RESOLVING THE PARADOX OF SEX AND RECOMBINATION

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Sexual reproduction and recombination are ubiquitous. However, a large body of theoretical work has shown that these processes should only evolve under a restricted set of conditions. New studies indicate that this discrepancy might result from the fact that previous models have ignored important complexities that face natural populations, such as genetic drift and the spatial structure of populations.

EVOLUTION OF SEX

One of the most enduring puzzles in evolutionary biology is why sexual reproduction is so widespread. Individuals that have survived to reproductive age have genomes that have already proved themselves in the current environment, so why should they risk mixing their genes with those of another individual? Theoretical analyses support the conclusion that genome mixing is a risky endeavour, and the conditions that favour the evolution of high rates of sex and recombination are often quite restrictive. One reason that an answer to the paradox of sex has been so elusive is that many mathematical models have focused on populations that are infinite in size, unstructured, and isolated from other species. However, from the very beginning, most non-mathematical explanations for sex and recombination have considered a finite number of genotypes that evolve in a biologically and/or physically complex world. In other words, we might have been looking for the key to the evolution of sex where the light is strongest and not where the key is most likely to be found.

The ubiquity of sexual reproduction is especially puzzling considering that this mode of reproduction is associated with several costs. First, there are the various costs associated with mating or conjugating. In many species, it takes time and energy to secure a mate; for example, to ensure pollination, many plants invest substantial resources in floral display and nectar rewards. Furthermore, the act of sexual reproduction is often slower than asexual reproduction, as seen in many microbes. During mating, individuals are typically less able to gather resources and evade predators. Mating also introduces the risk of sexually transmitted diseases and parasitic genetic elements. In species with separate sexes or mating types, costly sexual conflicts can arise — for example, the seminal fluid of *Drosophila* contains toxins that reduce the fitness of mated females[1]. Second, there are the various costs of producing offspring sexually, such as the infamous twofold cost of sex. In sexual reproduction, the unit of reproduction is the couple, whereas in asexual reproduction it is the individual. Unless the sexually reproducing couple can produce twice as many surviving offspring as the asexual individual, sexual individuals will necessarily have a lower reproductive output per capita. At one extreme, if sexual couples and asexual individuals produce the same average number of offspring, because one sexual partner does not contribute resources to the offspring, the reproductive output per individual for asexual species is twice that for sexual species, hence the twofold cost of sex. Last, it is risky to produce offspring by randomly mixing genes with those of another individual. With such substantial costs of sex, it might be expected that any mutant allele that shifts resources towards asexual reproduction would rapidly outcompete and displace its more sexual kin. By all accounts, sex should be an evolutionary dead-end, a relict that is observed only rarely.

Contrary to this expectation, the vast majority of species reproduce sexually, at least occasionally. These sexual processes can be subdivided into two categories: symmetric and asymmetric. In asymmetric sexual reproduction, a fragment of the genome is transferred

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from a donor individual to a recipient. Sexual processes in bacteria are almost always asymmetric, including TRANSDUCTION, TRANSFORMATION and CONJUGATION[2]. Although most bacteria show some level of asymmetric sexuality, the extent of genetic mixing varies from vanishingly rare, as in the obligatorily intracellular *Rickettsia prowazekii*, to commonplace, as in *Deinococcus radiodurans*[3]. In symmetric sexual reproduction, two genomes fuse (syngamy) and subsequently separate (meiosis), each time producing cells that contain different mixtures of genes as a result of chromosomal segregation and recombination. Symmetric sex results in an alternation of haploid and diploid phases in a life cycle and is exclusively a eukaryotic phenomenon. Although asymmetric processes (such as horizontal transfer) have been implicated in gene transfer into eukaryotic genomes[4–6], such events are extremely rare relative to the rate of symmetric sex, which has been observed in the vast majority of eukaryotic species. Whereas many eukaryotes, especially PROTISTS, plants and fungi, are able to reproduce asexually, few are exclusively asexual[7]. When Vrijenhoek and colleagues[8] compiled a list of the known asexual vertebrate species, they were only able to identify 22 fish, 23 amphibians and 29 reptiles, including the Amazon molly *Poecilia formosa*, mole salamanders of the genus *Ambystoma* and whiptail lizards of the genus *Cnemidophorus*. Together these represent a tiny fraction of the ~42,300 known vertebrate species[9]. Furthermore, asexual eukaryotic species tend to be isolated on the tree of life; only rarely is a genus or larger taxonomic group composed entirely of asexual species. So universal is this rule that exceptions become celebrities, especially if their asexuality is ancient[10]. The most famous of these ancient asexuals are the bdelloid rotifers, an entire class of ~360 widespread species that show no signs of mating or genetic mixing[11]. Diplomonads, of which a gastric parasite, *Giardia*, is one example, are potentially even older asexuals. They are thought to represent one of the earliest diverging groups of eukaryotes[12] (but see REF. 13), but sexual reproduction has never been observed in this group. Of course, failure to see sexual reproduction does not mean that it never occurs. Indeed, many species that were previously considered asexual have subsequently been caught in the act[10,14,15].

The widespread occurrence of sex, despite its seemingly overwhelming costs, is known as the paradox of sex. To begin, we review proximate, or direct, explanations for the evolution of sex and recombination, which account for sex and recombination in the light of their immediate consequences on fitness, without considering the advantages of genetic mixing. We then turn to evolutionary, or indirect, explanations, which account for the evolution of sex and recombination in terms of the advantages of mixing genetic material from two individuals. Given the enormous body of literature on the subject, we focus on what we consider to be the more plausible explanations; the interested reader should read other reviews[16–18] for further information.

TRANSDUCTION
The exchange of genetic material from one cell to another that is mediated by a virus or phage.

TRANSFORMATION
The uptake of DNA by a bacterium from the surrounding environment.

CONJUGATION
In prokaryotes, the transfer of DNA from a donor cell to a recipient cell that is mediated by direct cell–cell contact.

PROTIST
A eukaryote other than animals, plants and fungi; often single celled.

Proximate explanations

The direct or proximate effects of asymmetric and symmetric sex are strikingly different. The asymmetric transfer of DNA creates the potential for sex to evolve simply because genetic elements that cause themselves to be copied and transferred to other individuals can spread in a population, as long as they infect new cells faster than they kill their host or otherwise reduce host fitness. In this case, the proximate effect of sex is the transfer of genetic elements, which enables them to spread in a manner analogous to the spread of a disease[2]. These elements, such as phages and bacterial plasmids, need not be beneficial to their hosts, although they would be more likely to spread if they increased host fitness — for example, by conferring antibiotic resistance or tolerance to new environmental conditions. Asymmetric sex might therefore represent an accidental by-product of the mechanisms that are encoded in genetic elements that enable these elements to spread[2]. A similar argument might even apply to eukaryotes. Although eukaryotic sex is, by and large, symmetric, cytoplasmic elements are often transferred in an asymmetric fashion. Furthermore, transposable elements can spread from one genome to another after syngamy. If transposable or cytoplasmic elements arise that make their host cells reproduce sexually with partners that would otherwise reproduce asexually, such sex drivers would spread through the population as long as the driving element was represented more often among sexual offspring than among the parents[19].

This intriguing hypothesis, based on the infectious properties of sex-driving elements, might explain the origin of sex, but it is less convincing as an explanation for the maintenance of sex. Eventually, any asexual genotype that was resistant to genetic exchange with individuals who carry a sex driver would avoid the costs of sex and eventually outcompete the sexual population. If resistance failed to evolve, the sex-driven element would spread to all potential hosts; this should eliminate its transmission advantage, at which point mutations that disrupt sex could accumulate. So, the indefinite maintenance of sex requires other benefits. Of course, in prokaryotes, sex might not be maintained indefinitely; rather, it might arise sporadically, after the appearance of altered genetic elements that became infectious and promoted their own transfer. In eukaryotes, however, symmetric sexual reproduction arose roughly one billion years ago. The cellular processes that are involved in syngamy, meiosis and gamete production have evolved to be extremely complex and involve hundreds to thousands of genes (1,416 such nuclear genes have been identified in *Caenorhabditis elegans*[20]). This indicates that, rather than arising sporadically, sexual reproduction has persisted for most of the evolutionary history of eukaryotes.

Few other proximate explanations for the ubiquity of sex exist. One other possible explanation is that genetic exchange arose to allow the repair of double-stranded DNA damage, in which an undamaged gene copy is used as a template[21]. However, in prokaryotes the evidence for the repair hypothesis is weak[22], and in eukaryotes this

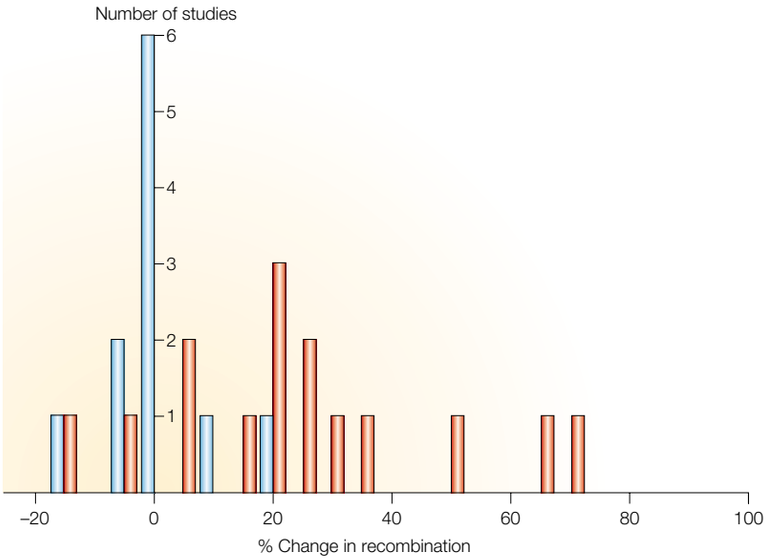


Figure 1 | **The percentage change in recombination after a period of strong selection.** The figure summarizes results from experiments in which recombination rates or numbers of chiasmata were measured over the course of artificial selection on characters that are unrelated to recombination (such as selection for flies that move upwards through a maze)[30]. Significant changes are shown in red (mean = 24.6% increase in recombination), and nonsignificant changes in blue (mean = 0.2%). Of the significant results, most showed an increase in recombination ($P = 0.007$). The median period of selection was 50 generations, and the median population size (where reported) was ~100 individuals.

hypothesis cannot explain the origin or maintenance of sex in populations that contain asexual diploids, which already carry two copies of each gene. Furthermore, it is less applicable to multicellular organisms, in which cell turnover can efficiently eliminate damaged cells[16].

Consequently, it is generally accepted that the long-term maintenance and ubiquity of eukaryotic sex cannot be explained as a proximate consequence of the inherent properties of sex itself. However, this does not mean that every aspect of eukaryotic sex has evolved to optimize genetic mixing. In particular, the number of CHIASMATA per chromosome pair is, on average, 1.56 across a wide array of protists, plants and animals, and does not vary substantially with chromosome number, gene number or genome size (REF. 23; P. Awadalla, personal communication). It is hard to reconcile this uniformity with the idea that recombination rates per chromosome have evolved to optimize the amount of genetic mixing in a population. Such an optimum should vary with the stability of the environment as well as with different characteristics of the organism, including gene density and generation time. A reasonable explanation for why crossover frequency per chromosome is so uniform across taxa is that chiasmata stabilize the pairing of homologous chromosomes during meiosis[24,25]. Homologous chromosomes that are joined by too few chiasmata can prematurely slip away from each other on the metaphase plate, whereas chromosomes that are joined by too many chiasmata can be too tightly intertwined to migrate to opposite poles during anaphase I (REF. 25). Either case can result in abnormal segregation of chromosomes. Indeed, studies have found a significant association between ANEUPLOIDY and atypically low or high numbers of crossovers[26–28]. Similarly, aneuploidy is more common when crossovers occur near the ends of a chromosome[28]. These data indicate that there are selective constraints on the number and distribution of chiasmata along chromosomes that might explain why the number of recombination events per chromosome is so remarkably uniform across a broad range of species.

Whereas selection to ensure proper segregation might constrain crossover rates to some extent, this constraint is not absolute. In some organisms, including *Drosophila* males, proper segregation occurs even without chiasmata[29]. Additionally, even minor changes in the number and position of chiasmata could have a substantial impact on the probability that recombination occurs between a given pair of loci. Indeed, several experiments have shown that recombination rates cannot be strongly constrained, because they do evolve in response to selection[16,30]. Results of artificial selection experiments in which selection is applied to traits other than recombination are summarized in FIG. 1. Recombination rates often increase after periods of strong artificial selection for other characteristics. This result is hard to explain on the basis of any proximate effect of recombination; the need to ensure proper segregation would, for example, dictate that recombination rates per chromosome should remain constant, regardless of the selection regime applied. Furthermore, the problem of ensuring proper segregation during meiosis can be entirely circumvented by reproducing asexually. To address the question of when and why selection favours eukaryotic sex and recombination, we must turn to evolutionary explanations.

Evolutionary explanations

Evolutionary biologists have put forward many hypotheses for the advantage of sex[17], and it is generally believed that a resolution to the paradox of sex will emerge from one or more of them. Mathematical models have tackled these hypotheses by using two approaches. In the first approach, the mean fitnesses at EQUILIBRIUM in sexual and asexual populations are compared (see the review by Rice on p241 of this issue[31]). This comparison specifies the conditions under which a sexual species is immune to invasion by a related asexual species that has been reproductively isolated for long enough to reach its own equilibrium. However, it does not address whether a newly arisen mutation that alters the mode of reproduction can spread or how evolution shapes the relative proportion of sexual and asexual reproduction in a species that is able to do both, as is true of many eukaryotes. Similarly, mean fitness comparisons do not address how the level of genetic mixing evolves in a species through changes in the frequency of recombination. Here, we narrow our focus to the second approach, which asks how the frequency of sex and recombination evolves within a population, given the existence of genes, called modifier loci, that alter this frequency.

CHIASMA
(pl. chiasmata). The cytological manifestation of genetic exchange between chromosomes, indicating that a crossover has occurred between homologous chromosomes.

ANEUPLOIDY
The presence of extra copies, or fewer copies, of some chromosomes.

EQUILIBRIUM
A state in which a system remains unchanged over time.

Table 1 | **Forces that generate genetic associations in populations**

Hypothesis	Source of genetic associations
Negative epistasis	Fitness interactions between loci
Dominance	Fitness interactions within a locus
Red Queen	Fitness fluctuations over time
Spatial heterogeneity	Fitness differences over space
Fisher–Muller	Random genetic drift

Most evolutionary explanations for sex and recombination posit that genetic mixing evolved to break down genetic associations within a population. This table summarizes the main hypotheses for how these genetic associations are generated.

Most of the evolutionary hypotheses for sex stem from the idea that sex generates greater variability because chromosomal segregation and recombination break down genetic associations (see TABLE 1). It is therefore thought that modifier alleles that increase the frequency of sex and recombination are favoured because they improve the ability of a population to evolve by increasing the genetic variation on which natural selection acts. Although this idea is simple and appealing, theoretical models have revealed several inherent problems: sex need not increase the genetic variation in a population; genetic variation can be selected against; and evolution need not favour increased levels of genetic exchange, even when genetic exchange does increase genetic variability and variability is favourable. Below, we address each of these problems and then turn to recent models that broaden the conditions under which selection favours genetic mixing.

Effect of sex on genetic variation. Sex has no effect on genetic variation in a population in which the observed frequency of each genetic combination is equal to its expected frequency. In other words, if the genes in a population are already well mixed, shuffling genomes further by chromosomal segregation and recombination will have no effect. Consider the effects of recombination on two genes (**A** and **B**) with two allelic variants each (for example, *A*/*a* and *B*/*b*), where alleles *A* and *B* both enhance a trait of interest. A genetic association between alleles at the two loci is measured by LINKAGE DISEQUILIBRIUM, *D*, which equals the difference between the observed and expected frequency of each HAPLOTYPE. The sign of *D* is arbitrary, so, for the purpose of this review, we let *D* be positive when the more extreme haplotypes in the trait (*AB* and *ab*) are over-represented in the population. Recombination breaks down non-random genetic associations and reduces the linkage disequilibrium in a population. If a fraction (σ) of the population reproduces sexually (with random mating) and if, during meiosis, the rate of recombination between genes **A** and **B** is *r*, the effective rate of recombination (ρ) between **A** and **B** is $\sigma \times r$. In the absence of all other evolutionary forces, such as selection, migration, mutation or GENETIC DRIFT, linkage disequilibrium decreases by the factor $(1 - \rho)$ each generation. As *D* nears zero, sex and recombination have no further effect on the dynamics of a population.

Consider, now, the effects of recombination in a population with some linkage disequilibrium. If *D* is negative, the extreme genotypes *AB* and *ab* are under-represented; hence, the genetic associations present in the population decrease variability. In this case, sex recombines the more abundant intermediate chromosomes (*Ab* and *aB*) to generate the less abundant extreme chromosomes (*AB* and *ab*), thereby bringing *D* closer to zero and increasing variability in the trait. If, however, *D* is positive in the population, there will already be substantial variation in the trait because the extreme genotypes are, by definition, over-represented. Sex recombines these extreme types (*AB* and *ab*) to produce the intermediate types (*aB* and *Ab*), thereby reducing variability in the trait. So, increasing genetic mixing, either by increasing the frequency of sex or recombination, might increase variability in a trait, but it need not. As this discussion indicates, whether sex increases genetic variability depends on the form of genetic associations that have built up over the course of time (see below).

Variation can be selected against. To make matters worse, even when sex does increase the amount of variation in fitness in a population, such variation need not be favourable. This was shown most convincingly by Feldman and co-workers[32–34], who demonstrated that, if a population is at an equilibrium at which genetic associations (disequilibria) persist, recombination is selected against, even if it does generate more variability in a population. Specifically, these models predict that any modifier allele that increases recombination will decline in frequency over time and will eventually be eliminated from a population. This result, known as the reduction principle, was shown to hold whenever a population is at equilibrium and under viability selection, in the absence of mutation, migration and genetic drift (for a review, see REF. 18). The reduction principle can be illustrated by a simplified one-locus example. Consider a diploid population in which the fittest individual is the *Aa* heterozygote — in the absence of sex, this genotype would spread to fixation in the population, eliminating variation in fitness. A modifier allele that arises at this equilibrium and brings about sexual reproduction would then produce fitness variation by regenerating the homozygotes (*AA* and *aa*). The variation produced by sex would, of course, reduce fitness compared with an asexual population composed entirely of the fittest individuals (*Aa*). Consequently, modifier alleles that promote sex are selected against, even though sex increases the amount of variation in the population.

Variation alone is not sufficient. The reduction principle highlights an obvious problem with sex: why should individuals that have survived to reproductive age risk breaking apart their successful gene combinations by undergoing chromosomal segregation and recombination? One possible answer is that the biotic and abiotic conditions of an organism are not constant. The pool of genes in a population is constantly changing through mutation, migration and selection. Populations will therefore never be at a static equilibrium, as assumed in proofs of the reduction principle. Theoretical studies

LINKAGE DISEQUILIBRIUM (*D*). A measure of genetic associations between alleles at different loci, which indicates whether particular haplotypes are more common than expected. We use the two-locus measure, D = frequency(*AB*) × frequency(*ab*) − frequency(*Ab*) × frequency(*aB*).

HAPLOTYPE
A haploid genotype. A diploid genotype comprises a maternal and a paternal haplotype.

GENETIC DRIFT
(also known as random drift). A phenomenon whereby the frequency of a gene in a population changes over time because the number of offspring born to parents that carry the gene is subject to chance variation.

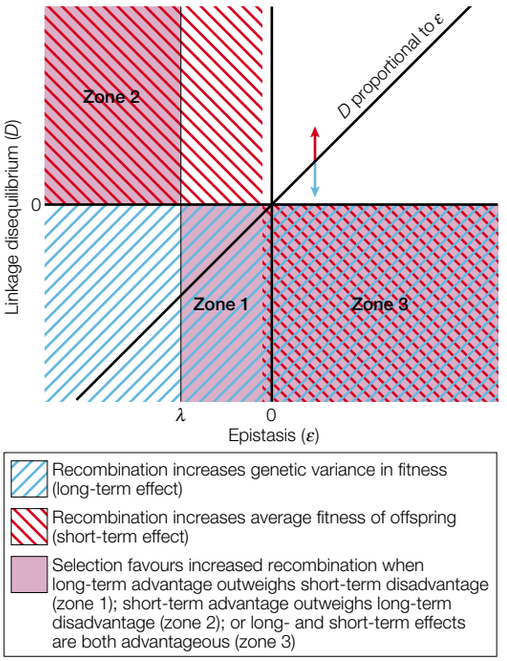
Box 1 | When does selection favour sex and recombination in a single large population?

Since 1967, this question has been addressed by using modifier models[53]. These models determine the fate of a newly arisen modifier allele that alters the effective recombination rate (ρ) between sets of loci by an amount $\delta\rho$. Although the modifier gene (**M**) does not directly affect fitness, it does so indirectly by altering the effective recombination rate between loci under selection. In the simplest haploid model with two selected loci (**A** and **B**), alleles *a* or *b*, when present alone, change the survival probability of a haploid individual by an amount s_a or s_b, respectively. When these alleles are present together, the survival of *ab* individuals is the product of the survival of *aB* and *Ab* individuals plus a quantity ε. This interaction term, ε, is called EPISTASIS. Assuming weak selection and a modifier allele that only slightly affects the rate of sex and/or recombination, Barton[37] showed that selection on the modifier is

$$\frac{\delta\rho}{\rho_{MAB}} D(\lambda - \varepsilon), \qquad (1)$$

where D is linkage disequilibrium, ρ_{MAB} is the rate at which sex and recombination break apart alleles at the **M**, **A** and **B** loci, ε is epistasis and λ is given by

$$-S_a S_b \left[\frac{1}{\rho_{MA}} + \frac{1}{\rho_{MA}} - 1\right].$$



This result holds whether beneficial alleles are sweeping through a population or are held in check at a MUTATION–SELECTION BALANCE[37]. Barton also showed that EQN (1) is the exact sum of selection on the modifier that arises from the long-term effects on the genetic variation plus the short-term effects on the average fitness of offspring. Interestingly, the long-term effect is very sensitive to the rate of recombination between the modifier and the selected loci because this rate determines whether the modifier remains associated with the allelic combinations that it creates long enough for any long-term benefits to accumulate. The short-term effect is much less sensitive to the relative positions of the loci and so becomes more important when linkage is loose.

EQN (1) determines the conditions under which selection favours an increase in the rate of sex and recombination (see figure). The conditions depend on the genetic associations (linkage disequilibrium, D, on the y axis) and on the fitness interactions (epistasis, ε, on the x axis) found in a population. Selection on a modifier reflects a balance between the long-term effects of changing the genetic variation (increased when the extreme genotypes are under-represented, that is $D < 0$; blue-hatched areas) and the short-term effects of changing the average fitness of offspring (increased when epistasis and disequilibrium have opposite signs, or more exactly when $(\varepsilon + s_a s_b)D < 0$; red-hatched areas). Overall, modifier alleles that increase the frequency of sex and/or recombination are favoured in zones 1–3 (purple areas). In a single large population that is subject to constant and weak directional selection, disequilibrium becomes proportional to the epistasis in fitness in the population (black diagonal line), in which case, sex and recombination are favoured only under weak and negative epistasis ($\lambda < \varepsilon < 0$). Factors other than epistasis that generate positive disequilibrium raise this line (for example, a positive correlation over space in the SELECTION COEFFICIENTS at two loci; red arrow), whereas factors that generate negative disequilibrium lower this line (for example, a negative correlation over space in the selection coefficients at two loci, random genetic drift; blue arrow).

EPISTASIS (ε). A measure of fitness interactions between alleles at different loci. In haploids, we use the two-locus measure, ε = fitness(AB) × fitness(ab) − fitness(Ab) × fitness(aB).

MUTATION–SELECTION BALANCE
The equilibrium at which selection that increases the frequency of a favourable allele exactly balances mutations that decrease the frequency.

SELECTION COEFFICIENT
A term that describes the difference in average fitness between two genotypes when fitness is measured relative to the average fitness of one of the genotypes (known as the reference genotype).

DIRECTIONAL SELECTION
Selection that favours one allele over all other alleles of a gene. The frequency of this beneficial allele can rise or can be held in check by recurrent mutation.

that have examined changing populations have shown that sex and recombination can indeed be favoured[34–38], whether beneficial alleles are sweeping through a population or are held in check by mutation. Here, we focus on the results from the most basic of these models, in which there is a single, large haploid population evolving in response to DIRECTIONAL SELECTION on genes **A** and **B** in the presence of alleles at a modifier gene (**M**) that alter the frequency of sex and/or recombination[34,37,38] (see also BOX 1). As described by Barton[37], there are two main evolutionary forces that act on the modifier alleles: long-term selection to increase the genetic variation in fitness in a population and short-term selection to have the highest average offspring fitness. There is a long-term advantage to sex and recombination whenever linkage disequilibrium is negative. With negative disequilibrium, the extreme genotypes are under-represented and can be regenerated by genetic mixing, thereby increasing the genetic variation in fitness, which improves the response to selection and increases mean

fitness in the long run. Whether or not a modifier allele will spread, however, depends also on the short-term effects of sex and recombination. When the genetic associations found in a population have been generated by selection in the current environment, breaking down these associations typically reduces the average fitness of offspring, a phenomenon known as the RECOMBINATION LOAD. If, however, the associations are opposite to what would be predicted by the current form of selection, this load can be reversed, causing a short-term advantage to recombination. Overall, as described in BOX 1, selection favours the spread of modifiers that increase the frequency of sex and recombination if the long-term benefit of sex outweighs the short-term disadvantage (zone 1 in BOX 1 figure), if the short-term benefit outweighs the long-term disadvantage (zone 2 in BOX 1 figure) or if there are both long-term and short-term benefits to sex (zone 3 in BOX 1 figure).

What sort of disequilibrium might we expect to find in a population? With no other forces generating genetic associations besides selection, the disequilibrium that develops takes on the same sign (negative or positive) as epistasis, ε, which is a measure of fitness interactions between loci[37,39]. For example, when the extreme genotypes are less fit than expected on the basis of the fitnesses of the intermediate genotypes (so that ε is negative, by definition), the extreme genotypes become less common than expected (negative D). So, in a single, large population in which epistasis is the only force that generates disequilibrium, sex and recombination are favoured only when epistasis is negative and weak (zone 1 in BOX 1 figure). Although sex and recombination increase genetic variation whenever there is negative epistasis generating negative disequilibria, the benefits of doing so outweigh the recombination load only when epistasis is weak. Only then do higher rates of sex and recombination evolve.

Examining the effects of sex on segregation. The previous section focused on the evolution of sex and recombination in a haploid population. In diploids, an additional factor comes into play: the segregation of alleles carried by homologous chromosomes. Here, we consider the results of a model in which there is one gene (**A**) subject to mutation and directional selection as well as a modifier gene (**M**), alleles of which alter the probability of sexual reproduction and, hence, the segregation probability of alleles at the **A** locus. As described below, the evolutionary forces that act on a modifier of segregation are virtually identical to those that act on a modifier of recombination.

In completely sexual populations with random mating, HARDY–WEINBERG genotypic proportions are achieved each generation. In asexual or partly sexual populations, however, departures from a Hardy–Weinberg state persist over time. These departures are measured by the INBREEDING COEFFICIENT, F, which is similar to linkage disequilibrium except that it describes associations between alleles at the same locus in a diploid rather than at two different loci in a haploid. When F is negative, the extreme genotypes (that is, the homozygotes) are under-represented in a population, and vice versa. Just as selection can generate linkage disequilibrium (D), selection can also generate a departure from Hardy–Weinberg proportions (F). The sign of F depends on how the alleles at the selected locus (**A**) interact to affect fitness. Although the DOMINANCE COEFFICIENT is the typical measure of these fitness interactions, we shall use a SINGLE-LOCUS INTERACTION measure, ι, which is equivalent to epistasis between two loci. It can be shown that, in partly sexual populations in which there is random mating between sexually reproducing individuals, F eventually becomes negative if ι is negative and becomes positive if ι is positive. For example, if a represents a partially recessive deleterious mutation (negative ι), a slight excess of heterozygotes accumulates (negative F). In this situation, there is a long-term advantage to a modifier that increases the frequency of sex, because segregation regenerates the homozygotes, thereby increasing genetic variation and improving the response of the population to selection.

Indeed, recent theoretical studies have shown that, at equilibrium between selection and recurrent deleterious mutations, sexual populations are fitter in the long run than asexual populations whenever selection causes F to be negative[40,41]. This advantage can be large enough to overcome the twofold cost of sex as long as the mutation rate (U) is sufficiently high ($U \gtrsim 1$ per haploid genome per generation) and mutations are almost completely recessive[40] or sexual reproduction is non-random and generates an excess of homozygotes[41]. However, this does not prove that a modifier allele that directs more reproductive effort to sexual reproduction will invade a population. Again, there is a second, short-term evolutionary force acting on the modifier. By breaking down the genetic associations that selection has built (measured by F), a modifier that increases the frequency of sex often reduces the average fitness of offspring. So, increasing the frequency of sex causes a segregation load similar to the recombination load discussed in the previous section. Consequently, modifier alleles that increase the frequency of sex (σ) do not always spread, even when they do increase the long-term mean fitness. For a population to evolve a higher rate of sex with random mating, genetic interactions (measured by ι) must be negative and sufficiently weak (S.P.O., unpublished data). In fact, the single-locus measure ι must satisfy the same mathematical condition for sex to be favoured as the two-locus measure ε (see BOX 1). As shown in FIG. 2, the conditions under which a higher frequency of sex is expected to evolve to promote segregation are actually quite restrictive.

Broadening the search for explanations. Unfortunately for the theories described above, empirical studies of two-locus epistasis (ε) have failed to show that weak and negative genetic interactions are common[31]. Furthermore, even though empirical studies of dominance[42] indicate that one-locus interactions (ι) are, on average, negative, ι is typically too strong to fall within the range required for the evolution of sex (FIG. 2). So, in

RECOMBINATION LOAD
The difference in fitness between offspring produced without recombination and those produced with recombination.

HARDY–WEINBERG EQUILIBRIUM
A state in which the frequency of each diploid genotype at a locus equals that expected from the random union of alleles — that is, where the inbreeding coefficient (F) is zero.

INBREEDING COEFFICIENT (F). A measure of genetic associations between alleles at the same locus, which indicates whether homozygotes (positive F) or heterozygotes (negative F) are more common than expected. For ease of comparison with linkage disequilibrium, we write the standard measure for F as $\{\text{frequency}(AA) \times \text{frequency}(aa) - [0.5 \times \text{frequency}(Aa)]^2\} / \{\text{frequency}(A) \times \text{frequency}(a)\}$.

DOMINANCE COEFFICIENT
The factor by which the selection coefficient is reduced in heterozygotes relative to homozygotes.

SINGLE-LOCUS INTERACTION (ι). A measure of fitness interactions between alleles at the same locus. We use the single-locus measure, $\iota = \text{fitness}(AA) \times \text{fitness}(aa) - \text{fitness}(Aa)^2$.

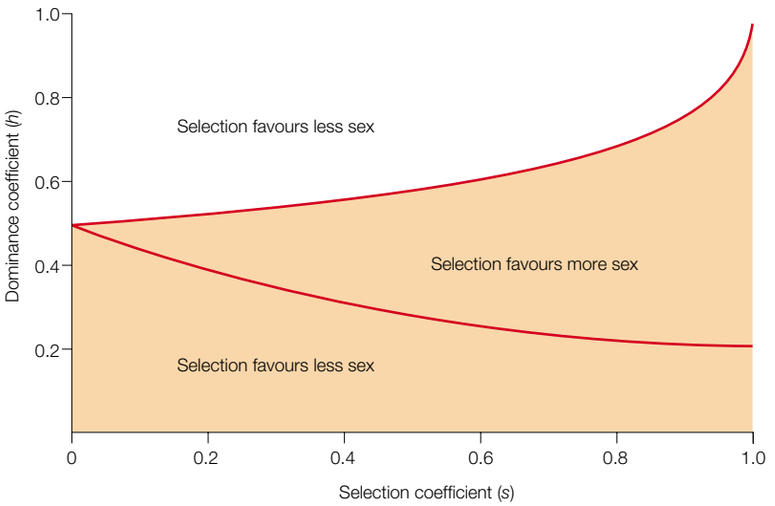


Figure 2 | **Conditions under which an allele that modifies the probability of sexual reproduction will spread by increasing the segregation of alleles at a selected locus.** We assume here that the fitnesses of *AA*, *Aa* and *aa* individuals are 1, 1 – *hs* and 1 – *s*, respectively, where *s* is the selection coefficient of allele *a* (*x* axis) and *h* is the dominance coefficient (*y* axis). Although sex increases the mean fitness at equilibrium in the shaded region (where the single-locus interaction ι is less than zero), a modifier that increases the frequency of sex is able to spread only in the central region. The position of the bottom curve depends on the probability of sexual reproduction among carriers of a rare modifier and is drawn for a modifier allele that equalizes the probability of sexual and asexual reproduction ($\sigma = 0.5$).

an attempt to find more general conditions that favour sex, we must turn to other forces that generate genetic associations in natural populations.

To begin, let us consider what conditions would be most favourable to the evolution of sex. Modifiers that increase the frequency of sex and recombination are especially likely to spread when the genetic associations that are present in a population (linkage disequilibrium, *D*) have the opposite sign to the current form of epistatic selection (ε) (BOX 1). In this case, selection can favour high rates of recombination, because an immediate advantage to sex comes from breaking apart disadvantageous gene combinations. There are two main processes that can generate such a mismatch: selection that varies over time and selection that varies over space.

Selection often fluctuates over time in response to a changing environment. Indeed, many historical explanations for sex are based on the idea that sex allows populations to retain variability and the potential to evolve in an ever-changing world[7]. In a model of fluctuating selection, however, Barton[37] found that the conditions that favour sex are only broadened when the sign of epistasis fluctuates rapidly, over ~2–5 generations. In this case, the epistasis and disequilibria in a population often have opposite signs, because the genetic associations are recently produced and have been generated mainly by the opposite type of epistasis. However, this model tracked evolutionary changes in only one species and did not consider changes in the environment caused by a co-evolving species, such as a predator or parasite. In a two-species model that took into account coevolution between a host and a parasite[43], rapid changes in epistasis over a few generations were also necessary for fluctuating selection to favour sex, and these were only observed when the parasite was highly virulent. Whether such strong coevolutionary interactions and rapidly fluctuating selection are commonplace remains to be seen.

If selection varies over space, migrants entering an area might carry different combinations of alleles from those that are favoured locally. In models with spatially heterogeneous selection, positive disequilibrium is generated by migration when some sites experience stronger selection than other sites or when alleles are favourable in some locations and unfavourable in others (a positive correlation in selection over space)[44,45]. In either case, on average, the migrants carry either worse alleles at each locus or better alleles at each locus, and this influx of extreme genotypes causes disequilibrium to rise above that expected on the basis of local fitness interactions. If the disequilibrium becomes positive, a population might find itself in a situation in which there is a mismatch between the genetic associations (*D*) that are present in a patch and the form of local selection (ε) — a mismatch that generates a short-term benefit to sex and recombination. However, this short-term benefit will outweigh the long-term disadvantage caused by breaking down the extreme genotypes only if there is strong negative epistasis (zone 2 in BOX 1 figure), for which there is little evidence. Conversely, migration can generate negative disequilibrium whenever two loci experience stronger selection in different patches (a negative correlation in selection over space)[44]. In this case, migrants arriving at a patch carry, on average, better alleles at one selected locus and worse alleles at the other. Disequilibrium then becomes more negative than expected on the basis of the local fitness interactions (epistasis). This form of spatial variation in selection is especially favourable to the evolution of sex and recombination. Not only are the conditions broadened under which a modifier allele that increases the frequency of sex and recombination is able to spread, but also it is possible for such a modifier to increase both genetic variation and offspring fitness (zone 3 in BOX 1 figure). Unfortunately, there is little evidence that migration commonly generates negative disequilibria, and there are theoretical reasons to believe that migration would more often generate positive disequilibria[44].

So far, all the models that we have reviewed assume that a population is infinitely large. Real populations are finite and, typically, small enough for allele frequencies to vary substantially around their expected frequencies because, by chance, some individuals have more offspring than others. This process of random genetic drift also generates variation in genotype frequencies, resulting in changes in the level of disequilibrium between any two loci. Intuitively, such random changes should sometimes decrease and sometimes increase genetic associations between extreme alleles, with no net effect on average. Whereas this is true when drift acts alone, if selection is present, drift causes linkage disequilibrium to become more negative over time[46]. Essentially, when drift creates positive

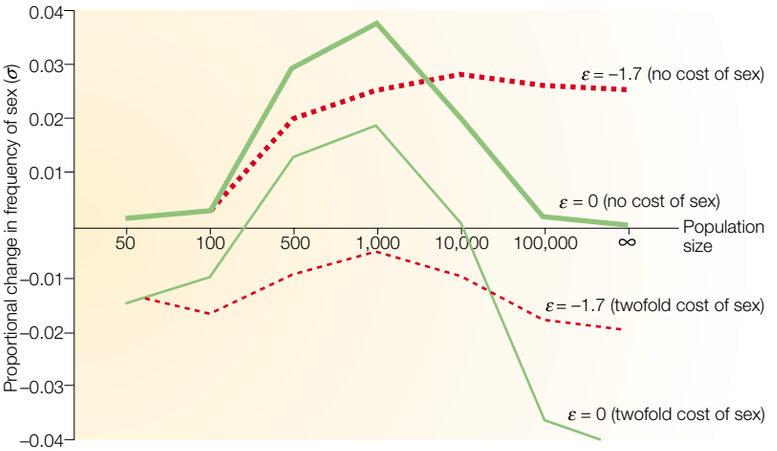


Figure 3 | **The proportional change in the frequency of sex as a function of population size after 50 generations of selection in a three-locus haploid model.** (See also BOX 1.) A single population was simulated, with all loci unlinked. The probability of two haploid individuals having sex (σ) was 0.02 if both carried the *M* allele, 0.03 if only one carried the *M* allele, and 0.04 if both carried the *m* allele. Initially, the frequencies of the *m*, *a* and *b* alleles were 0.5, 0.01 and 0.01, respectively. The average change in the frequency of sex was determined from 100,000 replicate runs. In each case, strong haploid selection with $s_a = s_b = 1$ was assumed. The solid curves represent cases without epistasis; the dashed curves give the proportional change in the frequency of sex when epistasis is present at the value that most strongly selects for sex in an infinite population ($\varepsilon = -1.7$). The bold curves represent cases without a cost of sex, whereas the thin curves incorporate a twofold cost of sex. Note that, for a modifier with a small effect on σ (as considered here), disequilibrium generated by drift alone selects for sex strongly enough to compensate for a twofold cost of sex unless the population is very small (because genetic variation is lost too rapidly) or very large (because drift is too weak). This result does not hold, however, for modifier alleles that cause large increases in the frequency of sex, because such alleles experience a much larger cost of sex and are selected against (not shown).

disequilibrium with more extreme genotypes and more genetic variation, selection proceeds more rapidly, boosting the frequency of the best genotype and eliminating the worst, thereby rapidly dissipating the disequilibrium. However, when drift creates negative disequilibrium, beneficial alleles find themselves more often in genetic backgrounds with deleterious alleles; selection then grinds to a halt as there is less to distinguish between the different intermediate genotypes, which causes the disequilibrium to dissipate slowly. As a consequence, on average, drift in the presence of selection generates negative genetic associations, which reduce the ability of a population to respond to selection. This process, known as the Hill–Robertson effect, can be thought of in terms of selective interference between loci, with selection becoming less efficient whenever linked loci are also under selection. Models that consider modifiers in finite populations have shown that drift tends to promote the evolution of sex and recombination[30,47] (FIG. 3). The negative disequilibrium that is generated by drift should favour the evolution of sex and recombination for a range of both positive and negative epistasis (zones 1 and 3 in BOX 1 figure). This result should only require that epistasis not be too strong, a condition that was confirmed by simulation (S.P.O., unpublished data). Although these results are based on directional selection, drift should also broaden the conditions that favour the evolution of a higher frequency of sex and recombination in the presence of both beneficial and deleterious mutations, deleterious mutations alone and host–parasite interactions[47–49]. The advantage of the drift theory for sex and recombination is that we know that drift occurs and that all populations are finite. Furthermore, a simulation study has shown that the force of drift can be greater than the maximum force of epistasis even in very large populations (for example, 100,000 individuals), as long as such populations are spatially structured[50]. It is therefore plausible that sex and recombination evolved because selection acts locally on relatively small populations, in which genetic mixing reduces the genetic associations built by drift and selection.

Conclusion

Sex has been central to discourse in evolutionary biology throughout its history. Foucault[51] challenges us to consider why the secrets of sex seem always to elude us and yet why we remain compelled to search out these secrets.

> Is it not with the aim of inciting people to speak of sex that it is made to mirror…something akin to a secret whose discovery is imperative (REF. 51, p. 35).

Discourses on sex have popular appeal — they engage an audience and provide relevance, even legitimacy, to areas of scientific enquiry. Certainly, this helps to explain why the evolution of sex, more than any other aspect of life, has received so much attention from evolutionary biologists, generating an enormous and complex theoretical discourse. Perhaps more importantly, however, understanding the evolution of sex requires the synthesis of every important process in evolutionary biology (selection, epistasis, mutation, migration, recombination and drift) and has motivated the development of a substantial number of mathematical tools in population genetics.

Evolutionary theory has, for the most part, shown that the answer to the paradox of sex is more elusive than we initially thought. Most biologists are comfortable with the idea that sex evolved to provide variability, but mathematical models have proved that this comfort is unwarranted: sex need not increase variability, variability need not be beneficial and evolution need not favour sex, even when it does increase variability and variability is beneficial. Nevertheless, models have shown that there are certain conditions under which higher rates of sex and recombination should evolve. For example, if fitness interactions between loci or within a locus are weak and negative, then alleles that increase the allocation of reproductive resources to sex will spread. However, the conditions on fitness are rather restrictive and it is unsettling to require that selection fortuitously meets them in the vast majority of eukaryotes in order to explain the ubiquity of sex.

Unfortunately, research that seeks to resolve the paradox of sex has been plagued by a fundamental discrepancy between the conditions that are most

amenable to mathematical study and the conditions that most favour sex in the natural world. The best example of this discrepancy is genetic drift. Deterministic models that ignore genetic drift are much simpler to analyse than stochastic models. However, deterministic and stochastic models do not generate the same predictions; for example, sex can be favoured in the stochastic model illustrated in FIG. 3 even when epistasis is absent or positive, which contradicts the results of the deterministic models. So, solving the paradox of sex requires that we embrace more of the complexities of the real world, and that we tackle evolutionary models of finite populations that are distributed over space and that are subject to selection generated by various ecological forces, including coevolving species (such as predators, competitors and parasites). In such models, many allelic combinations will be locally rare or absent, allowing greater benefits of sex and recombination to emerge. Indeed, recent studies that have tackled some of these complexities have broadened the conditions under which sex is favoured[30,44,50,52]. However, many questions remain. These studies typically ignore the costs of sex by assuming that sex always occurs and by restricting the focus to modifiers that alter the frequency of recombination. Whereas these models, or their slight variants, can also predict the fate of alleles that modify the frequency of sex, they must incorporate fitness differences between modifier alleles to account for the costs of sex. In the stochastic simulations reported in FIG. 3, we found that higher rates of sex evolved even in the face of a twofold cost of sex in populations of intermediate size even without epi-stasis. In this example, however, the frequency of sex was similar for all modifier genotypes, and hence the cost of sex imposed only weak selection on the modifier alleles. It remains to be seen which models allow selection for a shift in resources that favours sexual over asexual reproduction when modifier alleles incur substantial costs of sex.

In addition to widening the scope of theoretical models, empirical tests designed to tease apart why sex is favoured are essential[31]. For example, to test the hypothesis that drift is a key ingredient, selection experiments, of the sort summarized in FIG. 1, should be conducted over a range of population sizes[30]. It is also important to measure the effects of sex on the genetic variation in fitness and on the recombination load in natural populations. Finding a substantial recombination load would, for example, tell us that the genetic associations (D) and fitness interactions (ε) match one another in sign, indicating that sex, if it is favoured, is maintained because of the long-term benefits of increasing genetic variation. Such measurements should be made in organisms in which sexually produced and asexually produced offspring differ little, except in their genetic composition, and in which the fitness of offspring can be measured over a lifespan. These measurements would tell us the proximate forces shaping the evolution of sex, therefore helping us to decipher what, ultimately, explains the paradox of sex.

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