Meiosis and the Causes and Consequences of Recombination

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Why have sex? The population genetics of sex and recombination

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Abstract

One of the greatest puzzles in evolutionary biology is the high frequency of sexual reproduction and recombination. Given that individuals surviving to reproductive age have genomes that function in their current environment, why should they risk shuffling their genes with those of another individual? Mathematical models are especially important in developing predictions about when sex and recombination can evolve, because it is difficult to intuit the outcome of evolution with several interacting genes. Interestingly, theoretical analyses have shown that it is often quite difficult to identify conditions that favour the evolution of high rates of sex and recombination. For example, fitness interactions among genes (epistasis) can favour sex and recombination but only if such interactions are negative, relatively weak and not highly variable. One reason why an answer to the paradox of sex has been so elusive is that our models have focused unduly on populations that are infinite in size, unstructured and isolated from other species. Yet most verbal theories for sex and recombination consider a finite number of genotypes evolving in a biologically and/or physically complex world. Here, we review various hypotheses for why sex and recombination are so prevalent and discuss theoretical results indicating which of these hypotheses is most promising.

Sexual reproduction is nearly ubiquitous in Nature [1,2]. Why it is so beneficial for individuals to mate with another individual, creating genetically mixed offspring, rather than asexually producing offspring, has been a long-standing puzzle in evolutionary biology, known as the 'paradox of sex' [3–7]. A sufficient explanation must address how the benefits of sex outweigh non-trivial costs. Immediate short-term costs include the time and energy devoted to finding a suitable sexual partner, the risk of disease transmission during mating and the risk of remaining unmated. Even if a suitable mate is found, parents risk producing offspring that are less fit than themselves, because sex and recombination can break apart the favourable gene combinations that enabled the parents to survive and reproduce. Finally, because sexually produced offspring inherit only half of their genes from a parent, sexual individuals must produce twice as many offspring as asexual individuals to retain the same genetic contribution per capita (the so-called '2-fold cost of sex'). In the face of these substantial costs, why is sexual reproduction so widely distributed among eukaryotes?

Current phylogenomic analyses suggest that sexual reproduction arose early, in a common ancestor to all living eukaryotes [8]. Consequently, we cannot compare attributes of eukaryotes that evolved sex with those that never did, leaving us with little hope of determining the key evolutionary forces acting in the first eukaryotes to engage in sex. Even if we cannot know why sex originated billions of years ago, we can still ask why sex is maintained in the many species that are capable of both sexual and asexual reproduction [1,9]. Specifically, what is the mechanism(s) that allows the maintenance of sexuality among the vast majority of eukaryotes?

Key words: drift, epistasis, evolution of sex, modifier theory, recombination, Red Queen hypothesis.

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Multiple hypotheses to explain the paradox of sex have been put forward by evolutionary biologists [7]. The most intuitively appealing explanation for sex and recombination is that they increase genetic variance in fitness, improving the response of a population to selection. As appealing as this explanation might be, it is not without its difficulties. Sex and recombination can actually reduce the amount of genetic variation in a population when other forces, notably selection and migration, promote genetic diversity [10,11]. Furthermore, increasing genetic variance can decrease the average fitness of offspring whenever favourable combinations of alleles are broken apart.

One approach to investigate the plausibility of these hypotheses is to track genetic changes at loci that modify the frequency of sex and recombination. By monitoring the frequency of 'modifier' alleles that increase the rate of sex and recombination, we can mathematically assess which biological scenarios allow the evolution of sex and recombination. In the present paper, we focus on three scenarios that differ principally in the forces generating genetic associations in populations: negative epistasis, species interactions and drift in populations of finite size.

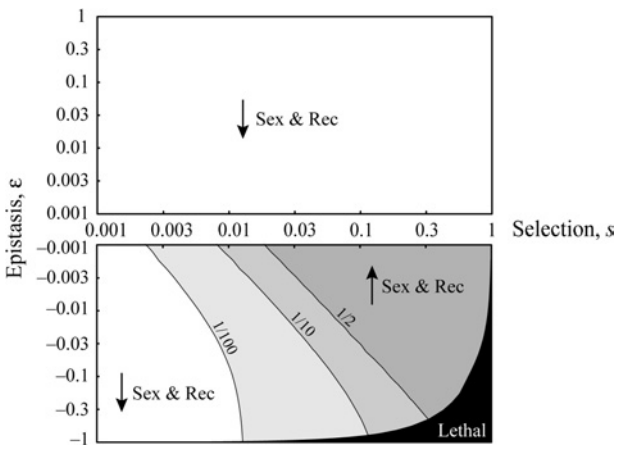
The negative epistasis hypothesis

The premise of this hypothesis is that fitness surfaces exhibit negative curvature [12–14]. This form of selection, known as negative epistasis, generates negative genetic associations among alleles (negative 'linkage disequilibrium'; [15,16]). Negative linkage disequilibrium implies that favourable alleles at one locus are found on chromosomes carrying deleterious alleles at other loci. Under this scenario, sex and recombination (and modifier alleles by proxy) can bring together favourable alleles on to the same chromosome as well as bring together deleterious alleles on to the same chromosome. This increased variance in fitness improves the response to selection, allowing the favourable alleles to rise in frequency more rapidly and the deleterious alleles to be purged more efficiently from the population.

Models examining the negative epistasis hypothesis have found, however, that a modifier allele increasing the rate of sex and recombination spreads within a population only when epistasis is negative and weak [10,17]. How weak depends on the amount of sex and recombination within the population (Figure 1), with especially restrictive conditions when genetic mixing is already high within a population. Why does strong negative epistasis select against sex and recombination? When the fitness surface exhibits extremely negative curvature, recombining chromosomes of intermediate fitness produces chromosomes that are, on average, much less fit, which prevents a modifier allele that increases the frequency of sex and recombination from spreading within the population. For the negative epistasis hypothesis to explain the ubiquity of sex, epistasis must be universally weak and negative. There cannot be much variation in epistasis among pairs of loci, as variability causes fewer pairs of loci to fall within the appropriate parameter range illustrated in Figure 1 [17].

Figure 1 | Weak and negative epistasis is required for sex and recombination to be favoured

In a deterministic model where individuals with zero, one and two mutations have fitness 1, $1-s$ and $(1-s)^2+\varepsilon$ respectively, modifier alleles that increase the frequency of recombination (Rec) spread only when epistasis is negative and small relative to selection, s. The different isoclines correspond to the initial level of recombination within a fully sexual population. Figure produced from exact numerical results in [17]; similar conditions are observed when mutations are advantageous [10].



Do empirical results suggest a preponderance of weak and negative epistasis? Although further research is warranted, the answer appears to be 'no' [18]. Most of the surveys find little epistasis, on average, with a large degree of variability among pairs of loci (e.g. [19,20]).

The restrictive theoretical conditions and the lack of strong empirical evidence suggest that the negative epistasis hypothesis is unlikely to explain the ubiquity of sex.

Species interactions

In Lewis Carroll's *Alice in Wonderland*, the Red Queen must constantly run just to keep in the same place, a metaphor that has been used to explain the evolution of sex. According to the 'Red Queen' hypothesis, species must constantly produce variability through sex and recombination just to keep apace of co-evolving species, including parasites, predators and competitors [1].

Models investigating the evolution of sex and recombination in the presence of co-evolving species have identified two regimes of interest [21,22]. In the first regime, selection on each gene is weak relative to the level of sex and recombination, in which case, the Red Queen models are no different in kind from the one-species models described above. That is, modifier alleles that increase the frequency of sex and recombination spread only if fitness interactions among species induce weak and negative epistasis. Yet species interactions often induce strong, not weak, epistasis. For example, if infection occurs when a parasite mimics a host or carries alleles that evade recognition by host resistance genes, only hosts carrying all of the wrong alleles will be susceptible to a particular parasite. With such strong epistasis,

the primary result of sex is to break down fit gene combinations – combinations that allowed the parents to survive and reproduce in the face of the current suite of parasites. Thus, in the regime of weak selection, species interactions generally favour reductions in the frequency of sex and recombination [22].

In the second regime, selection is very strong, causing epistasis to fluctuate over short time frames. In this case, allelic combinations favoured by selection in the recent past (and thus relatively abundant) can be currently deleterious. By breaking apart these maladapted gene combinations, increased rates of sex and recombination can evolve. For the fluctuations to be fast enough, selection must be strong, but how strong is 'strong'? Again, this depends on the current level of sex and recombination within a population. In populations that rarely recombine, a 20% reduction in fitness upon infection and an average of one parasite interaction per host per generation is sufficient [21]. In populations with moderate levels of sex and recombination, however, more severe host–parasite interactions are typically required [22]. Importantly, the more loci that are involved in mediating host–parasite interactions, the weaker selection is per locus and the less often sex and recombination are favoured [22]. Furthermore, even in cases where sex and recombination are favoured, the spread of the modifier allele is often very slow (frequency changes of only a few per cent over the course of 10 000 generations) and would easily be reversed in the presence of costs of sex [22].

Are the conditions required for the Red Queen hypothesis likely to be met in Nature? The key requirement appears to be strong selection per gene mediating the species interactions, such that combinations of alleles switch from being advantageous to disadvantageous and back again over the course of a few generations [10,23]. Such strong selection requires (i) a high incidence of species interactions, (ii) a large effect on fitness of these interactions, (iii) a large genetic component to the variation in who survives and who dies and (iv) a genetic basis that involves more than one, but not many, loci. In particular, various non-genetic factors that influence the outcome of a disease (nutritional status, stress, age at infection and previous exposure of the immune system to related diseases) will reduce the strength of selection experienced by genes involved in resistance and immunity. It seems doubtful to us that strong selection per gene is sufficiently commonplace for the Red Queen hypothesis to explain the ubiquity of sex, but data are sorely needed.

The finite population hypothesis

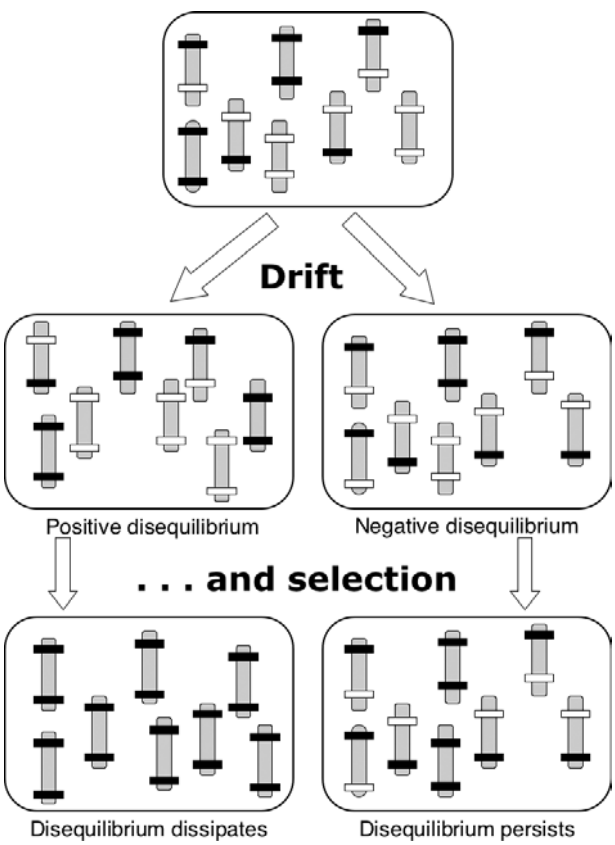
If selection, abiotically or biotically induced, does not explain why sex is so common, what does? Interestingly, the answer might lie in the fact that real populations are finite in size, so that selection does not act in the idealized way assumed in the above deterministic models.

All populations are finite and experience random fluctuations in genotype frequencies, a process called random genetic drift. As illustrated in Figure 2, when drift is the only major influence on the evolution of a population, it does not, on average, generate associations among genes. Yet when selection and drift act together, good alleles appearing by chance in good backgrounds (positive disequilibrium) are rapidly fixed by selection, which dissipates the linkage disequilibrium. When good alleles appear by chance in bad genetic backgrounds (negative disequilibrium), selection stalls because favourable alleles are hidden within individuals of intermediate fitness. This allows negative linkage disequilibrium to persist over much longer periods of time.

Tracking the mean and variance for each possible genotype in a finite population, the linkage disequilibrium between selected loci becomes negative, and a modifier increasing the frequency of sex and recombination increases, on average, even in the absence of epistasis [10,24]. Furthermore, simulations in a finite population appear to be much less

Figure 2 | Negative disequilibrium persists under drift and selection in finite populations

Good alleles (black bars) are just as likely to find themselves in good genetic backgrounds (positive disequilibrium) as in bad genetic backgrounds (white bars; negative disequilibrium). On average, we do not expect drift alone to have much influence on the associations among genes. However, with selection also acting, the picture is different. Good alleles in good backgrounds are rapidly fixed in the population, dissipating positive disequilibrium. When good alleles are present in bad genetic backgrounds, selection is inefficient, because favourable alleles are mostly located in individuals of intermediate fitness. This results in the persistence of negative disequilibrium over longer periods of time.



sensitive to the form of fitness interactions (epistasis) than deterministic simulations of an infinite population, with sex and recombination being favoured with positive epistasis, no epistasis, as well as negative epistasis in the presence of either directional selection favouring beneficial alleles [25] or purifying selection eliminating deleterious mutations [25a]. These results are interesting; incorporating random genetic drift fundamentally changes the direction of evolution predicted by these models.

Although variants of the drift hypothesis for the evolution of sex and recombination have existed for a long time [24,26–29], it had never been a favourite among the contending hypotheses to explain the ubiquity of sex. In all honesty, most of us thought that drift could play an important role in small populations or in asexual populations (e.g. through 'Muller's ratchet'; [30]) but that drift was unlikely to be important in most species of large population size. Surprisingly, recent work has shown that drift remains a powerful force even in very large populations as long as multiple loci are under selection [25a,31] or populations are spatially structured [32], both of which are reasonable. Indeed, drift can even select for sex and recombination in an infinitely large, but spatially structured, population, because of the fluctuations in genotype frequency that occur within local patches or demes [32]. Even with a substantial cost of sex, selection in finite populations can favour the spread of modifier alleles that increase the frequency of sex [5,25a,32].

Empirically, the drift hypothesis appears to be the least restrictive. It works under a broad range of fitness surfaces, whether negatively or positively curved. The main requirement is that selection be present, with either beneficial alleles spreading through a population [25,31–35], or deleterious alleles held in check by selection [25a], or a mixture of the two [36]. The main empirical question is whether or not selection acts often enough and strongly enough to prevent the loss of sex with its attendant costs. It might be in this context, providing the source of selection needed for drift to favour sex and recombination, that species interactions might be most important.

Although more theoretical and empirical work is necessary, it appears now that the most likely explanation for the ubiquity of sex lies in the vagaries of drift, with sex and recombination unlocking the genetic variability hidden in chromosomes of intermediate fitness, which came to predominate in finite populations subject to selection.

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