensive for larger values of R and less interfering alleles. **B.** Parallelism among replicate simulations was calculated as the Pearson correlation (r) of the observed selection coefficient among ten runs from the same ancestral population. Increasing the R increases this correlation only when it is small and/or the number of interfering mutations is high.

by the fact that sex and recombination can oppose selection in maintaining beneficial genetic combinations, as there is evidence that co-adapted genotype combinations, due to epistasis or overdominance, are common [12, 57, 116, 117]. Variable recombination rates along the genome (heterogeneous recombination landscapes) might mitigate this issue by preserving beneficial genotype combinations in low-recombining genomic regions as when populations adapt to local environmental conditions [12, 118, 119]. It is unclear, however, how recombination will evolve when modifiers of dispersal or modifiers the genetic architecture of selected loci also segregate in the population cf. [120]. Furthermore, the presence of co-adapted genotype combinations should itself depend on ancestral rates of sex and recombination [58, 84, 121, 122].

While the long-term adaptive consequence of high rates of sex and recombination may be tied to polygenicity [64, 65], theoretical studies suggest that modifiers of sexual reproduction may be more likely to evolve due to their short-term fitness effects via segregation, rather than by enhancing long-term adaptation [23, 24, 42].

Under random mating, however, short-term effects generally only favor modifiers of sex when deleterious alleles are dominant [123], whereas recessive deleterious mutations, which appear to be more prevalent, tend to cause a segregation load and disfavor higher rates of facultative sexual reproduction. Higher rates of sexual reproduction are favored under conditions of excess homozygosity, where it can produce beneficial heterozygotes by masking deleterious recessive alleles or exposing overdominant alleles [42, 124]. Therefore, population structure because of inbreeding between relative and self-fertilization, which generate excess homozygosity, may be important in explaining the evolution of obligate sexual reproduction. Focusing on levels of heterozygosity and the potential for heterozygote advantage would be particularly helpful when studying the evolution of sexual reproduction in experimental systems.

The direct fitness effects of recombination, through its molecular consequences of crossover during in meiosis (increasing for example the extent of chromosome missegregration and aneuploidies), have been suggested as key drivers in the evolution of recombination, such as during adaptation to different temperatures [125]. Nevertheless, there is strong experimental evidence supporting a role forindirect selection in the evolution of recombination [63, 71]. One of the main conclusions from the experiments on the evolution of sexual reproduction, and particularly the evolution of recombination, is that modifiers recombination are favored when they generates beneficial genotype combinations within their local genomic neighborhood, rather than through a genome-wide increase in the efficacy of selection and more extensive adaptation [63, 67, 102].

Polygenic adaptation and the evolution of recombination may often be poorly correlated when selection and recombination rates are heterogeneous across the genome [63]. Several factors should influence the strength of indirect selection on recombination modifiers and its alignment with polygenic adaptation, including breeding mode, the polygenicity of recombination itself, and whether modifiers act globally (trans) or locally (cis) when interacting with genomic features, such as chromatin accessibility or transposon content [34, 126, 127]. Breeding mode is important because any factor that increases linkage disequilibrium increases the duration that a modifier remains associated with the genotypes it produces, thereby changing the strength of indirect selection, and possibly the direction of selection, by extending the size of the local genomic region that drives indirect selection [128]. When recombination itself is polygenic due to the segregation of multiple crossover modifiers [35], conflicts may arise between them with opposite effects. Local indirect and independent selection on multiple modifiers across the genome might also average out and align or not with the effects of the modifier on genome-wide recombination rates and thus on polygenic adaptation. It is uncertain whether indirect selection would be significant if each modifier's effect on recombination is small or highly localized. If the evolution of recombination is primarily driven by modifiers of local recombination rates, rather than the genome-wide modifiers, indirect selection should correlate with the maintenance co-adapted genotype combinations.

Gaining deeper insights about the evolution of sex and recombination in eukaryotes, along with their adaptive significance, will require mapping and identifying the genetic

modifiers of sex and recombination. This will enable the development of new experimental models allowing for the manipulation of modifier associations with selected alleles in more relevant genomic, demographic and ecological scenarios for natural populations than studied so far.

Simulation methods. Individual-based simulations of diploid populations were implemented using *SLiM* 4.0.1 [129], using the default Wright-Fisher models for mutation, selection, and reproduction. Ancestral populations with standing genetic diversity were obtained through 1000 generations of reproduction with recombination (map length values specified in the legend of the figures) with an average of one mutation per genome (i.e., mutation rate $u = 1/\text{Ł}$, where L is the number of loci). Unless otherwise indicated in the figure legend, all mutations have a selection coefficient sampled from an exponential distribution with an expected mean of 0.005. Simulations start from an ancestral population and differ in their map length or the presence and position of an explicit genetic modifier of recombination. For each ancestral population generated, 10 simulations per parameter set were performed for 500 generations. The mutation rate during these 500 generations was set to 0. The simulation scripts, results and modeling details are available in our GitHub repository.

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