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Evolution of Sex: Why Do Organisms Shuffle Their Genotypes?

Review

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Sexual processes alter associations among alleles. To understand the evolution of sex, we need to know both the short-term and long-term consequences of changing these genetic associations. Ultimately, we need to identify which evolutionary forces — for example, selection, genetic drift, migration — are responsible for building the associations affected by sex.

Introduction

There are a number of reasons why sex might be disadvantageous. In species where males provide little or no resources to their offspring, females pay the full cost of reproduction yet only provide half of each sexually produced offspring's genes. In contrast, if a female were to produce an offspring asexually, she would transmit twice as many genes at the same energetic cost per offspring. This is the infamous 'two-fold' cost of sex [1,2]. Such a cost does not exist if both parents contribute equal resources to the production of offspring; even in these cases, however, sex may be expensive because of the costs of searching for mates and the costs of engaging in mating, including an increased risk of predation or infection by a sexually transmitted disease [3,4]. In unicellular organisms, sex can be a slow process and this use of time may represent a substantial cost when an individual could replicate asexually at a rapid rate.

Even in the absence of all of these extrinsic costs of sex, the genetic shuffling caused by sexual processes does not seem like a good idea. Selection is expected to make good allele combinations disproportionately common. Genetic mixing will tend to break down this excess of favorable allele combinations, creating unfavorable combinations in the process [5,6]. From this perspective, it is difficult to see why genetic mixing would not be minimized.

Sexual processes are not physiologically essential for reproduction. Many species are capable of both sexual and asexual reproduction; this is illustrated by facultative sexuality in *Chlamydomonas*, *Saprolegnia* and *Daphnia*. In other groups, vertebrates for example, most species are obligately sexual but there are also a few asexual species. Even within some obligately sexual species, the extent of genetic mixing caused by sex is reduced by the complete suppression of recombination in some individuals; for example, there is no recombination in male *Drosophila melanogaster*. These observations suggest that reproduction with less or no genetic mixing is possible. Nonetheless, some degree of genetic mixing occurs in the vast majority of species (see [7] for a review of reproductive modes).

Explaining the observed levels of genetic mixing has been an on-going challenge for evolutionary biologists for several decades [1,2,7]. Most of this review will focus on recent work on the subject. Though much effort has been spent on explaining the average level of genetic mixing within a species, less attention has been paid to understanding the intraspecific variation in genetic mixing. Within species, there can be variation in the level of genetic mixing that occurs between the sexes, among different genomic regions, and among fitness and/or environmental states. The final section of the review will consider this variation and efforts to understand it.

Sex Alters Genetic Associations

Genetically, the most obvious feature of sexual reproduction is that it causes alleles to be shuffled into different combinations. In diploids, two chromosomal processes, *recombination* and *segregation*, are responsible for the genetic mixing that occurs during sex. Recombination changes how alleles at different loci on the same chromosome are organized — for example $AB \times ab \rightarrow AB, Ab, aB, ab$ — whereas segregation changes how alleles on homologous chromosomes are packaged into individuals — for example $A/A \times a/a \rightarrow A/a$. I now consider how this genetic shuffling affects populations.

There are two ways typically used to describe a population genetically. First, a population can be described by the distribution of genotype frequencies. For example, in a haploid model with two di-allelic loci, the population could be fully described by the frequencies of genotypes *AB*, *Ab*, *aB* and *ab*. Alternatively, this population could be described by the allele frequencies, p_A and p_B, along with the pattern of associations among these alleles. In this example, the only association needed is the association between the **A** and **B** loci, C_{AB}, more commonly known as the two-way linkage disequilibrium. In diploids, there are also associations between alleles at the same locus on homologous chromosomes. For example, consider a diploid model with a single di-allelic locus. The population could be described by the frequencies of genotypes *A/A*, *A/a* and *a/a*, or by the allele frequency p_A and the association $C_{A/A}$. This association is more commonly known as the inbreeding coefficient or homozygosity index.

Genetic associations are conventionally defined such that positive values indicate alleles are packaged into individuals in such a way that increases the allelic variance among individuals, whereas negative values indicate alleles are organized in such a way that decreases the allelic variance among individuals (Box 1 and figure in Box 2). Characterizing a population by its allele frequencies and patterns of associations makes it simpler to understand how genetic mixing affects populations. Genetic mixing does not change allele

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Box 1

Genetic associations and the effects of genetic mixing.

Effects of segregation: Here we examine the effects of segregation by considering a single di-allelic locus in a diploid organism. Let us examine how sex affects three different populations. Prior to reproduction, all three populations have the same allele frequency, $p_A = \frac{1}{2}$, but they differ in how *A* alleles are packaged into individuals (see Table 1 below). The intralocus association $C_{A/A}$ can be measured as the covariance between an individual's allelic state at its first copy of the **A** locus and its allelic state at the second copy of the **A** locus. In Population S1, *A* alleles are distributed randomly among individuals: there is no association, $C_{A/A} = 0$. In Population S2, individuals with an *A* allele on one chromosome are more likely than expected by chance to carry another *A* allele on the homologous chromosome so the association is positive, $C_{A/A} > 0$. In Population S3, individuals with an *A* allele on one chromosome are less likely than expected by chance to carry another *A* allele on the homologous chromosome so the association is negative, $C_{A/A} < 0$. Relative to the case of $C_{A/A} = 0$, the allelic variance among individuals, *V*, is larger when the association is positive and is smaller when the association is negative.

If these populations reproduced asexually, the genotype distribution of the offspring is expected to be exactly the same as the parents so there would be no change in the variance. Let us now consider what happens if these populations reproduce sexually. Assuming random union of gametes, the distribution of offspring genotypes depends only on p_A. Because $p_A = \frac{1}{2}$ for all three populations, the expected distribution of offspring genotypes is the same for all three populations. Specifically, the frequencies of *A*/*A*, *A*/*a*, and *a*/*a* is $\frac{1}{4}$, $\frac{1}{2}$, and $\frac{1}{4}$, respectively, so that the allelic variance among individuals would be $V = 0.125$.

In Population S1, there is no change in the variance; when there is no association prior to reproduction, sex has no effect. In Population S2, the variance changes from 0.25 to 0.125; thus, when the association is positive prior to reproduction, genetic mixing reduces the variance. In Population S3, the variance changes from 0 to 0.125; thus, when the association is negative prior to reproduction, genetic mixing increases the variance. Though Populations S2 and S3 represent opposite extremes, they illustrate what happens in general with positive and negative associations.

Effects of recombination: Here we examine the effects of recombination by considering a model with two di-allelic loci in a haploid organism. Let us examine how sex affects three different populations. Prior to reproduction, all three populations have the same allele frequency, $p_A = p_B = \frac{1}{2}$, but they differ in how *A* and *B* alleles are packaged into individuals (see Table 2). The interlocus association C_{AB} can be measured as the covariance between an individual's allelic state at locus **A** and its allelic state at locus **B**. In Population R1, *A* and *B* alleles are distributed randomly with respect to each other: there is no association, $C_{AB} = 0$. In Population R2, individuals with an *A* allele are more likely than expected by chance to carry a *B* allele so the association is positive, $C_{AB} > 0$. In Population R3, individuals with an *A* allele on one chromosome are less likely than expected by chance to carry a *B* allele so the association is negative, $C_{AB} < 0$. Relative to the case of $C_{AB} = 0$, the allelic variance among individuals, *V*, is larger when the association is positive and is smaller when the association is negative.

If these populations reproduced asexually, the genotype distribution of the offspring is expected to be exactly the same as the parents so there would be no change in the variance. If these populations reproduce sexually, then the genotype distribution of offspring may different from the parents. Offspring distributions are shown in Table 2, assuming free recombination. As was the case with segregation, sex increases the variance when associations are negative prior to reproduction but sex decreases the variance when associations are positive.

Table 1. Changes in variance due to sex in a single locus diploid model.

	Prior to reproduction					After sex					Change
	A/*A*	*A*/*a*	*a*/*a*	$C_{A/A}$	*V*	*A*/*A*	*A*/*a*	*a*/*a*	$C_{A/A}$	*V*	ΔV
S1	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	0	$\frac{1}{8}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	0	$\frac{1}{8}$	0
S2	$\frac{1}{2}$	0	$\frac{1}{2}$	$+\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	0	$\frac{1}{8}$	$-\frac{1}{8}$
S3	0	1	0	$-\frac{1}{4}$	0	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	0	$\frac{1}{8}$	$+\frac{1}{8}$

Populations S1–S3 each have the same allele frequency but the alleles are initially distributed differently. For each population, the table shows the genotype frequencies and the intralocus association, $C_{A/A}$, before and after sex. The variance, *V*, reported here is the allelic variance among individuals defined as the variance in allele frequency of the focal allele, *A*, among individuals.

Table 2. Changes in variance due to sex in a two locus haploid model.

	Prior to reproduction						After sex						Change
	AB	*Ab*	*aB*	*ab*	$C_{A/B}$	*V*	*AB*	*Ab*	*aB*	*ab*	$C_{A/B}$	*V*	ΔV
R1	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	0	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	0	$\frac{1}{2}$	0
R2	$\frac{1}{2}$	0	0	$\frac{1}{2}$	$+\frac{1}{4}$	1	$\frac{3}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{3}{8}$	$\frac{1}{8}$	$\frac{3}{4}$	$-\frac{1}{4}$
R3	0	$\frac{1}{2}$	$\frac{1}{2}$	0	$-\frac{1}{4}$	0	$\frac{1}{8}$	$\frac{3}{8}$	$\frac{3}{8}$	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{4}$	$+\frac{1}{4}$

Populations R1–R3 each have the same allele frequency but the alleles are initially distributed differently. For each population, the table shows the genotype frequencies and the linkage disequilibrium, C_{AB}, before and after sex. The variance reported here is the allelic variance among individuals defined as the variance in sum of allele frequencies of the focal alleles, *A* and *B*, among individuals.

frequencies but it does alter genetic associations. Typically, genetic mixing breaks down genetic associations. Recombination breaks down associations among alleles on the same chromosome, for example C_{AB}, whereas segregation breaks down associations between alleles at the same locus on homologous chromosomes, for example $C_{A/A}$.

Consequences of Breaking Down Genetic Associations

A widely held belief is that sex increases variance and the benefit of sex must be related to this increase in variance. However, the claim that sex increases variance is not always true at the population level (see Box 1). Whether genetic mixing increases or decreases the variance depends on the sign of associations prior to sex. If associations are negative prior to sex, then these associations are suppressing the allelic variance among individuals. Because sexual processes diminish the magnitude of negative associations, sex results in an increase in the variance. Conversely, if associations are positive prior to sex, then these associations are enhancing the amount of allelic variance among individuals. By breaking down these positive associations, sex results in a decrease in the variance.

So, depending on the sign of associations prior to reproduction, sex may increase or decrease the variance. What are the consequences of causing such a change? Both the short-term and long-term effects must be considered when answering this question. Sex changes the variance by rearranging how alleles are distributed among individuals by converting intermediate genotypes to extreme genotypes — for example, *A*/*a* × *A*/*a* → *A*/*A*, *A*/*a*, *a*/*a* — or vice versa. There are immediate (short-term) effects of these rearrangements on the mean fitness of offspring whenever alleles interact to affect fitness through dominance or epistasis. In general, increasing the variance will be beneficial in the short term only if the average fitness of extreme genotypes is higher than that of intermediate genotypes. In the long term, it is good to have increased the variance if selection is directional (or will be in the future), because adaptation occurs more rapidly with increased variance.

These concepts are most easily demonstrated by way of a simple example. Imagine a population in which all individuals are of genotype *A*/*a* (see Population S3 of Box 1). Let the fitnesses of *A*/*A*, *A*/*a*, and *a*/*a* be: $w_{A/A} = 1$, $w_{A/a} = 0.9$ and $w_{a/a} = 0.2$, respectively. Sex will convert some *A*/*a* types to *A*/*A* and *a*/*a*. In the long run, this is good because it increases the variance in part by producing *A*/*A*, which is the best type. In the short term, however, conversion of *A*/*a* types to *A*/*A* and *a*/*a* is detrimental, because the fitness of the intermediate type is greater than the average fitness of the two extreme types: $w_{A/a} > (w_{A/A} + w_{a/a})/2$. This example focuses on the effects of segregation; an analogous example could be made using recombination.

Weighting Short-Term *versus* Long-Term Effects

How should these short-term and long-term effects be weighted when considering the evolution of genetic mixing? As illustrated below, the answer to this question depends on the amount of gene flow between low-sex and high-sex types. One way to model the evolution of genetic mixing is to consider a locus **M** that modifies the amount of genetic mixing. This locus could affect an individual's investment in sexual *versus* asexual reproduction or modify its recombination rate; for the sake of discussion we will imagine that it affects the former. We will assume that the *m* allele results in more genetic mixing than does the alternative, *M*. Loosely, we can think of the population as consisting of two subpopulations representing the *M*- and *m*-bearing haplotypes, which we will call the low- and high-sex types, respectively. An increase in the relative abundance of the high-sex type is equivalent to the evolution of increased genetic mixing.

In the extreme case where genotypes carrying the *M*/- genotypes are obligately asexual, there will be no gene exchange of alleles on the *M*-haplotype with alleles on the *m*-haplotype. In this case of no gene-flow between the two subpopulations, the model is analogous to an ecological model of species competition. In such a case, long-term effects are of primary importance in determining the fate of the modifier. Consider again the example described above where, initially, all individuals are heterozygous at the *A* locus and $w_{A/A} = 1$, $w_{A/a} = 0.9$, and $w_{a/a} = 0.2$. Imagine that individuals carrying the *M* allele at the **M** locus are obligately asexual, whereas *m*/*m* individuals produce all of their offspring sexually. At the beginning of the second generation, all *M*/*M* and *M*/*m* individuals are *A*/*a*, and their mean fitness is 0.9. Because their parents reproduced sexually, only 50% of *m*/*m* individuals are *A*/*a*, the remaining 50% are evenly split between being *A*/*A* and *a*/*a*. Thus, the mean fitness of *m*/*m* individuals in this generation is only 0.75. However, despite its initial disadvantage, the *m*/*m* genotype will eventually displace *M*-bearing genotypes because some *m*/*m* individuals carry the *A*/*A* genotype, which is the most fit, whereas none of the *M*-bearing genotypes do.

Let us reconsider the scenario above with one small change. Imagine that, rather than being obligately asexual, *M*-bearing genotypes produce 80% of their offspring asexually but the remaining 20% are produced sexually; as before, *m*/*m* individuals produce 100% of their offspring sexually. Because *m*/*m* individuals engage more heavily in sex, these genotypes are initially associated with more variance at the *A* locus than are the *M*-bearing genotypes. The *m* allele will enjoy a long-term advantage of having created more *A*/*A* genotypes only to the extent that the *m* alleles remain linked with the *A*/*A* genotype. The long-term benefit of creating *A*/*A* types is diminished whenever *m*/*m* genotypes engage in sex with *M*-bearing genotypes. In essence, the *m*/*m* types pay the cost of producing *A*/*A* types — by producing *a*/*a* types as a byproduct of sex — and then transmit this good genotype, through sex, to the competing *M*-bearing genotypes. In general, the importance of the long-term effect diminishes the more mixing there is between the low-sex and high-sex types (Box 2).

A large number of models examine a set of obligately asexual genotypes competing against a set of obligately sexual genotypes. Muller's Ratchet [8], Kondrashov's mutational deterministic model [9], Hamilton's Red Queen models [10,11], as well as many others

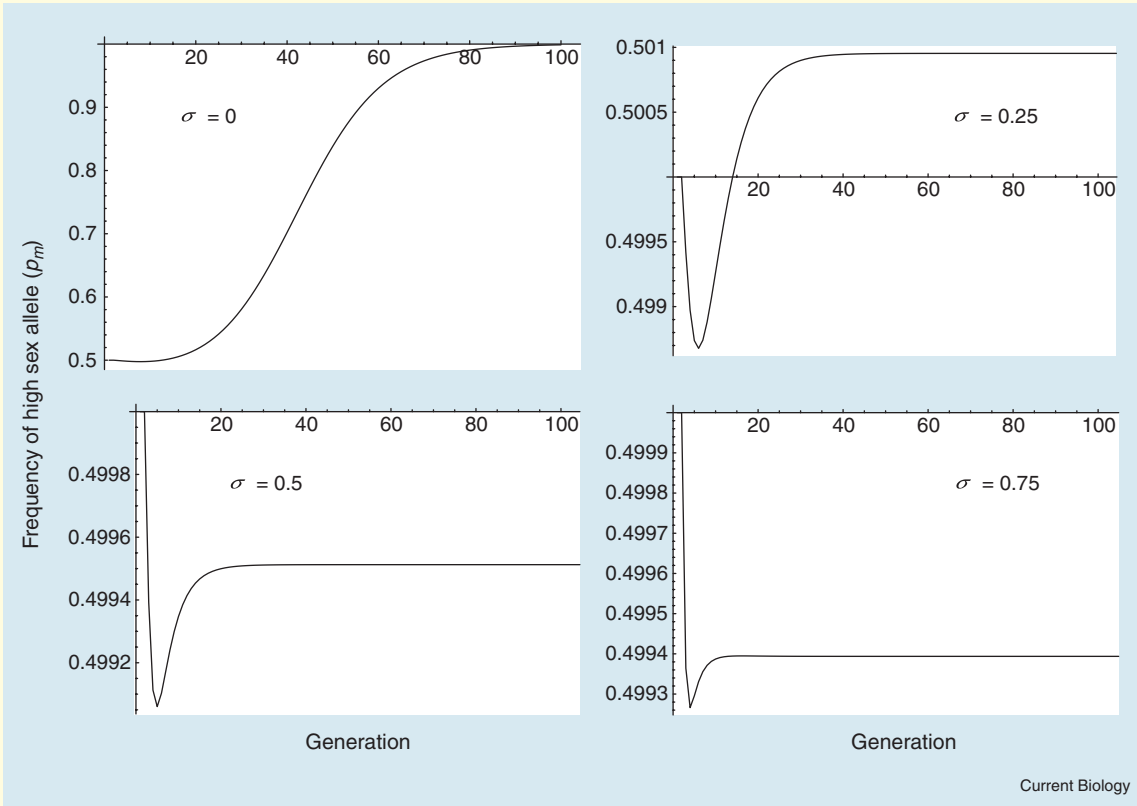
Box 2

Gene flow between high- and low-sex types determines the importance of the long-term effect.

Consider a single di-allelic locus **A** that affects fitness in a diploid organism. Let the fitnesses of *A*/*A*, *A*/*a*, and *a*/*a* be $w_{A/A} = 1$, $w_{A/a} = 0.9$, and $w_{a/a} = 0.2$, respectively. We will assume that initially all individuals are *A*/*a*. A second di-allelic locus **M** determines reproductive mode. *M*/*M* and *M*/*m* individuals produce a fraction σ of their offspring sexually and the remaining fraction, $1 - \sigma$, asexually; m/m individuals produce a fraction $\sigma + \delta\sigma$ sexually and the remainder asexually.

We will assume that initially all individuals are heterozygous at the **A** locus, i.e., there is initially a very strong negative association between alleles at this locus: $C_{A/A} < 0$. Sex will reduce the magnitude of this association, thereby increasing the variance, which is advantageous in the long-term. However, in the short-term sex is disadvantageous because it converts *A*/*a* to *A*/*A* and *a*/*a* and $w_{A/a} > (w_{A/A} + w_{a/a})/2$. Because the *m* allele causes more sex, it will enjoy the long-term advantage of sex but also suffer the short-term disadvantage. The relative importance of the long-term advantage is mediated by the amount of gene flow between the high- and low-sex alleles; this gene flow is determined by the parameter σ, which gives the baseline level of sex for all genotypes.

Using simulations, we track the evolution of sex by following the frequency of the *m* allele as the *A* sweeps to fixation. These simulations assume that the initial frequency of *m* is $p_m = 0.5$. In the plots shown below, *m* initially declines in frequency, reflecting its short-disadvantage; it then increases in frequency, reflecting its long-term advantage. If the final frequency of *m* is greater than 50% (i.e., there has been a net increase in p_m) this implies that the long-term advantage of sex has outweighed the short-term disadvantage. The long-term advantage tends to outweigh the short-term disadvantage when the amount of gene flow between *M* and *m* backgrounds is low (low values of σ) but not when it is high (high values of σ).



Plots show the frequency of the high-sex allele *m* in simulations described in Box 2. Different plots show simulations in which the baseline level of sex, σ, was 0%, 25%, 50%, or 75%. In the simulations, $\delta\sigma = 0.02$ and the recombination rate between the *M* and *A* locus was 0.4.

(for example [12–15]) fall into this category. Such models are appropriate for representing the evolution of sex in many natural systems where genotypes that are asexual are obligately so (for example [16,17]). As there is no gene flow between the low-sex and high-sex types, the winner of the sex *versus* asex battle is determined by the long-term effects only. However, the results from such models tell us little about the conditions for the gradual evolution of sex, because they ignore short-term effects. For example, in the absence of explicit costs of sex, the mutational deterministic model shows that a sexually recombining population will have a higher mean fitness than non-recombining populations at mutation–selection balance if deleterious

mutations interact synergistically (negative epistasis) [9,18]. This difference in mean fitness at equilibrium results from the long-term advantage to recombination that exists with negative epistasis. However, in a population that has a low, but non-zero, level of recombination, negative epistasis is an insufficient condition for selection to drive the spread of a modifier allele that increases the rate of recombination. Additional conditions must be met [19–21], because the modifier's fate depends on short-term as well as long-term effects. This review focuses on the gradual evolution of sexual processes and thus considers both short-term and long-term effects.

Evaluating Short-Term and Long-Term Effects

To summarize, genetic mixing can either increase or decrease the variance depending on whether genetic associations prior to reproduction are negative or positive. Moreover, increasing the variance may or may not be beneficial. In the long term, increasing the variance is good. In the short term, increasing the variance is bad if the average fitness of extreme types, $\overline{w}_E$, is lower than that of intermediate types, $\overline{w}_I$. The sign of $\overline{w}_E - \overline{w}_I$ is determined by non-linear components of selection — epistasis and dominance.

Ultimately, we would like to know which evolutionary forces determine the sign and magnitude of genetic associations and have good estimates of the non-linear components of selection that determine how changes in variance affect mean fitness. However, great insight into understanding sex could be gained if we were able to answer two seemingly simple questions pertaining to the effects of sex on fitness. Are sexually produced offspring more or less variable in fitness than asexually produced offspring? This will tell us whether there is a long-term advantage or disadvantage to sex. Second, is the mean fitness of sexually produced offspring greater than the mean fitness of asexually produced offspring? This will tell us whether there is a short-term advantage or disadvantage to sex.

There is a shocking lack of quantitative data relating to these most basic questions. Unfortunately, many of the best available studies should be interpreted with caution. Charlesworth and Charlesworth [22] found evidence that the mean fitness of recombinant chromosomes in *Drosophila melanogaster* was less than that of non-recombinant chromosomes. The chromosomes had been collected from the field and fitness was assessed in the lab, so it is difficult to clearly interpret these results because the genetic associations were generated in one environment but the effects of breaking them down were examined in another.

Recent studies of the consequences of sex in *Chlamydomonas* found that sexually produced offspring have lower mean fitness, but greater variance, than asexually produced offspring [23,24]. The populations used in these experiments were created by mixing a small number of isolates originating from different geographic locations. Thus, the associations in these populations resulted from sampling, admixture and/or local selection in the field; again, the associations were not generated by processes reflective of the environment in which the consequences of breaking them down were assessed.

Kelly *et al.* [25] found that the average fitness of sexually derived offspring was considerably greater than that of clonal offspring in the sweet vernal grass *Anthoxanthum odoratum*. Unlike other studies, they studied a natural population and assayed fitness in the field, so their study provides the most realistic assessment of the short-term consequences of sex. Without more empirical data, it is impossible to know whether the results of this study, which are in the opposite direction to those in the *Drosophila* and *Chlamydomonas* studies, are reflective of the effects of sex in general. In fairness, collecting such data is very difficult. Ideally, parents should be from a natural or quasi-natural population, for example a large, long-term lab culture. The sexually derived and asexually derived offspring that are compared should be produced in a similar manner — it is non-ideal, for example, to compare asexual offspring produced by budding with sexual offspring produced from resting eggs. Finally, fitness should be assessed in the environment from which the parents were derived.

An alternative is to take a theoretical approach to investigate how various evolutionary forces shape genetic associations. Once associations are known, one can determine whether sex will increase or decrease variance and then evaluate the consequences of such a change. In the following sections, I shall consider these issues first with respect to recombination and then with respect to segregation.

Selection for More Recombination

As recombination primarily affects associations between alleles at different loci on the same chromosome, for example two-way linkage disequilibria, I shall focus on these associations in this section. The simplest scenario to consider is when selection is the only evolutionary force affecting associations [19,20,26,27]. Defining epistasis as the deviation from multiplicative effects, then the disequilibrium generated by selection will be of the same sign as epistasis. That is, associations are expected to be negative when epistasis is negative and positive when epistasis is positive. Consequently, recombination should increase variance when epistasis is negative and decrease it when epistasis is positive. The short-term effect of recombination is usually negative because epistatic selection creates an excess of favorable allele combinations, and recombination destroys these combinations. That is, recombination typically produces extreme types when intermediates are better and vice versa. The short-term effect is positive only under very narrow conditions (epistasis must be negative but weaker than the additive expectation). Considering both long-term and short-term effects, recombination is predicted to increase only when epistasis is both negative and weak [19]. Empirical studies indicate that epistatic interactions are variable in both sign and magnitude [28–30]. Such variation will tend to cause selection against recombination even if epistatic interactions are weakly negative on average [21].

As described above, the short-term effects of recombination are usually negative, at least when selection is constant. But if selection changes so that allele

combinations previously favored are disfavored in the following generation — specifically, the sign of epistasis changes — then the effects of recombination will be beneficial in the short-term. To have consistent selection for higher levels of recombination by this mechanism requires that fluctuations in the sign of epistasis be rapid, on the scale of two to five generations [19]. It is difficult to imagine that such fluctuations would be common from abiotic sources of selection. Fluctuations in epistasis are sufficiently rapid in some host-parasite models, but they are too slow in many others [31,32]. If fluctuations in epistasis are too slow, or non-existent, then the short-term effect of recombination is usually negative because recombination destroys the associations built by, and favored by, selection.

The picture can change if epistatic selection is not the dominant force shaping genetic associations. For example, migration contributes to disequilibrium whenever demes differ in allele frequency, as might be expected when selection varies among demes. When migration is the dominant force shaping disequilibrium, recombination is favored under a different, more complicated, set of conditions than in the absence of migration [33,34]. For example, recombination can be favored when selection on linked loci negatively covaries among demes and epistasis is positive. In such a situation, migration among demes generates negative disequilibrium. Recombination reduces this disequilibrium by converting intermediate types into extreme types. In addition to the long-term benefits of creating extreme types, this conversion is beneficial in the short term because extreme types are more fit, on average, than intermediate types if epistasis is positive. Though it is clear that migration has the potential to alter the conditions favoring recombination, it is difficult to imagine that the required pattern of epistasis and spatial covariance in selection occurs frequently enough to account for observed levels of sex and recombination.

Non-random mating can also affect linkage disequilibrium and thus alter the conditions for recombination. For example, for populations at mutation–selection balance, recombination is favored under broader conditions if there is positive assortative mating for fitness than if mating is random [35]. Conditions favoring recombination are also different in populations that undergo some degree of inbreeding [36–38]. For example, Roze and Lenormand [38] found that, with sporophytic selfing, recombination is favored whenever there is negative dominance-by-dominance ($d\times d$) epistasis. In this situation, recombination is favored by a short-term advantage. Recombination reduces the frequency of double homozygotes produced by selfing, which is beneficial because double homozygotes are particularly unfit if $d\times d$ epistasis is negative. There is some limited evidence for negative $d\times d$ epistasis from inbreeding studies [39]. Consistent with the theory, there is a positive correlation between selfing and recombination rates in plants [38]. To the extent that models of sporophytic selfing serve as a proxy for other forms of inbreeding (including population subdivision), this advantage of recombination may apply quite broadly. This advantage is unlikely to select for sex, however, because the benefit of recombination here arises from the fitness difference between two types of sexually produced offspring — selfed *versus* outcrossed offspring — rather than between sexually produced *versus* asexually produced offspring.

Another force that can create disequilibrium is genetic drift. Just as drift can cause allele frequencies to increase or decrease, drift can cause positive or negative changes in disequilibrium. When drift creates positive disequilibrium, the disequilibrium is consumed by selection, as selection increases the frequencies of both beneficial alleles simultaneously. When drift creates negative disequilibrium, the response to selection is hindered, and the negative disequilibrium persists. Thus, by virtue of its interaction with selection, drift is expected to generate negative disequilibrium, a phenomenon known as the 'Hill–Robertson effect' [40,41]. Drift can be the major source of disequilibrium provided that epistasis is not too strong. Because drift tends to cause negative disequilibrium, recombination will increase variance and thus be favored via a long-term advantage [42–44]. However, if epistasis is sufficiently negative, there will be a short-term disadvantage to increasing variance and recombination may be disfavored.

Nonetheless, this idea, whose origins are attributed to Fisher [45], Muller [46] and Morgan [47], is one of the most promising explanations for genetic mixing as all populations experience both drift and selection. As this theory relies on drift, it would appear to require small population sizes, but this requirement is lessened when more loci are under selection [48]. In fact, drift-based selection for recombination can occur even in infinite populations provided they are subdivided into small finite demes such that drift occurs locally [49].

In the drift-based theory, recombination evolves because it accelerates adaptation. Empirical evidence indicates that adaptive evolution occurs more rapidly with recombination. For example, rates of adaptation appear to be elevated in regions of the genome that experience higher rates of recombination [50]. Experimental evolution studies have shown that recombination increases the rate of adaptation [51–55]. Using an elegant experimental design to control for the initial frequency of beneficial alleles, Poon and Chao [54] showed that recombination provides the biggest boost to adaptation in situations when drift is strongest.

Though the evidence described above indicates that recombination can increase adaptation, it does not prove that increased recombination evolves as a result. The best evidence for the drift-based theory of recombination is the observation that recombination rates tend to increase as a by-product of artificial selection on traits unrelated to recombination (reviewed in [44]). Of course, drift is likely to be particularly strong in populations subject to artificial selection, as they tend to be much smaller than natural populations.

Selection for More Segregation

In diploids, though not haploids, the evolution of sex can also be influenced by the effects of segregation. Segregation is responsible for altering associations between alleles on homologous chromosomes, for example homozygosity, $C_{A/A}$. We will begin by considering selection as the only force shaping these

associations. Just as epistasis is the key component of selection for recombination, dominance is critical to understanding segregation. In this context, it is useful to use the analogy with epistasis and define dominance as a deviation from multiplicative effects, for example $w_{A/A} = 1$, $w_{A/a} = 1 - s$, and $w_{a/a} = (1 - s)^2 + \iota$ where ι represents dominance. Dominance affects homozygosity in the same manner that epistasis affects linkage disequilibrium. That is, we expect the intralocus association to be positive (excess homozygosity) if dominance is positive and to be negative (excess heterozygosity) if dominance is negative.

Because sex reduces the magnitude of the association, there is a long-term advantage to sex when dominance is negative (deleterious alleles are recessive). However, there is almost always a short-term disadvantage to segregation because segregation breaks down the associations generated by selection. Because of this short-term disadvantage, the net selection on sex is usually negative when selection is the only force affecting genetic associations; analogous to the recombination case, segregation is only beneficial under weak selection if dominance (as defined by ι) is weak and negative [56]. Thus the results of a model of segregation exactly parallel the recombination results when non-linear selection, dominance or epistasis, is the only force shaping the associations.

However, selection need not be the only force affecting intralocus associations. Inbreeding, via selfing or population structure, can strongly affect associations between alleles on homologous chromosomes. Inbreeding causes an excess of homozygotes as well as double homozygotes (*MA*/*MA*, *Ma*/*Ma*, *mA*/*mA*, *ma*/*ma*). Because the high-sex types, *m*/*m*, engage in more sex than low-sex types, *M*/*M*, the former more quickly moves from a homozygous background to a heterozygous one (*mA*/*mA* × *ma*/*ma* → *mA*/*ma*), which is advantageous in the short-term if the fitness of the heterozygote is greater than the average of the two homozygotes: $w_{A/a} < (w_{A/A} + w_{a/a})/2$. (This result assumes selection is weak; results differ when selection is strong [56,57].) Because deleterious mutations tend to be recessive and most populations experience some inbreeding through population subdivision, it is possible that this advantage to segregation could be reasonably important if mutation rates are not too small [56].

The importance of drift has not been formally evaluated with respect to segregation, though preliminary work suggests that drift also generates selection for segregation (my unpublished data). Segregation alleviates the negative intralocus associations created by drift, increasing variance and thereby enjoying a long-term advantage. However, the effects of drift in selecting for sex are likely to be mostly a result of recombination rather than segregation in very large metapopulations.

So far we have assumed that an individual's fitness depends only on its own genotype ('genotypic selection'). In this case, we only need consider the associations between alleles within the same genome. However, in some cases an individual's fitness may depend, in part, on the similarity of its genotype to that of its relatives. Such 'similarity selection' might occur when offspring are exposed to parasites transmitted by their own mothers [58] or when offspring compete with their siblings for a variable set of resources ('tangled bank', see [7]). When this type of selection occurs, we must also consider associations between alleles carried by relatives. Segregation changes such associations — asexually produced offspring share more alleles in common with their mothers than do sexually produced offspring. Even though similarity selection may be weak relative to genotypic selection, its effects on segregation can be large [59]. This is because similarity selection acts on associations between relatives, which are large as they are produced by inheritance. In contrast, genotypic selection acts on associations within individuals that tend to be small if they are created by weak forces (such as weak non-linear selection or drift in large populations).

Variation in sexual processes with-in species

Within populations, sexual processes do not occur at a constant rate across time and space. This intraspecific variation has been somewhat ignored by both empiricists and theoreticians even though it is both inherently interesting and potentially informative to the question of why genetic mixing is so common.

The most striking pattern is that, in many facultatively sexual species, sex occurs when conditions become unfavorable, for example, if there is over-crowding or when winter approaches (see [7]). Further, sexually-produced eggs are often dormant and stress-resistant (resting eggs), capable of weathering harsh conditions until the environment improves. Perhaps the simplest explanation for this pattern is that organisms reproduce sexually in unfavorable conditions because the costs of sex are lowest at these times (S.P. Otto, personal communication). In unfavorable conditions organisms may be incapable of rapid asexual reproduction so that the difference in the rates of asexual *versus* sexual reproduction is minimized when conditions are poor.

A related phenomenon is plasticity in recombination rates. In a number of organisms, increased recombination rates have been observed under certain types of stress. For example, in *D. melanogaster*, recombination rates increase when flies are reared under non-optimal thermal or nutritional conditions [60,61]. Recent studies show that plants infected with pathogens have higher rates of recombination [62,63]. Do these empirical data indicate that organisms in poor condition have higher rates of recombination? If so, then we might expect that recombination rates are higher in individuals whose genotypes are poorly matched to the current environment. Data on this issue are scant though Tucíc *et al.* [64] did find a pattern consistent with this expectation (but see [65]). Theory predicts selection only favors modifiers that increase the recombination in individuals with bad genotypes if the species is haploid [66–68]. In diploids such plasticity is neutral, at least under simple modes of selection, so the observed patterns may simply reflect a more general physiological response [66].

Recombination rates often differ between the sexes. In some cases, recombination is completely repressed

in one sex but not the other. If sex chromosomes are heterogametic, the achiasmatic sex is the heterogametic sex; this is the Haldane–Huxley rule (reviewed in [7]). In other cases, recombination occurs in both sexes but with quantitative differences. These cases do not follow the Haldane–Huxley rule, and sexual dimorphism in recombination is thought to exist for different reasons than with sex-limited achiasmy [69,70].

Recent theory has identified two likely reasons for quantitative differences in recombination between the sexes [71]. The first is based on differences in selection between male and female gametes. Imagine that there was epistatic selection on male gametes (but not female gametes) such that only *AB* haplotypes were successful. In this case, all individuals would be *AB*/–, where haplotypes are listed as paternal/maternal. There would be strong selection in males for reduced recombination so that a larger fraction of their gametes would be *AB*. In a nice test of the theory, Lenormand and Dutheil [70] examined levels of sexual dimorphism in plant taxa expected to differ in levels of male and female haploid selection. Consistent with predictions, the ratio of male to female recombination tended to be low when haploid selection was either strong in males or weak in females.

The second reason for sex differences in recombination is based on fitness differences due to imprinting. Imagine that, because of imprinting, individuals only expressed the alleles received from their fathers. Assuming the combination *AB* is especially fit, then following selection *AB*/– would be overrepresented. Again, there would be strong selection in males to reduce recombination so that a larger fraction of their offspring would inherit, and express, the AB haplotype. In humans, there is only weak evidence for imprinted regions having elevated levels of dimorphism in recombination [72,73].

At the within-genome level, variation in recombination is well documented. Recombination rates differ among chromosomes and within chromosomes across broad regions, for example recombination is low in centromeric regions relative to telomeric regions. One of the more interesting recent discoveries is the large variation in recombination that exists at a much finer scale. Recombination hotspots are short genomic regions (~1–2 kilobases) that exhibit much higher rates of recombination than surrounding regions; they have been found in some organisms, such as yeast and primates, but not all (for example, they have not been found in *Drosophila melanogaster* or *Caenorhabditis elegans*).

These hotspots evolve rapidly; hotspots occur in different locations in humans and chimps despite their recent common ancestry and high degree of DNA similarity [74–76]. Despite the rapid evolution of hotspots, recombination rates over somewhat larger regions (around 5 megabases, for example) appear relatively stable, suggesting evolutionary constraint at this scale [77]. The turnover in hotspots is consistent with the idea that hotspots self-destruct by inducing double strand breaks in their sequence [78,79]. The apparent constraint may be related to the role of recombination in aiding the proper segregation of chromosomes during meiosis [80]. However, such a constraint might be expected to act at the level of the entire chromosome but not necessarily on smaller regions. Moreover, such a constraint is not absolute because, as previously discussed, it is possible to have proper meiosis without any recombination at all.

Conclusions

Theoretically, we have an increasingly better understanding of how selection on sex operates under different scenarios and how these scenarios relate to one another. Empirically, we really know very little about sex. We do not even know how sex typically affects the mean and variance in fitness in nature. We know even less about the forces generating variation in sexual processes within species. Studying this variation, both empirically and theoretically, should reveal interesting biological patterns and, hopefully, provide important insights into why organisms shuffle their genotypes.

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