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 allelic combinations maintained by selection. We here review experimental evolution studies on the adaptive significance of sex and recombination in constant environments, emphasizing insights gained from population genomic data. We discuss evidence showing how meiotic segregation (sex) and crossing-over (recombination) disrupt negative disequilibrium between alleles within and between loci and as a consequence increase the fitness variance of populations and enhance selection efficacy. While sexual reproduction can facilitate adaptation when compared to asexual reproduction, the advantages of high rates of sex and recombination under facultative sexual reproduction or facultative outcrossing and self-fertilization are less clear, especially when overdominance and epistasis 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 beneficial allele combinations.

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

Introduction

Sexual reproduction in eukaryotes is widely recognized for its role in generating genetic variation, which fuels adaptation to novel environments by combining and shuffling genotypes, despite its significant physiological and ecological costs (Weismann, 1891; Fisher, 1930; Burt, 2000). With sexual reproduction, genetic variation is generated during "sex" through the meiotic segregation of homologous chromosomes, as well as through "recombination" and the crossing over between non-sister chromatids (Gray and Cohen, 2016; Lenormand et al., 2016). Gene conversion also affects recombination rates, but we will ignore it here (Korunes and Noor, 2017). In prokaryotes and viruses, genetic mixing is common, and may contribute to adaptation, although the underlying replication processes are not necessarily tied with reproduction (Bell, 1982; Maynard Smith, 1990; Redfield, 2001).

Understanding the evolution of recombination has been the primary focus in efforts to explain the widespread occurrence of sexual reproduction (Otto and Lenormand, 2002; Otto, 2021). Much of the reasoning emphasizes the ability of recombination to reduce selective interference by breaking negative linkage disequilibrium (LD), that is, by breaking the associations between deleterious and beneficial alleles at different loci (Felsenstein, 1965; Eshel et al., 1970). The disruption of negative LD increases the variance in fitness within a population, thereby enhancing the efficiency of natural selection and the evolutionary responses of traits related to fitness (Fisher, 1930; Muller, 1932, 1964; Hill and Robertson, 1966; Otto, 2021). The evolution of sex through segregation is likewise important to understand adaptation and the prevalence of sexuals, as segregation can increase the fitness variance of a population, and selection efficiency, through the disruption of within-locus negative associations in heterozygotes (Kirkpatrick and Jenkins, 1989; Roze and Michod, 2010; Roze, 2014).

When explaining the evolution of sex and recombination, comparisons are often made between sexually and asexually reproducing populations, which are relevant for the emergence of sex and recombination when adaptation occurs from a limited supply of new mutations, or to answer whether sexual populations can resist the invasion of asexual mutants (Maynard Smith, 1990; Redfield, 2001). These comparative arguments imply differential group selection between sexual and asexual lineages, which is not necessarily the case when individuals with variable sex and recombination rates must compete for similar resources in the same habitat and have the opportunity to mate with each other (Burt, 2000). For instance, genetic modifiers that increase sex or recombination rates might facilitate adaptation to a novel environment in the long-term, due to an increase in fitness variance of the population, while not always being favored on the short-term by individual selection due to the disruption of beneficial allele combinations (Feldman and Liberman, 1986; Lewontin and Hubby, 1966; Eshel et al., 1970; Barton, 1995; Roze, 2014).

Evolution experiments have been a favorite approach to test for the adaptive consequences of sex and recombination (Charlesworth and Barton, 1996; Otto and Lenormand, 2002; Otto and Barton, 2001; Rice, 2002). Our goal here is to highlight a few of these evolution experiments, particularly those that have placed population genetic observations at the center of the debate [see also Desai (2013); Sharp and Otto (2016); Cvijovic et al. (2018)]. Time-series analysis of the genomic diversity found in

experimental populations is now possible, and several studies have attempted to measure the genetic basis of adaptation under different rates of sex and recombination. In addition, observations from natural populations indicate that recombination rates vary along along chromosomes, generating recombination rate "landscapes", which themselves are heritable due to genetic differences between individuals in the distribution of crossover position and number (Brazier and Glémin, 2022; Venu et al., 2024; Johnston, 2024). How selection on genetic modifiers of crossover position and number relates to adaptation, particularly when there are many selected loci across the genome (polygenic adaptation), is an open problem.

We review illustrative evolution experiments conducted in constant environments, although the evolution of sex and recombination in fluctuating environments is a significant topic in its own right (Becks and Agrawal, 2010; Morran et al., 2011; Gray and Goddard, 2012a; Kerstes et al., 2012; Masri et al., 2013; Haafke et al., 2016; Lynch et al., 2018). We begin by briefly summarizing the main theoretical predictions for the evolution of sex and recombination and then discuss four related questions in the context of experimental evolution: Does sexual reproduction facilitate adaptation compared to asexual reproduction? How does adaptation depend on the realized frequency of sex and recombination? Can selection explain the evolution of sex and recombination? What is the evidence for selective interference in population genomic data? We finish by suggesting directions for future experimental research.

Theoretical background

Sex and recombination alter genotype frequencies when there is a departure from Hardy-Weiberg and linkage equilibrium within loci and between loci (Felsenstein, 1965; Eshel et al., 1970; Otto, 2003). Such disequilibrium are expected to be common in finite populations, as new mutations arise in phase with the genetic background in which they occur (Fisher, 1930; Muller, 1932), and in a heterozygous state in diploid organisms (Kirkpatrick and Jenkins, 1989). Disequilibrium can also occur due to selection on particular allele combinations, or because finite populations cannot contain all possible alleles at the many loci across the genome (Hill and Robertson, 1966; Eshel et al., 1970; Roze and Michod, 2010; Otto, 2021). 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 (Nordborg and Donnelly, 1997; Martin et al., 2006; Roze, 2009; Roze and Lenormand, 2005; Teterina et al., 2023).

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 (Felsenstein, 1965; Eshel et al., 1970; Otto, 2003). With negative epistasis for example — as when deleterious alleles at different loci act synergistically and beneficial alleles act antagonistically — selection leads to negative linkage disequilibrium (LD) and to an excess of genotypes in the population containing deleterious and beneficial alleles. By breaking negative LD, 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 (Felsenstein, 1965; Eshel et al., 1970). In the short-term, however, breaking (positive or negative) LD generated by epistasis can reduce offspring fitness. A balance between these short-term and long-term effects of epistasis will then dictate the evolution of recombination (Barton, 1995). Similarly, when beneficial alleles are partially-dominant, or deleterious alleles partially-recessive, selection will favor negative disequilibrium and an excess of heterozygosity in the population because heterozygotes are fitter on average than their parent homozygotes. Sex, by producing homozygotes through segregation will reduce excess of heterozygosity and thus increase the fitness variance of the population but, like recombination, at the expense of a fitness loss in offspring generations (Otto, 2003).

Besides dominance and epistasis, negative disequilibrium in a population, within and between loci, can also arise from the interaction of genetic drift and selection, in what is known as the Hill-Robertson effect (Hill and Robertson, 1966; Felsenstein, 1974; Barton and Otto, 2005; Roze and Barton, 2006). In any finite population, stochastic fluctuations in genotype frequencies generate both positive and negative disequilibrium. However, selection eliminates positive disequilibrium as the fitter genotypes, which combine beneficial alleles, sweep to fixation, while the worst genotypes, combining deleterious alleles, are purged from the population. Negative disequilibrium will therefore persist for longer due to selective interference among beneficial and deleterious alleles. Genetic modifiers increasing sex and recombination rates can then be selectively favored as they reduce this interference and allow beneficial alleles to spread more rapidly (Barton and Otto, 2005; Roze and Barton, 2006).

In asexual populations, clones carrying different beneficial mutations also interfere with each other, limiting adaptation (Fisher, 1930; Muller, 1932). Asexual populations may further face the so called Muller's ratchet as clones with less deleterious alleles cannot be recreated without genetic mixing (Muller, 1964). Analogous processes to those occurring in sexuals are expected to generate an excess of heterozygotes in finite diploid asexual populations (Kirkpatrick and Jenkins, 1989; Roze and Michod, 2010).

Sexual reproduction facilitates adaptation

Most experimental evolution studies about the adaptive significance of sex and recombination compared sexual with asexual populations, usually using microorganisms such as the budding yeast *Saccharomyces cerevisiae* and the green alga *Chlamydomonas reinhardtii*. [In Table 1 we highlight the evolution experiments here discussed, see also Otto and Lenormand (2002); Rice (2002); Sharp and Otto (2016); Cvijovic et al. (2018); Desai (2013).] A few of these studies accounted for the possibility that the environment inducing sexual reproduction, typically starvation or population density, influenced adaptation. This was achieved by ensuring that the asexuals underwent the same environmental manipulation as sexuals without triggering sexual reproduction, by maintaining a single mating type (Lachapelle and Bell, 2012) or through genetic engineering of meiosis preventing segregation and recombination (Goddard et al., 2005; Gray and Goddard, 2012b).

Many of these experiments have conclusively shown that sexual reproduction generally increases the fitness variance of populations and accelerates adaptation to new

environments, when compared to asexual reproduction. The advantage of sexual reproduction over asexual reproduction is particularly evident in harsh, novel environments, but less so in benign conditions to which populations already adapted to. For instance, in benign environments, one study found more extensive adaptation in sexual than in asexual populations (Zeyl and Bell, 1997), another observed no differences (Gray and Goddard, 2012b), and a third one reported a reduction of mean population fitness with sexual reproduction (Renaut et al., 2006). These mixed results can be attributed to weaker selection in benign or to the segregation of predominantly deleterious alleles once adaptation has been achieved (Hartfield et al., 2010); these explanations not being mutually exclusive, as shown by a study where an increase in mutation rates reduced adaptation in asexual populations under stressful conditions but not in more permissive environments (Gray and Goddard, 2012b).

In several studies comparing sexual with asexual reproduction, experimental populations were maintained under predominant haploidy, with diploidy being expressed only during a few sexual cycles (Colegrave, 2002; Kaltz and Bell, 2002; Lachapelle and Bell, 2012; McDonald et al., 2016; Kosheleva and Desai, 2018). In these conditions, the adaptive significance of sexual reproduction is due to recombination, as the effects of sex in the maintenance of heterozygosity should be minimal in the near absence of diploid selection. In the study of Kosheleva and Desai (2018), sexual reproduction facilitated adaptation in diploid yeast populations, although the effects of segregation and recombination in this case remained difficult to disentangle. Segregation is expected to confer an advantage to sexuals over asexuals by reducing deleterious loads (Haag and Roze, 2007) or by generating more homozygotes with beneficial alleles. Asexual populations on the other hand will be hindered because they maintain heterozygosity (Kirkpatrick and Jenkins, 1989). In general, comparing ploidy treatments is complicated by the fact that diploid populations usually have higher mean fitness and lower fitness variance than haploid populations due to the masking of recessive deleterious mutations. In Kosheleva and Desai (2018) in particular, there was a relatively smaller advantage of sex under diploidy than haploidy, which could also be explained by overdominance (Lewontin and Hubby, 1966; Sellis et al., 2016).

In the context of asexual reproduction and the evolution of horizontal gene transfer, it is worth mentioning experiments with the RNA bacteriophage Φ6, where multiple virions can infect the same cell (Malmberg, 1977; Poon and Chao, 2004), or with *Escherichia coli*, where F-plasmid conjugation between cells is possible (Cooper, 2007). These experiments showed that adaptation is facilitated when there is opportunity for genetic mixing between virions or cells. Interestingly, in Cooper (2007), a beneficial mutation spread significantly faster in conjugating *E. coli* populations compared to non-conjugating populations, suggesting that selective interference can explain impaired adaptation under asexuality (Desai, 2013; Cvijovic et al., 2018).

More comprehensive results about selective interference were found with population genomic data from yeast experiments (Kao and Sherlock, 2008; Lang et al., 2013; McDonald et al., 2016). In these experiments, adaptation in asexuals involved the spread of clones, each carrying beneficial mutations together with neutral and deleterious mutations. In contrast, sexual populations tended to display independent allele

frequency changes at many loci across the genome, suggesting that selective interference is reduced when compared to asexual populations (McDonald et al., 2016). As expected from theory, deleterious mutations often hitchhike with beneficial ones in asexual populations while recombination in sexual populations facilitates their independent evolution. Yet, how many loci can be independently selected is an unresolved problem. One yeast experiment with facultative sexuals found that selection occurred at fewer than ten loci across replicate populations (Burke et al., 2014), a much smaller number when compared with experiments in exclusive sexuals, such as *Drosophila simulans* (Barghi et al., 2020), and raising questions about how variable sex and recombination rates determine the extent of selective interference and the polygenicity of adaptation (see next section).

It is expected that sex and recombination are favored when many selected alleles interfere with each other (Weissman and Barton, 2012; Weissman and Hallatschek, 2014). Consistent with this idea, conjugating *E. coli* and sexual yeast experimental populations show stronger adaptive responses in treatments with higher mutation rates compared to their asexual counterparts (Cooper, 2007; Gray and Goddard, 2012b; Peabody V et al., 2017). Moreover, small population size bottlenecks, by reducing overall genetic diversity, reduce the advantage of sexual reproduction vs asexual reproduction in the green alga *C. reinhardtii* (Colegrave, 2002). Smaller population sizes can, however, also enhance selective interference (Otto and Barton, 2001; Iles et al., 2003; Barton and Otto, 2005; Roze and Barton, 2006; Roze, 2021), as supported by the benefit of genetic mixing in the RNA bacteriophage Φ6 undergoing bottlenecks (Poon and Chao, 2004).

Adaptation and variable sex and recombination rates

The experiments outlined so far provide insights into the prevalence of sexual reproduction over asexual reproduction. However, their relevance in understanding how different rates of sex and recombination influence adaptation is limited (see introduction). Furthermore, rates of sex and recombination are generally low in microbial experimental evolution. For example, budding yeast populations in the laboratory typically undergo one round of sexual reproduction every 25 to 120 (mitotic) generations (Goddard et al., 2005; Gray and Goddard, 2012b; McDonald et al., 2016; Kosheleva and Desai, 2018). With six crossovers per chromosome per meiosis (Mancera et al., 2008), much less than one crossover per chromosome per generation are expected on average.

It has been suggested that "a little sex goes a long way" (Hurst and Peck, 1996). This is usually meant as: even rare segregation or crossing-over events generate novel allele combinations that can be selected if adaptation depends on a small number of loci (Kirkpatrick and Jenkins, 1989; Green and Noakes, 1995). As mentioned above, several theoretical models suggest, however, that selective interference is stronger, and the long-term advantage of sex and recombination greater, when adaptation is highly polygenic and many of the selected alleles are tightly linked (Weissman and Barton, 2012; Weissman and Hallatschek, 2014; Hermisson and Pennings, 2005).

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 a mutator	Use of the *spo11/spo13* genetic system enables identical environmental conditions between asexual and sexual populations. Sex has no effect in a benign environment (30°C) but facilitates adaptation to a harsh environment (37°C). Increasing mutation rates by deleting the MSH2 gene impairs adaptation of asexual populations but not sexual populations.	Goddard et al. (2005); Gray and Goddard (2012b)
	Haploid	Adaptation sex/asex	One round of sex every 90 generations	New mutations	In haploid populations, sex facilitates adaptation to a peptone dextrose medium by disrupting association between beneficial and deleterious mutations	McDonald et al. (2016)
	Haploid or diploid	daptation with varying sex and recombination	One round of sex every 40 or 120 generations.	Standing genetic variation	Sex prevents loss of fitness variance and facilitate adaptation to a peptone dextrose medium. No difference is observed between rare and frequent sex.	Kosheleva and Desai (2018)
Chlamydomonas reinhardtii	Haploid	Adaptation sex/asex	8 successive rounds of sexual reproduction	New mutations	Sex facilitates adaptation to a sodium bicarbonate medium, beingreduced in populations having undergone a small population size bottleneck.	Colegrave (2002)
	Haploid	Initial round of sexual reproduction	Adaptation with varying sex and recombination	Standing genetic variation	Following an initial mean fitness reduction, sexual populations show higher fitness variance and faster adaptation to different media, compared to asexual populations.	Colegrave et al. (2002)
	Haploid	Adaptation with varying sex and recombination rates	1 to 3 rounds of sexual reproduction during about 150 generations	Standing genetic variation	Following an initial mean fitness reduction, sexual populations show enhanced adaptation to different media, especially with a larger number of sexual rounds.	Kaltz and Bell (2002)
	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).	Lachapelle and Bell (2012)
Drosophila melanogaster	Diploid	Evolution of recombination	Obligate, outcrossing	Standing genetic variation	Increased recombination evolves in response to artificial selection, often in both directions. Increased recombination occurs in a large portion of the genome but not in all genomic intervals.	(Korol and Iliadi, 1994; Aggarwal et al., 2015)
	Diploid	Evolution of recombination	Obligate outcrossing	Standing genetic variation	Higher recombination rates evolves when artificial selection is applied to bristle number (both directions), but reduced recombination evolves when artificial stabilizing selection is applied.	(Rodell et al., 2004)
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 and NaCl. Sex is associated with an increase in fitness variance and a decrease in mean fitness.	(Becks and Agrawal, 2012)
Caenorhabditis elegans	Diploid	Evolution of outcrossing rates	Obligate and partial, facultative outcrossing.	Mutagen-induced mutations	Outcrossing facilitates recovery from mutation loads and adaptation.	(Morran et al., 2009)
	Diploid	Evolution of a modifier of crossover position	Partial, facultative outcrossing	Standing genetic variation	The modifier *rec-1* mutant smooths the recombination landscape limiting adaptation but is indirectly favored by selection because of hitch hiking with beneficial genotypes it creates in its local genomic neighborhood.	(Parée et al., 2025)

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

Adaptation from standing genetic variation is typically polygenic (Hermisson and Pennings, 2005; Barghi et al., 2020; Barrett and Schluter, 2008). In evolution experiments, adaptation from standing genetic variation is usually studied by crossing different wild isolates or isogenic inbred lines to create genetically diverse (multiparental) hybrid populations (Kaltz and Bell, 2002; Lachapelle and Bell, 2012; Lachapelle and Colegrave, 2017; Kosheleva and Desai, 2018; Teotónio et al., 2017; Macdonald and Long, 2007). Results from these experiments have not been conclusive. 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 (Kosheleva and Desai, 2018). In green algae populations derived from 16 parental isolates, but not in those derived from two parental isolates, frequent rounds of (environment-imposed) obligate sexual reproduction delay extinction in a gradually deteriorating environment compared to facultative sexual reproduction (Lachapelle and Bell, 2012). In another experiment with green algae, 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 effect (Kaltz and Bell, 2002). Hence, neither higher levels of standing genetic variation always lead to higher adaptation nor does frequent sexual reproduction always facilitate adaptation.

The question of whether natural populations harbor enough selected alleles to generate the interference explaining obligate sexual reproduction or high sex and recombination rates remains unresolved (Otto, 2021). The number of independently selected alleles should depend on demographic history and factors such as population size and frequency of bottlenecks, population subdivision or predominant reproduction mode (Ellegren and Galtier, 2016). As a result, the choice of the organism can influence experimental outcomes. The specific methods used to derive experimental populations (e.g., through funnel or round-robin designs) will also impact the observations that are made. For example, populations derived from crosses between distant isolates might generate standing genetic variation, but if these isolates differ in their initial adaptation to the experimental environment, outbreeding depression might occur, and positive disequilibrium be common, with sex and recombination in these cases limiting adaptation. Some of these issues can be alleviated with domestication by maintaining populations in the laboratory environments until they near a selection-recombination equilibrium before starting with the treatments of interest (Simões et al., 2010; Teotónio et al., 2017).

Lack of clear evidence for enhanced adaptation under frequent sexual reproduction may result from a balance between higher fitness variance and reduced mean fitness that is difficult to detect. Populations with standing genetic variation are expected to be prone to recombination loads due to the disruption of beneficial epistatic interactions at multiple loci that were favored by prior selection (Hansen, 2006; Neher and Shraiman, 2009). Populations with standing genetic variation should also be prone to segregation loads due to the disruption of heterozygotes with beneficial pseudo-overdominant or truly overdominant alleles (Lewontin and Hubby, 1966; Lewontin et al., 1974; Bierne et al., 2000).

Several experiments support the existence of segregation and recombination loads. For example, recombinant lines of *Drosophila spp.* derived from wild populations exhibit reduced fitness compared to lines with recombination-suppressing chromosomal inversions or male-derived chromosomes (as males are achiasmatic), reviewed in Charlesworth and Barton (1996). Recombination loads may also explain the fitness loss observed following a round of sexual reproduction in haploid populations of the green alga *C. reinhardtii* with standing genetic variation derived from wild progenitors (Colegrave et al., 2002; Kaltz and Bell, 2002; Renaut et al., 2006). In the nematode *Caenorhabditis elegans*, a modifier of crossover position that increases recombination rates in chromosomal centers, which should contain epistatic loci (Chelo and Teotónio, 2013; Noble et al., 2017; Cutter et al., 2009), reduces the mean fitness of a domesticated population with standing genetic variation (Parée et al., 2025). Reduced mean fitness is also observed in sexually vs asexually produced offspring in field-derived populations of the monogonont rotifer *Brachionus calyciflorus* (Becks and Agrawal, 2011, 2012). In this latter case, however, and because of diploidy, reduced fitness may be attributed to either a recombination or a segregation load. In general, segregation and recombination loads can cause an immediate fitness loss in offspring generations that may be offset by enhanced selection over time (Charlesworth and Barton, 1996; Colegrave et al., 2002; Kaltz and Bell, 2002); it may be that there is a limit beyond which sex and recombination no longer have an effect on adaptation or even become limiting (Lewontin and Hubby, 1966; Neher and Shraiman, 2009; Lobkovsky et al., 2016), but conclusive experimental evidence is needed.

Facultative sex and facultative outcrossing under selection

Increased rates of sexual reproduction can be selected against despite their potential role in facilitating adaptation. In some evolution experiments, sexual reproduction may evolve because of (inadvertent) selection on traits unrelated to meiotic segregation and crossing over. This is the case of experiments using facultative sexuals, such as monogont rotifers, which show phenotype differentiation between sexual and asexual individuals in egg resistance to harsh environments or between individuals in sexual or ploidy identity (Becks and Agrawal, 2012). In these organisms, observed changes in the rates of sexual reproduction may often result from phenotypic plasticity (Sasso et al., 2018; Seudre et al., 2020; Hartfield, 2016). In addition, phenotypic plasticity can vary with individual fitness, as in the white clover *Trifolium repens* where stress-sensitive individuals tend to allocate growth resources to sexual reproduction traits (Griffiths and Bonser, 2013). Plasticity to engage in sexual reproduction can itself evolve. In the green alga *C. reinhardtii*, for instance, increased rates of spontaneous sexual reproduction evolve when sexual offspring are artificially selected or when there is a single mating type in the population (Bell, 2005).

In the rotifer *B. calyciflorus*, an increase in the rate of sexual reproduction was observed during adaptation (Becks and Agrawal, 2012). This increase was associated with higher fitness variance and a decline in the mean fitness of sexual offspring when compared to asexual offspring. Because females in this species are diploid, changes in offspring fitness suggest disruption of negative linkage disequilibrium (Barton, 1995) but also the segregation of homozygotes with deleterious recessive alleles (Roze and

Michod, 2010; Roze, 2014). In the experiments of Becks and Agrawal (2012), however, the increase of sexual reproduction was transient. Once adaptation occurred, a reversal to lower levels of sexual reproduction was observed; these results being explained because of weak selection in already-adapted populations (see above) or because of transgenerational environmental effects on the frequency of sexual reproduction. In the sister species to *B. calyciflorus*, transgenerational effects reduce the tendency for sexual reproduction in lineages undergoing more sexual rounds (Seudre et al., 2020). Interestingly, frequent sexual reproduction is observed in *B. calyciflorus* populations when in more complex environments and where a higher number of selected loci could underlie adaptation (Luijckx et al., 2017).

Evidence for the evolution of traits associated with sexual reproduction also comes from experiments on the evolution of facultative outcrossing and self-fertilization. Outcrossing rates can change through a plastic response, such as increased outcrossing rates following a heat stress in the fava bean *Vicia faba* (Bishop et al., 2017), or they can change through selection for reproductive assurance, such as the evolution of self-fertilization in the absence of pollinators in the yellow monkeyflower *Mimulus guttatus* (Bodbyl Roels and Kelly, 2011; Tusuubira and Kelly, 2024) or the evolution of hermaphroditism in male-female populations of the nematode *C. elegans* (Theologidis et al., 2014).

By increasing homozygosity, self-fertilization increases the fitness variance of a population and facilitates the selective purging of deleterious recessive alleles. However, increased homozygosity also decreases effective recombination (Nordborg and Donnelly, 1997), increasing selection interference and possibly reducing mean population fitness in the presence of overdominant loci (Nordborg et al., 1996; Bierne et al., 2000). In line with these population genetic mechanisms, the evolution of outcrossing with adaptation in experiments with *C. elegans* may be driven by both the masking of recessive deleterious alleles and to the expression of overdominant alleles in heterozygotes (Teotonio et al., 2012; Chelo and Teotónio, 2013; Chelo et al., 2019). Also in line with these population genetic mechanisms, in the hermaphroditic freshwater snail *Physa acuta*, self-fertilizing populations show fast adaptation during a limited number of generations while outcrossing populations maintain a consistent response during experimental evolution (Noël et al., 2017).

Further evidence that the evolution of outcrossing impacts adaptation comes from several experiments with *C. elegans*. In *C. elegans*, hermaphrodites either self-fertilize or outcross by mating with males but not with each other (Stewart and Phillips, 2002). In experiments depending on *de novo* mutation for evolution, outcrossing rates can transiently increase upon exposure to a mutagen (Cutter, 2005; Manoel et al., 2007; Morran et al., 2009). However, this increase remains modest even under environmental conditions where obligate male-female populations show more extensive adaptation (Morran et al., 2009), suggesting that the evolution of outcrossing rates is limited because beneficial genotypes are unlikely to remain associated for long with the hermaphrodite lineages that tend to outcross more often (Lande and Porcher, 2015).

Increased outcrossing rates have also been observed in *C. elegans* carrying nuclear and mitochondrial mutations impairing mitochondrial functions (Wernick et al., 2019;

Bever et al., 2022). These observations are relevant to the "mitochondrial sex hypothesis" (Havird et al., 2015), which posits that in recombining populations, high mutation rates in mitochondria are maintained by selection of compensatory nuclear mutations. However, deleterious mitochondrial mutations and their compensatory nuclear mutations are beneficial epistatic combinations that can be disrupted by outcrossing and the shuffling of mitochondrial and nuclear genomes (Nguyen et al., 2023).

Selection for recombination and polygenic adaptation

Early experiments on the evolution of recombination typically measured the response to artificial selection in *Drosophila spp.* populations carrying large chromosomal inversions suppressing recombination (Charlesworth and Barton, 1996; Rice, 2002). These studies showed that recombination increases selection responses by increasing the fitness variance of the population. However, inversions suppress recombination over large portions of the chromosomes and are possibly not representative of the modifiers of recombination segregating in natural populations, such as those modifying crossover position or number (Johnston, 2024).

Theoretical models indicate that modifiers of crossover position or number hitchhike with the allele combinations they create in their genomic neighborhood and less so with more distant genotypes (Otto and Feldman, 1997; Roze, 2021). To illustrate the evolution of recombination in a polygenic adaptation context, we run computer simulations with varying distances between many selected loci along a chromosome and a modifier of crossover position that uniformly changes recombination rates between them (Figure 1). These simulations indicate that the distance to selected alleles determines the strength of indirect selection on the modifier (Figure 1A,C,D), a result that was already known (Roze, 2021). Further, when the modifier changes recombination rates between selected alleles non-uniformly, the direction of indirect selection will then depend on whether the modifier is located near them (Figure 1B,C,E). However, while selection for the modifier depends on its position, its effects on recombination among all selected alleles across the chromosomes is the same independently of its position and should not impact (genome-wide) polygenic adaptation. A modifier of crossover positions that results in a more uniform recombination across selected alleles should maximize genetic mixing and shuffling and thus reduce selective interference (Veller et al., 2019).

For indirect selection to result in the evolution of recombination, selected loci need to be in close proximity to recombination modifiers. This is plausible in many experiments where increased recombination rates evolved as a correlated response to artificial selection (Korol and Iliadi, 1994; Aggarwal et al., 2015), as recombination rates often increase across large portions of the genome, and selected traits, such as stress resistance, are often highly polygenic (Lynch and Walsh, 1998). Additionally, the segregation of multiple recombination modifiers in the experimental populations increases the likelihood that modifiers are located near the selected alleles. The strong selection pressures usually applied in these experiments [e.g., only 30 individuals out of 300 contributing to the next generation in Korol and Iliadi (1994)] may further allow the modifiers to be indirectly selected with more distant selected loci (Roze, 2021).

Fig. 1 Indirect selection on modifiers of crossover position. The figure shows 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 ($s \sim Exp(0.005)$) introduced per generation at each of 10^4 loci across the chromosome. After burn-in, a neutral recombination modifier was introduced in 500 randomly sampled genomes. We modeled the evolution of recombination under four different scenarios (**A,B**). The black line represents the chromosome, the purple and green circle represent the deleterious and beneficial alleles, the blue circle the modifier. **A**. In scenarios a and b, individuals homozygous for the modifier allele (M) have a 3-fold chromosomal map length (R_M) increase relative to the ancestral map length (R_m; assuming the modifier alleles are co-dominant). **B** In scenarios c and d, one of the modifier alleles increases the map length in a first interval, i, and reduces it in an adjacent interval, j, by a factor 3. **C.** The modifier allele frequency during 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 linear model: $modifier.freq \sim generation$) as a function of the genetic distance of the modifier to selected loci, for scenarios a,b, and in two additional scenarios (dots = mean; error-bars = 95% CI). Indirect selection decreases log-linearly with the genetic distance between the modifier and selected loci. **E.** Indirect selection coefficients for scenarios c,d are positive when the modifier is located in interval i, where it increases recombination, and negative when it is located in interval j, where it decreases recombination.

The evolution of recombination rates in response to artificial selection has been quantified in many different species (Otto and Barton, 2001; Otto and Lenormand, 2002; Rodell et al., 2004; Aggarwal et al., 2015), including domesticated species (Ross-Ibarra, 2004; Bursell et al., 2024). Increased recombination rates tend to evolve when the trait is selected in a different direction (Korol and Iliadi, 1994; Rodell et al., 2004; Aggarwal et al., 2015), indicating that pleiotropy (where the responding allele affects both the selected trait and recombination rates), or spurious initial associations between the modifier and selected loci, are unlikely to explain the evolution of recombination. Rather, these experiments suggest that modifiers are indirectly selected because they enable more efficient selection on the targeted trait. In experiments where artificial stabilizing selection was applied, reduced recombination rates evolved (Rodell et al., 2004), a result explained by recombination among the fitter genotypes at optimal trait value generating less fit genotypes (Charlesworth et al., 1993; Whitlock et al., 1995). Other experiments in *D. melanogaster* have shown the evolution of recombination rates at particular genomic locations (Kohl and Singh, 2018; Winbush and Singh, 2021, 2022). However, in these latter experiments, the environmental conditions imposed, such as temperature, may affect proper crossover formation and directly affect individual fitness, explaining selection of the modifiers independently of their recombination effects on selected alleles (Grushko et al., 1991; Samuk et al., 2020).

Recently, the evolution of recombination was investigated by following the evolution of a known modifier of crossover position in *C. elegans* (Parée et al., 2025). Mutant populations for the *rec-1* gene redistribute crossovers to chromosome centers while not changing crossover number (Parée et al., 2024). Chromosome centers contain less genetic diversity and less fitness variance than flanking regions, and as a consequence, *rec-1* mutant populations showed impaired adaptation (Parée et al., 2025). However, the *rec-1* mutant allele was favored by selection because it increases recombination rates in its genomic neighborhood. Consistent with the Hill-Robertson effect

mentioned in the introduction, stronger selection on the recombination modifier *rec-1* was observed at smaller population sizes.

Detecting selective interference

The extent of selective interference in a population will determine the benefits of recombination on adaptation (Otto, 2021). Yet, detecting selective interference from the genomic diversity data that is now typically collected from evolution experiments is challenging. It requires identifying selected loci and estimating negative linkage disequilibrium between them, which is not trivial when adaptation is polygenic and there is an astronomical number of genotypes to measure (Macdonald and Long, 2007; Long et al., 2015; Schlötterer et al., 2015). Most studies use presumably neutral markers, such as single-nucleotide variants, that themselves must be in linkage with selected alleles to be informative. Only rare studies have shown disruption of negative linkage disequilibrium between a small number of selected alleles, e.g., McDonald et al. (2016). Instead, average genome-wide estimates of marker allele frequency dynamics have been used.

One way to estimate linkage between selected loci is by measuring the correlation between marker allele frequencies at each replicate population undergoing experimental evolution (McDonald et al., 2016; Parée et al., 2025; Burke et al., 2014; Barghi et al., 2019). For instance, in the *C. elegans rec-1* experiments mentioned above, adaptation was associated with higher correlations of allele frequency change in genomic regions with reduced recombination rates (Parée et al., 2025). The temporal covariance of allele frequency change is another metric that can be used to detect linked selection (Buffalo and Coop, 2019). In this case, it is assumed that changes in the allele frequencies of the (neutral) markers depend on the genetic backgrounds with selected alleles. If so, then the change in allele frequency of a given marker in a period should be less correlated with its frequency change at subsequent periods as recombination swaps markers among genetic backgrounds (Buffalo and Coop, 2019). Although this method has faced some criticism (Lynch and Ho, 2020), the expected reduction in temporal covariance between distant time intervals was observed in experiments with *D. melanogaster* and the marine copepod *Acartia tonsa* (Buffalo and Coop, 2020; Brennan et al., 2022). In the *D. melanogaster* study, there was an excess of negative temporal covariance, further indicating that marker alleles reversed their frequency trajectories, and reflecting the disruption of negative linkage disequilibrium or the presence of epistasis (Buffalo and Coop, 2020).

It has also been argued that selective interference can be measured as the non-parallel genomic diversity responses among replicate populations during experimental evolution (Kosheleva and Desai, 2018). Recombination should increase parallelism by allowing the same alleles to be independently selected across replicates. Kosheleva and Desai (2018) calculated the standard deviation of marker allele frequencies between replicates across generations as the inverse of parallelism (divergence), finding that it is lower in sexual than asexual yeast populations. Yet, recombination can diminish parallelism when calculated as the correlation of marker allele frequency change among replicates [referred to as the "convergence correlation" in Buffalo and Coop (2020)]. In this case, parallelism might be high in the first few generations but it should

quickly decay because ancestral lineages recombine and the fitness of specific genetic backgrounds will then determine marker frequency trajectories.

Fig. 2 Parallelism of genomic diversity responses among replicates of experimental evolution. Similarly to Figure 1, standing genetic variation of the ancestral population was generated was modeled R=50 cM and an average of one mutation per genome per generation, now for a total of 10^5 loci. Both neutral alleles ($s = 0$) and selected alleles [$s \sim Exp(0.005)$] were modeled with varying numbers indicated above the panels (proportion of p_{neutr} and p_{sel} in the chromosome, respectively). With a higher the number of selected alleles, the stronger interference between them. Adaptation was simulated during 500 generations with several map lengths (R; in cM). **A.** Adaptation is faster and more extensive for larger values of R and lower number of selected alleles. **B.** Parallelism among replicates was calculated as the Pearson correlation (r_s) of selection coefficients among ten simulation runs and from the same ancestral population. Increasing R increases this correlation only when it is small and/or the number of selected alleles is high.

We adapted the simulation model of Figure 1 to better understand this dual effect of recombination on the parallelism of replicate responses during experimental evolution (Figure 2). We simulated adaptation from standing genetic variation under different recombination rates and different numbers of selected alleles. Results show that the relation between recombination and parallelism among replicate simulations is non-monotonic. Parallelism increases with recombination only under conditions of low recombination rates and a high number of selected alleles. Conversely, with weaker selective interference, increased recombination rates decrease parallelism despite facilitating adaptation. While higher parallelism with recombination may indicate strong selective interference, low parallelism does not necessarily indicate its absence.

Future research directions

Evolution experiments have established that sexual reproduction facilitates adaptation by breaking negative disequilibrium between selected alleles, and this may in part explain the prevalence of sexual reproduction over asexual reproduction. However, evidence supporting a role for high rates of sex and recombination in adaptation remains limited. While adaptation is undoubtedly highly polygenic, it is still unclear whether a sufficient number of alleles can be independently selected to provide an advantage to high sex and recombination rates. This uncertainty is compounded by the opposing effects of segregation and recombination on the maintenance of beneficial epistatic or overdominant alleles (Peters et al., 2003; Sellis et al., 2016; Johnson et al., 2023). Variable recombination rates across the genome might help maintain beneficial alleles in low-recombining genomic regions, such as when populations adapt to local environmental conditions (Kenig et al., 2015; Altenberg et al., 2017; Wolf and Ellegren, 2017; Venu et al., 2024). In this scenario, however, it remains an open question whether recombination evolves when modifiers of dispersal, or modifiers affecting dominance and epistasis, also segregate within populations (Proulx and Teotónio, 2022).

While the consequences of high rates of sex and recombination for adaptation may depend on the number of selected alleles (Weissman and Barton, 2012; Weissman and Hallatschek, 2014), several theoretical models suggest that modifiers of traits associated with sexual reproduction are likely to evolve (Otto, 2003; Roze and Michod,

2010; Roze, 2014). Under random mating, segregation effects should favor sexual reproduction when deleterious alleles are dominant (Roze and Michod, 2010; Glemin and Ronfort, 2013). Recessive deleterious alleles, which appear to be common in natural populations, further tend to create segregation loads that disfavor higher rates of sexual reproduction under random mating. High rates of sexual reproduction can be favored when excess homozygosity occurs, as this allows heterozygotes to mask deleterious recessives or expose overdominant alleles to selection (Otto, 2003; Dolgin and Otto, 2003; Bierne et al., 2000; Chelo and Teotónio, 2013; Chelo et al., 2019). Population subdivision, inbreeding among relatives, or self-fertilization – which generally increase homozygosity – may play an important role in explaining the evolution of sexual reproduction (Teterina et al., 2023; Roze and Lenormand, 2005; Roze, 2009). Overall, many of these ideas have yet to be tested with experimental evolution.

The direct fitness effects of modifying crossover position and number, such as compromising DNA repair or the segregation of homologous chromosomes during meiosis, could play a significant role in the evolution of sex and recombination (Kleckner et al., 2004; Hunt, 2006; Otto and Payseur, 2019; Fernandes et al., 2018; Morgan et al., 2021). There is strong experimental evidence, however, that indirect selection can also drive the evolution of modifiers crossover position and number (Aggarwal et al., 2015; Parée et al., 2025). These modifiers are expected to be favored when they generate beneficial genotypes in their local genomic neighborhood, rather than by enhancing genome-wide selection efficacy and facilitating polygenic adaptation (Otto and Feldman, 1997; Roze, 2021). Any factor that increases linkage disequilibrium prolongs the association between a recombination modifier and the genotypes it produces. This in turn alters the strength of indirect selection and may even shift its direction by expanding the genomic region associated with the modifier (Stetsenko and Roze, 2022). As shown with evolution experiments in *C. elegans*, polygenic adaptation may often be weakly related with selection of modifiers of crossover position across the genome (Parée et al., 2025).

When recombination itself is polygenic, driven by the segregation of multiple crossover modifiers (Johnston, 2024), selection conflicts may arise between them if they have opposing effects on recombination among selected alleles. Our understanding of how recombination evolves with multiple modifiers across the genome remains is still at a very early stage. Selection on multiple modifiers across the genome might average out, aligning or diverging from the effects of a given modifier on genome-wide recombination rates. It is further unclear whether indirect selection is substantial when the recombination effects of a modifier are highly localized to its genomic neighborhood, e.g., (Ubeda et al., 2019). If the evolution of recombination is primarily governed by modifiers of local recombination rates, rather than genome-wide, indirect selection may help with the maintenance of adaptation to local environmental conditions (Wolf and Ellegren, 2017; Venu et al., 2024).

In conclusion, advancing our understanding about the evolution of sex and recombination, as well as their adaptive significance, will require identifying the genomic location of sex and recombination rate modifiers together with the selected loci. Additionally, it is worth considering whether our current understanding is biased by the predominant focus on microbial and metazoan experimental evolution, highlighting the

need for greater attention to underrepresented organisms such as plants and multicellular fungi. These efforts will certainly pave the way for developing new experimental models manipulating modifier associations with selected alleles in genomic, life-history, or ecological contexts that are more representative of natural populations than those studied to date.

Simulation methods. The individual-based simulations of diploid populations were implemented using *SLiM* 4.0.1 (Haller and Messer, 2023), using the default Wright-Fisher models for mutation, selection, and reproduction. Ancestral populations with standing genetic variation were obtained by 1000 generations of reproduction with recombination (map length values specified in the legend of the figures) with an average of one mutation per genome (mutation rate of $u = 1/L$, 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 a modifier of recombination rates. 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. Simulation scripts, results and modeling details are available in our GitHub repository and in Dryad.

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