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FOURTEEN

The Evolution of Sex

MARIA E. ORIVE

The evolution of sex has arguably produced one of the most diverse and expansive bodies of theory within evolutionary biology, leading both to extensive verbal arguments and to a large quantity of mathematical models. It nevertheless remains an active area of theoretical and experimental research, implying that not all of the questions raised by the presence of sex across the tree of life have been answered. It is important, however, when discussing the evolution of sex to carefully delineate what is meant by "sex," since biologists often use the term to describe at least four different biological phenomena: (1) the existence of separate sexes (or dioecy); (2) anisogamy, or the fusion of two dissimilar gametes; (3) meiosis, a specialized form of cell division leading to the production of gametes, which may or may not include genetic recombination; and, finally, (4) genetic recombination itself. The vast majority of the theoretical considerations for the evolution of sex have focused on this final definition, and thus it is the evolution of recombination that I have chosen to focus on here.

We should also take care to differentiate between sex, which changes the genetic state of cells or individuals, and reproduction, which produces ecologically distinct individuals that are largely independent of one another (G. Bell 1982). There can be sex in the absence of reproduction—consider bacterial conjugation, where there is transfer of genetic material between two cells, but no increase in cell number. There likewise can be reproduction (an increase in the number of individual living organisms) in the absence of sex, if we consider all of the various forms of clonal reproduction that do not change the genetic makeup of clonal offspring (e.g., G. Bell 1982; Hughes 1989; Klimes et al. 1997). Finally, it is important to clarify that I am using the term "recombination" in the general sense of the bringing together of genes inherited from different parents; see Maynard Smith (1988a) for a

discussion of the usage of "recombination" versus "crossing over." I am also focusing on lineages that recombine their entire genomes regularly, which necessarily excludes some forms of recombination, such as horizontal or lateral gene transfer and gene conversion. As such, the focus is on recombination of genomes within species (for a discussion of the concept of species as it relates to genetic interconnectivity, see Nathan and Cracraft, chap. 6; for a discussion of the role of lateral gene transfer in genealogical patterns of lineage diversification, see Kearney, chap. 7). Frank and Fox (chap. 9) argue that the overall process of evolutionary change can be partitioned into the processes of natural selection, where information about the environment is accumulated, and transmission of that information. The theory of the origin and maintenance of sexual recombination seeks to explain how natural selection shapes this transmission itself, and thus lies at the intersection of these two aspects of evolutionary change for sexual organisms.

Mechanistic Theories

The early evolutionary origins of recombination likely involve the repair of DNA damage, an idea tracing back at least as far as E. C. Dougherty (1955), wherein he considered two different aspects of sex—the transfer of DNA molecules between two or more cellular compartments, and the recombination of DNA molecules within a cellular compartment. This second step would be an advantage in the case of DNA damage and the evolutionary cause for the origin of DNA recombination; genetic transfer is more likely to have evolved secondarily. This mechanistic theory of the evolution of recombination was called the "repair hypothesis" by Bernstein et al. (1988), who distinguished it from theories that depend on the distribution of genetic variation (Bernstein et al. 1985). It is not clear, however, why genetic exchange (crossing over) of the DNA molecule beyond the repair site is necessitated by DNA repair. As an example, Maynard Smith (1988a) notes that a process equivalent to double-strand repair occurs in mating-type exchange in yeast, without crossing over beyond the repair site. Further, studies of natural transformation in prokaryotes show a lack of evidence for regulation of the process by DNA damage (Redfield 1993). Nevertheless, it seems likely that DNA repair played a role in the early evolution of recombination in the ancestor of modern eukaryotes, as evidenced by the relationship between the molecular machinery of DNA repair and that of recombination and crossing over (Redfield 2001; Lieber 2010).

Other mechanistic hypotheses for the evolution of recombination include those assuming that proper segregation of chromosomes during

Table 14.1. The Theory of the Evolution and Maintenance of Sexual Recombination

Domain: The evolutionary origin and maintenance of sexual recombination.

Propositions:

1. Sex and recombination incur costs when segregation within a locus or recombination between loci breaks up genotypes of high fitness.
2. Evolutionary explanations for the evolution of sex rest on the role of recombination in breaking up and forming nonrandom genetic associations (linkage disequilibria).
3. Negative linkage disequilibrium always favors recombination via its long-term effect on population fitness.
4. The linkage disequilibria underlying the long-term advantage of recombination can be formed via random, stochastic processes (drift processes) or via deterministic, nonrandom processes (epistasis, population structure).
5. Two differing evolutionary forces act on modifiers of recombination: short-term selection on individuals to have the highest mean offspring fitness and long-term selection to increase the genetic variation in population fitness.
6. Environmental or genomic heterogeneity in the form of selection fluctuating over time or space, the interaction between genetic drift and linkage, or structure imposed by epistasis and genomic architecture, expands the conditions under which increased recombination is favored.
7. Genomic processes such as gene conversion, horizontal gene transfer, and phenotypic assortment provide alternatives to sexual recombination for breaking up negative disequilibrium and allowing an escape from long-term population fitness decline in asexual lineages.

meiosis is dependent on the formation of chiasmata, resulting in recombination as a by-product of a system for the proper sorting of homologous chromosomes. However, efficient chromosomal disjunction occurs without the formation of chiasmata in the heterogametic sex of organisms with both male heterogamy (such as *Drosophila*) and female heterogamy (*Lepidoptera*) (Burt et al. 1991). Thus, this mechanistic explanation does not adequately explain the persistence of recombination for many taxa. The vast majority of the theories developed to explain the persistence of recombination have focused instead on the costs of sex and on the effects of recombination on genetic variation.

Costs of Sex

No discussion of the evolution of sex can be complete without clarification of what is meant by the "cost of sex" and how evolutionary theory has addressed this idea. That sexual reproduction involves a real cost is implied by the existence of life cycles where organisms (such as aphids and rotifers) reproduce asexually to take advantage of abundant resources and switch to sexual reproduction only when resources begin to disappear (for a review of such cyclical parthenogenesis, see De Meester et al. 2004).

Theory has focused on two different costs associated with sexual reproduction: the cost of producing males, and the cost of breaking up genotypes. The cost of producing males (or the cost of male function in hermaphrodites) depends on the existence of anisogamy. The key assumption is that two forms of gametes exist, and the number of more costly gametes (the eggs) limits the number of new individuals that can be produced each generation. Consider a population of sexually reproducing individuals of size N, half of which are females ($N/2$) and half of which are males (Maynard Smith 1978a). If the number of eggs that can be produced by a single female is k, and the probability that an egg will contribute to the next generation is s, this population will produce $Nsk/2$ new individuals in the next generation. Contrast this with an asexual (parthenogenetic) population that is similar in every way (including the number of eggs that can be produced and their probability of survival). Here all N individuals are parthenogenetic females, and thus the number of new individuals is Nsk. This contrast between $N/2$ versus N individuals producing the limiting gamete type is then the so-called "twofold cost of sex" (or more accurately, the twofold cost of anisogamy); the asexual population will, all things being equal, increase at a rate double that of the sexual population. The same argument holds for the comparison between a hermaphroditic or monecious sexual population and an asexual population, if we assume that half of the total reproductive contribution is allocated to eggs and the other half to sperm for the sexual population, while the full reproductive contribution is allocated to parthenogenetic eggs for the asexual population. So what keeps sexual species, once they have evolved anisogamy, from evolving parthenogenesis? Most answers have focused on contrasting the advantage of no longer producing males with advantages reaped from continuing recombination. What is clear, however, is that discussions of the cost of males are best placed in the context of the maintenance of sexual reproduction once it has arisen, since anisogamy is believed to have arisen from isogamous sexual reproduction, after the early evolution of sexual reproduction (Parker et al. 1972; Randerson and Hurst 2001).

A more subtle cost lies in the very aspect of sexual reproduction that is often seen as its chief advantage—the breaking up by recombination of parental genotypes. Any adult organism that survives to a reproductive stage has passed through the selective sieve of survivorship and is more likely to have an advantageous genotype than the average newly formed zygote. Why should it then subject that genotype to dissolution? Imagine a heterozygous genotype at a single locus with high fitness. Sexual reproduction will lead, on average, to a decrease in heterozygosity in its offspring,

and fitness will decrease, a process termed "segregation load" (G. Bell 1982). Likewise, if we consider genotypes across loci, recombination will break up high-fitness multilocus genotypes. This cost of sexual reproduction underlies much of the theory that will be addressed here (proposition 1, table 14.1). The opposite side of this same coin, however, lies at the heart of many of the most well-developed theories of the evolution of sex—what recombination breaks apart, it also brings together. And it is the bringing together of either beneficial or deleterious mutations (the dissolution of negative linkage disequilibrium, in the language of population genetics) that will be the focus of this chapter. Evolutionary explanations for the evolution of sex and recombination rest on the role of recombination in breaking up and forming linkage disequilibrium (proposition 2, table 14.1). That this is the key to the "queen of problems in evolutionary biology" (G. Bell 1982) is widely agreed upon. But where researchers have disagreed is in the specifics of how best to model the interactions of mutation, selection, and finite population size in shaping the evolution of sex.

Optimality Theory versus Modifier Theory

Two contrasting theoretical approaches have been applied to the evolution of sex; here I will discuss the scope of each approach, along with important examples of each. The first is optimality theory, which is based on optimization of a specific criterion such as individual or population mean fitness, times to fixation of beneficial mutations, rates of evolution, or genetic loads. It is assumed that evolution proceeds in the direction that optimizes the criterion with respect to the evolutionary parameters of interest. Such models do not assume that organisms can or will be optimal. They are also agnostic regarding the ability of natural selection to optimize in any particular case, which will depend on the details of the population under natural selection (Parker and Maynard Smith 1990).

For the evolution of recombination, optimality arguments (also called equilibrium models, Otto and Lenormand 2002) define some central criterion to be optimized and consider the effects of changing recombination rate on this criterion, often employing (most often implicitly) group selection arguments (Goodnight, chap. 10). The success of increased or decreased rates of recombination is inferred from comparisons of the value of the optimization criterion, which is often a characteristic of a group. Groups with a more optimal value of the criterion are assumed to outcompete and replace other groups, pointing to the direction that recombination will evolve. These group-selection-type of arguments go back to Weismann

(1891), who argued that sex was selected for its effect on the genetic structure of populations or species, rather than individuals, acting to create the "material upon which natural selection may work" (G. Bell 1982). These models of the evolution of sex focus on how recombination redistributes both beneficial mutations (the Fisher-Muller model) and deleterious mutations (Muller's ratchet) and how that redistribution by recombination in turn sets the value of the optimality criterion.

In contrast to models based in optimality theory, a second large family of models asks when and under what conditions sex and recombination can evolve and spread. Many of these models are based on the idea of a modifier locus that alters the level of recombination or segregation and that interacts with loci determining fitness. These models thus constitute a modifier theory of the evolution of sex and recombination (Feldman et al. 1996). In contrast to optimality models, they are explicitly models of individual selection that focus on defining the specific conditions under which alleles acting to regulate the rate of recombination can increase in frequency, and they are dynamic and nonequilibrial. In a single large population with a constant environment, modifiers of recombination (haploid model) or modifiers of segregation (diploid model) can spread only under very restrictive conditions (Otto and Lenormand 2002). Both require weak, negative genetic interactions (across loci for modifiers of recombination, across alleles at the same locus for modifiers of segregation) in a relatively limited parameter space. Only the addition of some sort of structure (spatial, temporal, genetic architecture) permits less restrictive conditions (proposition 6, table 14.1). Examples include structure generated by selection fluctuating over time for a single species, or for two or more interacting species (Red Queen); structure imposed by selection that varies over space in a system including migration; structure arising via the interacting effects of genetic drift and linkage (Hill-Robertson effects); and structure generated by epistasis and genomic architecture.

Key Optimality Models of the Evolution of Sex

The Fisher-Muller Model

While some early arguments regarding the evolution of sex focused on the generation of new genotypes (Weismann 1891; East 1918), it is clear that in the absence of nonrandom associations of alleles across loci (linkage disequilibrium), the creation of new beneficial combinations of alleles by recombination is exactly balanced by their loss (Felsenstein 1988). It is

only in the presence of negative linkage disequilibrium (the presence of an excess of haplotypes containing both beneficial and deleterious alleles) that recombination gives a benefit. Both Fisher (1930) and Muller (1932) described a model where recombination was advantageous within a population because it brought together favorable mutations that initially arose on different genetic backgrounds (and so arose in negative linkage disequilibrium, to use modern terminology; proposition 3, table 14.1).

The Fisher-Muller model posits a population that is finite but large enough so that multiple advantageous mutations can arise during the same time period. In the absence of recombination, new mutations arising on different genetic backgrounds (in negative disequilibrium) cannot go to fixation at the same time. They necessarily compete against one another unless they arise in the same clonal lineage. The advantage to the population is in the rate of fixation of beneficial mutations, and so a "rate of evolution" optimality argument lies at the heart of this model. Finite population size is an important aspect pointed out by Felsenstein (1974, 1988). In an infinite population, two new mutations would each arise at a rate governed by the mutation rate, μ, and a proportion μ_2 of new individuals (in a haploid population) or new gametes (in diploids) would be double mutants. The population would then be in linkage equilibrium, and recombination would give no advantage to such a population over a population without recombination.

Related to the Fisher-Muller model is the Hill-Robertson effect or Hill-Robertson interference (Hill and Robertson 1966; Felsenstein 1974), which describes an interaction between genetic drift and selection caused by genetic linkage. In a finite population, as described above for complete linkage (for asexual lineages), linked genes interfere with each other's ability to fix. With free recombination, a favorable mutation that arises is "seen" by selection against many different genetic backgrounds. Good and poor backgrounds on average tend to cancel each other out, and thus the average fitness of individuals carrying the mutation will depend only on the selective advantage of the particular mutation. In the case of linkage, the chance association between the favorable mutation and the genetic background will tend to persist. The average fitness of individuals carrying the mutation will now also depend on the genetic background within which it arose. Beneficial mutations arising on good backgrounds will increase in frequency more than equally beneficial mutations arising on poor backgrounds. This leads to greater variation in fitness for individuals carrying beneficial mutations, and thus increases the random variation in the frequency of such mutations from generation to generation. In effect, linkage

increases the amount of genetic drift accompanying selection and causes a reduction in the effective population size for the locus where the beneficial mutation arose. The chance that the favorable mutation will fix will thus be less, on average, under linkage than under free recombination. This is true even in the absence of any epistatic effects between loci; Hill and Robertson (1966) assumed additive fitness effects. Interference between beneficial mutations can reduce the rate of accumulation of beneficial mutations even in fully sexual populations, by decreasing the average probability that an individual new mutation will fix by a proportion that depends on the density of adaptive sweeps (Weissman and Barton 2012).

Muller's Ratchet

The modern interpretation of the model proposed by Muller (1964) focuses on deleterious mutations, but in truth Muller's ratchet is a variant of the earlier Fisher-Muller model (Felsenstein 1988). We imagine an asexual lineage with some number of loci where deleterious mutations may arise. In a population of finite size, these may occasionally fix owing to drift. Once a deleterious mutation is fixed, the number of deleterious mutations in the most fit haplotype (the haplotype with the lowest number of deleterious mutations) increases from n to $n + 1$. Correspondingly, the population mean fitness decreases, and the "ratchet" clicks forward. In the absence of back-mutation and recombination, there is no way to regain the more fit, n mutation haplotype, and so as is true of a physical ratchet, there is no way to move backward to higher fitness. How does recombination allow a population to escape the ratchet? Recombination between haplotypes containing deleterious mutations at two different loci leads to a haplotype containing both mutations and another free of both mutations. The haplotype with one fewer deleterious mutation can thus be reconstituted by recombination.

Felsenstein (1988) pointed out that Muller's ratchet is a variant of the Fisher-Muller model, if we focus on the unmutated, favorable variant at each locus. The difference between this formulation and the original Fisher-Muller model is that in considering Muller's ratchet, we are assuming that the beneficial alleles are at high frequency because the beneficial alleles are the preexisting wildtype alleles, whereas in the Fisher-Muller model the beneficial alleles are new mutations and thus start at low frequency.

The optimality criterion here is the expected number of individuals in the optimal, zero mutation class. A higher expected number for this class

means a higher mean fitness for the population because it is assumed that fitness drops with the number of mutations; thus, this model focuses on genetic load. The relative fitness of an individual with k mutations is $(1 - s)^k$, where s is the selective disadvantage per mutation. For a finite population of size N undergoing deleterious mutations at a rate of U per genome per generation, the expected number of individuals in the zero class is given by Haigh (1978):

$$E(n_0) = Ne^{-U/s}. \tag{14.1}$$

If $E(n_0)$ is large, Muller's ratchet moves slowly if at all, and deleterious mutations accumulate independently of one another. If $E(n_0)$ is small, the ratchet rapidly moves the population distribution along k, increasing the number of deleterious mutations in the average individual. The process is most important for slightly deleterious mutations and small populations, where drift can drive the ratchet. This process, all other things being equal, sets an upper limit on the genome size of strictly asexual lineages; if U increases as genome size increases, then $E(n_0)$ necessarily decreases as genome size increases, making the ratchet more important for larger genomes (Maynard Smith 1988a). This has been an argument for why lineages of asexual eukaryotes (with larger genome sizes) should not persist over long evolutionary timescales.

The Red Queen and Her Court

In addition to linkage disequilibrium generated stochastically, there are a large number of models of the evolution of sex where the linkage disequilibrium broken up by recombination is generated deterministically. In these models, epistatic interactions can be generated by selection fluctuating over time or space. Perhaps the most well-known members of this family of models are based on the Red Queen model (Van Valen 1973), so-named for a famous passage in Lewis Carroll's *Through the Looking-Glass* (1871), "it takes all the running you can do, to keep in the same place," an allusion to the need to constantly evolve in order to maintain current fitness in a changing environment. In the presence of environmental fluctuations (either abiotic or biotic), the optimal genotype changes from generation to generation (Jaenike 1978a; Hamilton 1980; G. Bell 1982). As pointed out by Maynard Smith (1988b, 1988a), this type of environmental fluctuation over time leads to selection favoring changes in the sign of linkage disequilibrium. For example, if the combination A_1B_1 is favored

in one generation, linkage disequilibrium will build up owing to an overrepresentation of that allelic combination. When this combination is no longer favored, recombination breaking up linkage disequilibrium will be favored. Selection therefore leads both to cyclical changes in multilocus genotype frequencies and to changing linkage disequilibrium.

Another family of models that also depends on selection to generate linkage disequilibrium includes those where the important environmental variation is spatial rather than temporal. These often focus on the benefit of recombination in the context of local competition among relatives, contrasting the production of genetically more homogeneous offspring with genetically heterogeneous offspring (Lenormand and Otto 2000). In one such model, termed the "tangled bank" (G. Bell 1982), genetic diversity translates into the ability to occupy ecologically diverse environments. In a spatially complex environment with heterogeneous resources, sexually produced offspring can exploit the complex environment more completely than can asexual offspring, who must compete with one another for a limited portion of the resources; the benefit of recombination here rests in the decrease in within-brood competition (Ghiselin 1974a; G. Bell 1982; Koella 1988). Another type of model that focuses on environmental heterogeneity is the lottery model in which genetically diverse offspring are more likely to include individuals of high fitness (G. C. Williams 1975; Maynard Smith 1976b). It is clear that the relative grain size of environmental heterogeneity versus the dispersal distance for offspring has an important effect. Production of genetically diverse offspring is also beneficial in a lottery model when local conditions change over time so that, in effect, the environment becomes heterogeneous for a spatially static distribution of genotypes (resulting in a Red Queen scenario), rather than the genotypes moving across a heterogeneous environment owing to dispersal. For both, recombination in a lottery model leads to an increased spread of genotypes over a fitness landscape (Vos 2009).

For the tangled bank, lottery, and Red Queen models, linkage disequilibria are formed via deterministic, nonrandom processes involving epistasis and population structure. They are in effect infinite-population size models, in contrast to the Fisher-Muller model where the linkage disequilibria underlying the benefit of recombination are formed via random, stochastic processes such as mutation in a finite population or drift caused by finite population size (proposition 4, table 14.1). The interacting effects of finite population size and selection are a key component to current models of the evolution of recombination, considered below.

Modifier Theories of the Evolution of Sex and Recombination

Modifier Theory in Large Populations

Two differing evolutionary forces act on modifiers of recombination: short-term selection on individuals favoring those having the highest mean offspring fitness, and long-term selection to increase the genetic variation in population fitness (Barton 1995; Otto and Lenormand 2002) (proposition 5, table 14.1). A theory considering the fate of a modifier allele (M) that alters the recombination rate between a set of loci must include analysis of both the association between those loci (linkage disequilibrium, D) and the amount and type of fitness interaction between the loci (epistasis, ε) (Nei 1967; Feldman et al. 1980; Feldman et al. 1996; Otto and Feldman 1997). If we define epistasis as the difference between allelic effects on fitness in unison and what we expect from the individual locus effects, we see that epistasis generates linkage disequilibrium of the same sign. Positive epistasis results in a greater improvement in fitness in unison for beneficial alleles and a less severe decrease in fitness for deleterious alleles (fig. 14.1), and thus leads to an overrepresentation of the allelic combination relative to that expected from the marginal frequencies (positive linkage disequilibrium, $D > 0$). Negative epistasis generates negative linkage disequilibrium ($D < 0$) and always favors recombination via its long-term effect on population fitness (proposition 3, table 14.1) as described above for optimality models. Recombination within allelic combinations of intermediate fitness (combining both beneficial and deleterious alleles and exhibiting negative D) results in haplotypes with high fitness (where beneficial alleles have been brought together) and haplotypes of low fitness (where deleterious alleles have been brought together), increasing the genetic variation in population fitness and allowing long-term selection to act. The short-term effects of recombination are more complex, however, and depend on the signs of both D and ε and on the form of selection on the loci.

In models for the evolution of recombination via modifiers, the focus is on the change in frequency of the modifier allele, Δp_M. Under weak selection, where alleles at two loci, A and B, change fitness by small amounts s_A and s_B individually and by s_{AB} when present together, the change in frequency for a modifier allele changing recombination by a small amount ∂r is given by

$$\Delta p_M = -\frac{\partial r\, p_M q_M D}{r_{MAB}}\left[\varepsilon + s_A s_B\left(\frac{1}{r_{MA}} + \frac{1}{r_{MB}} - 1\right)\right], \tag{14.2}$$

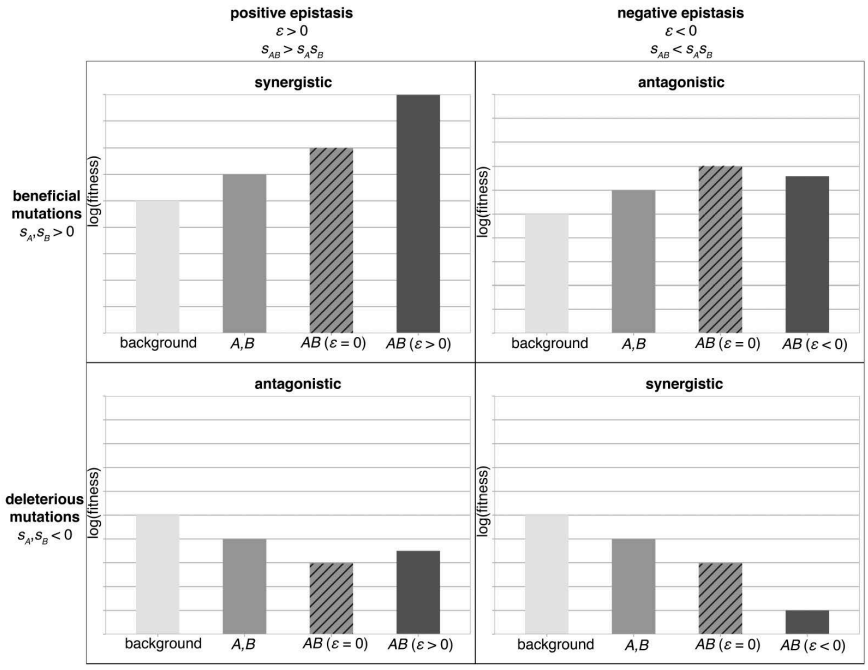

Figure 14.1. Relationship between positive vs. negative fitness epistasis, and antagonistic vs. synergistic fitness effects. Epistasis shown as deviation from multiplicative fitness ($\varepsilon = s_{AB} - s_A s_B$) with equal effects of the alleles A and B individually ($s_A = s_B$) to more easily contrast the individual effects with those of the alleles in unison (s_{AB}). Log(fitness) utilized so that multiplicative fitness effects are additive. Each panel shows: background fitness level (light gray), individual effect of alleles A and B (dark gray), joint effect of A and B in absence of epistasis ($\varepsilon = 0$, dark gray hatched), and joint effect of A and B in presence of epistasis ($\varepsilon \neq 0$, black). Note that positive epistasis implies a greater improvement in fitness in unison for beneficial alleles (synergistic fitness effects) while implying a less severe decrease in fitness for deleterious alleles (antagonistic fitness effects); negative epistasis results in the reverse relationship (smaller improvement in fitness in unison for beneficial alleles [antagonistic] and greater decrease in fitness for deleterious alleles [synergistic]).

where r_{MAB} is the rate of recombination for M, A, and B, r_{MA} is the rate for M and A, r_{MB} is the rate for M and B, and ε is the amount of epistasis, measured here as the deviation from multiplicative fitness, $\varepsilon = 2s_{AB} - s_A s_B$ (adapted from eq. A1.5e, Barton 1995). This change in allele frequency reflects both the short- and long-term effects of selection on the modifier allele. Negative D acts to make the change in the modifier frequency positive (as long as the term in the square brackets in 14.2 is positive) and is sensitive to the rate of recombination between the modifier locus and the fitness loci (r_{MAB}). The modifier allele must stay in association with the beneficial

allelic combination it creates long enough for their increase in frequency to lead to an increase in frequency of M, a result of the long-term effects of selection. In contrast, the effect of short-term selection is more complex. The effect of changing the average fitness of offspring is greatest when D and ε have opposite signs, or more exactly, when $(\varepsilon + s_A s_B)D < 0$ (Otto and Lenormand 2002). Although epistasis generates disequilibrium of the same sign, other factors can generate either positive or negative disequilibrium; for example, spatial correlations in selection coefficients can generate positive disequilibrium, while random genetic drift can generative negative disequilibrium. These and other forces can influence the relative effect of epistasis on the short-term results of recombination.

In this model, recombination modifiers of small effect are favored in response to two forces: fluctuating epistasis and directional selection. Fluctuating epistasis may arise in the presence of biotic coevolution, as in Red Queen-type models, if the epistasis imposed by one species is in direct response to linkage disequilibrium arising in the other species (Nee 1989). Less restrictive are the conditions under which recombination modifiers are favored in response to directional selection: epistasis between loci must be both weak and negative (Barton 1995). Weak epistasis seems plausible under many biologically reasonable scenarios, but whether epistasis is generally negative is less clear. Theory on fitness interactions between loci has posited that negative epistasis arises from stabilizing selection on additive quantitative traits (Maynard Smith 1988a; B. Charlesworth 1993) or that negative epistasis is necessary to avoid excessive mutational load under deleterious mutations (Kondrashov 1988, but see MacCarthy and Bergman 2007). While work on artificial gene networks has suggested that negative epistasis can evolve as a consequence of sexual reproduction (Azevedo et al. 2006), it is not clear if natural gene networks have the same type of connectivity (Leclerc 2008). Empirical studies measuring epistasis have found mixed results, with some reporting $\varepsilon < 0$, some finding $\varepsilon > 0$, and some finding variable or no epistasis (summarized in de Visser and Elena 2007 and Kouyos et al. 2007, see references therein).

Modifier Theory in Small Populations: The Importance of Drift

The relative roles played by linkage disequilibrium and epistasis in promoting the spread of recombination modifiers becomes much easier to disentangle when drift acts as a stochastic force generating nonrandom associations. Directional selection acting on beneficial alleles in finite populations generates negative linkage disequilibrium (on average) because

associations in positive linkage disequilibrium (either beneficial with beneficial or deleterious with deleterious alleles) are rapidly either fixed or lost when they arise by chance (Barton and Otto 2005). Combinations uniting beneficial and deleterious alleles persist the longest, causing recombination modifiers to increase in frequency. The strongest examples of this effect are seen in small populations (Otto and Barton 2001), in large populations with genetic drift imposed by spatial structure (G. Martin et al. 2006), or in populations subject to directional selection at multiple loci (Iles et al. 2003). This effect of genetic drift in conjunction with directional selection requires a high rate of beneficial sweeps acting to remove haplotypes in positive disequilibrium. In populations of small ($2N = 100$) to intermediate ($2N = 10^4$) sizes, Otto and Barton (2001) showed that this effect of linkage disequilibrium generated by random genetic drift was often stronger than the effect caused by selection for recombination generated by epistasis.

Drift is acting in the background of all populations, large and small. A truly synthetic theory for the fate of recombination modifiers needs to allow for the stochastic effects of finite population size. In discussing Hill-Robertson interference, I noted that linkage increases the amount of genetic drift accompanying selection near a selected locus, reducing the effective population size for the locus where the beneficial mutation arose (or, conversely, in the presence of purifying selection against deleterious mutations). Keightley and Otto (2006) showed that purifying selection against repeated deleterious mutations provided an advantage to modifier alleles and, what is more striking, that this advantage increased with increasing population size. The advantage arises because recombination frees the focal locus from Hill-Robertson interference, thus allowing deleterious mutations to be purged by selection. This advantage was greater than the force of epistasis in generating disequilibrium, and thus the form of epistasis (its magnitude and sign) is not critical in determining the advantage to the modifier allele. The surprising result that this stochastic effect was larger in larger populations (where genetic drift is overall weaker) is due to the fact that larger populations, all other things being equal, maintain more polymorphic loci, increasing the opportunity for Hill-Robertson interference. The maximum advantage of the recombination modifier occurs for deleterious mutations of intermediate effect, and the conditions corresponding to the largest advantage of sex are those where Muller's ratchet is expected to be strongest (Gordo and Campos 2008). This model gives a truly modern and complete treatment of the role of negative linkage disequilibrium in the evolution of recombination; both selection and genetic

drift play key roles in how selection on a new mutation affects the fate of other loci and how recombination frees loci from the weight of linkage. However, the effects of indirect selection drop off quickly as the rate of sex in the population increases, implying that in the absence of other forces that enhance indirect selection such as spatial or temporal structure, the advantage provided by recombination in the face of purifying selection in finite populations may not be enough to explain the evolution of obligate sex (Roze 2014).

The rate of evolution for recombination modifiers (eq. 14.2) relies on the product of weak epistasis, disequilibria, current allele frequencies, and the incremental change in recombination, and is itself expected to be small. Despite this, experimental results in *Drosophila* have shown relatively large differences in sibling species' recombination rates (True et al. 1996). Whether these are likely to have arisen via this type of weak selection is unknown, although marked differences in the suppression of recombination near the centromere suggest that other mechanistic effects may play a larger role.

The Intersection of Recombination Theory with Genomic Architecture, Epistasis, and Fitness Landscapes

I now turn to a consideration of what recent theory and models of genomic architecture (including the form and extent of epistasis and both the global and local properties of fitness landscapes) can tell us about the generation of linkage disequilibrium and the evolution of sex. As previously discussed, empirical studies measuring epistasis have found mixed results. However, in a multilocus model considering a broad range of epistatic effects, Kouyos et al. (2006) found that epistatic interactions of a given strength could generate very different types of linkage disequilibrium. Epistatic interactions had the greatest impact when selection was weak, and so the evolution of recombination under mutation-selection balance might be driven by a small number of interactions under weak selection, rather than by the average epistasis of all interactions. It is this latter quantity that is generally measured in empirical studies, leaving open the question as to whether epistasis is a major force in generating the linkage disequilibrium that can drive the evolution of recombination.

How are epistatic interactions generated biologically and when might we expect to see the negative epistasis predicted by theory to favor recombination and sex? One ecological explanation for the generation of negative epistasis is density-dependent regulation of population size under

limiting resources via truncation selection (Crow and Kimura 1979; Kondrashov 1988; de Visser and Elena 2007). If individuals carrying more than some threshold number of deleterious mutations are completely inviable while individuals that fall under the threshold survive, selection imposes an extreme form of negative epistasis. Metabolic control theory also predicts negative epistasis under some conditions (de Visser and Elena 2007). Szathmáry (1993) showed that selection for maximum flux along an enzymatic pathway caused deleterious mutations to show positive epistasis, while selection for optimum flux caused negative epistasis. If maximum flux is important with plentiful resources, but optimum flux is important when resources are scarce, negative epistasis should be observed under highly competitive (low resource) situations (de Visser and Elena 2007).

Kondrashov's (1984, 1988) mutational deterministic hypothesis posits that negative epistasis amongst deleterious mutations is necessary to avoid excessive mutational load. If the per generation genomic deleterious mutation rate is greater than one ($U > 1$), the more efficient removal of deleterious alleles in the presence of recombination leads to an advantage of sex that can be more than twofold, overcoming the twofold cost of producing males. He argued that selection acting on many deleterious mutations independently leads to a mutational load incompatible with survival (in populations of moderate size) unless there is synergistic epistasis between deleterious alleles (negative epistasis for their deleterious effects [Kondrashov 1995]). Finding large values of U may thus be indirect evidence of negative epistasis for deleterious mutations. For this to be a general explanation for the evolution and maintenance of sex and recombination, both $U > 1$ and synergistic epistasis for deleterious mutations would need to be common. In organisms where genomic mutation rates have been estimated, there is mixed support for genomic mutation rates greater than one, with evidence of U near or above one in at least some eukaryotes (de Visser and Elena 2007; Kouyos et al. 2007; Hartfield and Keightley 2012).

The mutational deterministic hypothesis focuses on the overall genomic rate of deleterious mutations and the resulting load experienced by populations. However, the distribution of mutational effects is also important. If both mildly deleterious alleles and strongly deleterious alleles occur, purging of strongly deleterious alleles by selection decreases effective population size, thereby increasing the strength of genetic drift, the rate of accumulation of mildly deleterious alleles, and the rate of Muller's ratchet (Gordo and Charlesworth 2001).

We need also to consider the interaction between sex and genetic architecture. Negative epistasis can be caused by genetic robustness—phe-

notypic stability or invariance in the face of repeated mutation or other perturbations (de Visser and Elena 2007). In this way, genetic robustness may itself favor recombination. This robustness, however, comes at a cost; it allows mutations to accumulate within the genome, eventually leading to a dramatic decrease in fitness. A. Gardner and Kalinka (2006) showed that intermediate levels of recombination allowed lineages to escape this cost. Recombination breaks down the association between the target gene, which is subject to deleterious mutations, and the robustness gene, decoupling the short-term benefit of robustness (increased fitness in the presence of a mutation) from the long-term cost (increased frequency of mutations at mutation-selection balance). This decoupling causes the benefit to be reaped only by the robust individuals, while the cost is paid by the entire population in the form of mutation load.

Recombination itself may cause negative epistasis, increasing the opportunity for its own evolution and persistence. Since recombination increases the variability in genetic backgrounds experienced by any particular locus from one generation to the next, it may select for greater genetic robustness in sexually reproducing organisms, which in turn generates negative epistasis. As discussed earlier, models using artificial gene networks showed that recombination increased negative epistasis by increasing robustness (Azevedo et al. 2006); however, whether natural systems are under this type of selective pressure is unclear. Rapid advances in the understanding of gene networks and the use of genomic data may answer this question.

More complex forms of epistasis are important in considering the potential advantages and disadvantages of recombination in the face of adaptive evolution. An important category of epistasis is sign epistasis, where the sign of an allele's fitness effect (whether it is beneficial or deleterious) varies across genetic backgrounds (Weinreich et al. 2005). This type of allelic interaction creates a "rugged" fitness landscape, with local minima and maxima, and constrains the possible pathways that can be taken by adaptive evolution (Crona et al. 2013). Consideration of the effects of sign epistasis and complex adaptive landscapes has led to contradictory results. Using an empirically derived fitness landscape showing sign epistasis between individually deleterious mutations, de Visser et al. (2009) used simulations of asexual and sexual populations to show a general disadvantage to recombination. They found a slight advantage of sex during early stages of adaptation, likely due to the formation of allelic combinations needed to reach local optima via the breakup of negative linkage disequilibrium, a Fisher-Muller effect. However, recombination generally prevented populations from escaping local maxima by breaking down "escape" genotypes.

In contrast to that study, which assumed uniform recombination across a nonstructured genome, Watson et al. (2011) considered a model with explicitly modular genomes. Their approach viewed genes as necessarily modular units within the larger genome, with tight linkage and high epistasis between sites within a locus, and free recombination and low or no epistasis between sites on different loci. This work borrows from ideas in evolutionary computation theory and the genetic algorithm literature, where genetic algorithms with sexual recombination outperform mutation-only algorithms owing to their ability to select on and recombine larger building blocks rather than small changes. In this optimality model, they considered not only how quickly sexual and asexual populations converged on the fittest genotype, but also whether the populations could escape local optima. Their individual-based simulations found the same "speed advantage" to recombination that is seen in the classic Fisher-Muller model, and also found that asexual populations became trapped in local optima, while the sexual populations were able to access the globally optimal genotype. By considering a fitness landscape that has different selectively accessible routes between alleles via mutation, we see that recombination frees alleles from their genetic backgrounds; in the absence of recombination, genotypes rather than alleles compete for fixation. Without recombination between loci, competition between alleles at one locus is interfered with by competition between alleles at other loci, so that clonal interference (as defined by Gerrish and Lenski 1998) not only slows the rate of evolution but also limits the net increase in fitness achievable via adaptive evolution.

Further computer simulation work that considered so-called "tunably rugged" fitness landscapes found a transitory advantage to recombination, which reverses at longer timescales when recombining populations are more likely to become trapped at local fitness peaks (Nowak et al. 2014). These studies deal with population dynamics at the limit where selection is strong compared with recombination, i.e., at the limit of tight linkage. An open question is how populations under relatively weak selection respond to these types of fitness landscapes. With relatively weak selection, recombination would be expected to play a greater role in breaking up linkage disequilibrium, allowing sexual populations to follow trajectories defined by "allele frequency space" rather than "genotype sequence space" (Watson et al. 2011), and thus escape the trap of local fitness maxima.

Finally, the time dependence of the advantage found by Nowak et al. (2014) necessitates consideration of fitness landscapes that themselves change with time. Under a changing fitness landscape, the transitory ad-

vantage of recombination can continue indefinitely, as long as the timescale of fitness landscape change is shorter than the timescale of advantage for asexual populations. A similar result was found for a model considering the fate of modifiers of recombination (amongst other evolutionary forces) under changing environments. Here, the evolutionary dynamics of recombination modifiers were shown to be sensitive to the particular details of environmental fluctuations (Carja et al. 2014). The rate of recombination evolved toward a nonzero value that decreased with increasing environmental variability, again pointing out the key importance of timescale. However, this model assumed an infinite population size, and so the effects of drift in generating negative linkage disequilibrium amongst selected loci were not considered. An obvious link exists between these findings and the Red Queen family of models where selection varies across time and/or space, and we once again see the importance of heterogeneity in expanding the conditions under which recombination is favored (proposition 6, table 14.1).

In the Absence of Sex: What the Study of Asexuality and Clonal Reproduction Can Tell Us about the Evolution of Sex and Recombination

The relative rarity of ancient asexual lineages within eukaryotes has been seen as evidence of the importance of sex and recombination. How, then, are those few ancient asexuals managing in the absence of sex? While it is not easy to prove a negative, so that a lack of evidence for sex is not quite the same thing as evidence for asexuality, ancient asexual lineages are thought to exist within protists, plants, fungi, and animals (Judson and Normark 1996). While there are large and diverse clades with no ancient asexual species, such as in the angiosperms where all fully asexual species are thought to be closely related to sexual species (Whitton et al. 2008), the fact that long-term asexuality can be found across the tree of life is nevertheless intriguing. Within these asexual lineages, there are groups both ancient and species rich, such as the bdelloid rotifers, the darwinulid ostracods, and various groups within the oribatid mites, implying that they are managing without sex quite well indeed (Mark Welch and Meselson 2000; Schön and Martens 2003; Maraun et al. 2004; Schaefer et al. 2006).

What can these "evolutionary scandals" (to paraphrase Maynard Smith 1986) tell us about the theory of the evolution of sex? Recent genomic work in the bdelloid rotifers implies that they have come up with alternative ways to slow Muller's ratchet and to generate the genetic variation nec-

essary to escape from local fitness optima. Flot et al. (2013) give evidence of ongoing horizontal gene transfer, likely mediated via double-stranded DNA breaks caused by repeated cycles of desiccation. Double-strand breaks also promote gene conversion during repair; concerted evolution mediated by gene conversion is proposed to slow Muller's ratchet, allowing restoration of the fittest genotype. As discussed above, a eukaryote with a relatively large genome in a finite population should be constantly accumulating deleterious mutations. In the model of Connallon and Clark (2010), gene conversion acts to increase the expected size of the zero-mutation class, $E(n_0)$ (eq. 14.1). In the work by Watson et al. (2011) discussed previously, the benefit of recombination in allowing populations to reach higher fitness maxima depended on the ability of the population to generate allelic diversity or to exploit standing genetic variation. Horizontal gene transfer produces genotypes that could not be produced by a single asexual lineage, allowing asexual lineages to escape local fitness maxima in much the same way that recombination frees sexual lineages from the same fate.

Another example where genomic architecture may facilitate long-term asexuality can be found in the ciliate *Tetrahymena*, where some asexual lineages may be millions to tens of millions of years old (Doerder 2014; Zufall 2016). Amicronucleate lineages of *Tetrahymena* that have lost the germline micronucleus, which allows for sexual reproduction, still retain a somatic macronuclear genome containing approximately forty-five copies of each chromosome. The process of "phenotypic assortment," which produces asexual progeny that differ in the number of copies of segregating alleles, generates genetic variation and allows selection to purge deleterious mutations, again providing a means for slowing Muller's ratchet in the absence of recombination (Zufall 2016). Thus, in lineages with long-term asexuality, genomic processes such as gene conversion, horizontal gene transfer, and phenotypic assortment may provide alternatives to sexual recombination for breaking up negative disequilibrium and allowing an escape from long-term population fitness decline (proposition 7, table 14.1).

Finally, a vast number of organisms engage in both asexual and sexual reproduction, with populations switching serially between the two modes, or having individuals follow one or the other route to reproduction within a generation. In models of these types of systems, increased asexual reproduction and decreased sexual reproduction can lead to higher mutation load and lower mean fitness (Muirhead and Lande 1997; Pálsson 2001). However, increased asexual reproduction can sometimes lead to higher mean fitness under relatively high genomic mutation rates (Marriage and Orive 2012). A key aspect is the relative numbers of recessive deleterious

mutations held in heterozygous or homozygous form; thus the interaction of ploidy and segregation with recombination is a vital consideration. When trade-offs exist between the proportions of the population undergoing asexual and sexual reproduction, including selfing, asexual reproduction leads to the maintenance of recessive or partially recessive deleterious mutations in heterozygous form and can shield a proportion of the population from deleterious mutations arising meiotically (Marriage and Orive 2012). Sexual reproduction in diploids can bring together deleterious mutations whose individual fitness effects would otherwise be unseen by selection; asexual reproduction in diploids acts to freeze this within-locus variation.

A recent review of empirical studies considering species with rare or cryptic sex (Hartfield 2016) found inconsistent evidence for the type of within-individual allelic sequence divergence expected under long-term asexual reproduction (the "Meselson effect" [Mark Welch and Meselson 2000; Butlin 2002]). It is not yet clear whether this less than expected amount of allelic divergence is caused by gene conversion or by other genome-wide forces such as the effects of linked selection. However, it is clear that a more nuanced understanding of how genetic diversity is shaped in the absence of sexual recombination will in turn greatly aid our understanding of how genetic diversity is shaped in its presence.

Overview and Summary

The theory of the evolution of sex is one of the richest and most quantitatively sophisticated bodies of theory within evolutionary biology. There are any number of ways to classify the various types of models within this field, and a rich history of these types of classifications exists (e.g., Maynard Smith 1978a; G. Bell 1982, 1985; Michod and Levin 1988; Kondrashov 1993; Feldman et al. 1996; Otto and Lenormand 2002). I have chosen to focus on the theory of recombination and to contrast two main theoretical approaches: optimality theory and modifier theory. These two approaches differ fundamentally in the role of selection: optimization of a specific criterion, often under implicitly group selection arguments, versus changes in recombination modifier frequency via direct individual selection. Tests of both of these bodies of theory, carried out in various experimental systems, give support for the potential role played by both types of selection, and utilization of genomic techniques and fitness assays points to the importance of various forces identified in the corresponding theories. For example, comparison of fitness after experimental adaptation in sexual and

asexual populations of yeast showed an increase in the rate of adaptation (the optimality criterion under consideration) in sexual populations (M. J. McDonald et al. 2016). Whole-genome sequencing of whole-population samples showed clear evidence that recombination alleviates clonal interference in the sexual populations, yielding a group-level advantage to sex. Experiments considering the maintenance of sex within populations of facultatively sexual rotifers have shown higher rates of sex evolving in spatially or temporally heterogeneous environments (Becks and Agrawal 2010, 2012). The fitness distributions of both sexual and asexual progeny give evidence that, at least under temporally changing environments, it is the long-term advantage of recombination in generating more variable progeny that results in an increase in sex (proposition 5, table 14.1).

In addition to differing with regard to the action of natural selection, there exists a clear contrast in how these two bodies of theory originated and developed, and in what aspects of the evolution of sex they sought to explain; my formalization of the constitutive theory of the evolution of sex makes this distinction clear. Historically, optimality theory and modifier theory differ in where they lie along an axis of verbal to quantitative models (Phillips, chap. 4). The initial development of the optimality theory of recombination was largely verbal (e.g., Fisher 1930; Muller 1932), although later work framed these ideas in an explicitly mathematical way. In contrast, modifier theory was from the very start a highly mathematical body of models, with an explicit relative frequency (and therefore relative fitness) approach to tracking the fate of modifiers of recombination. In addition, the equilibrium versus nonequilibrium nature of optimality versus modifier theory can also be seen to reflect a different frame of reference for the question "Why recombination?" Optimality theory contrasts populations with and without sexual recombination and describes key differences between them; modifier theory asks what processes actively shape the evolution of sexual recombination. In general, recombination theory has moved decisively to a more quantitative, process-focused body of theory, mirroring other bodies of evolutionary theory in this regard.

At the core of modern theory for the evolution of sex is the buildup and breakdown of linkage disequilibrium and the role that negative linkage disequilibrium plays in favoring the evolution of recombination. This negative linkage disequilibrium, whereby positive and negative fitness alleles find themselves bound on the same genetic background, can be generated both stochastically and deterministically. A great deal of the more recent theory for how evolution can favor recombination focuses on determining the relative roles of genetic drift due to finite population size and of epis-

tasis generated by selection in creating negative disequilibrium, all in an explicitly mathematical framework.

Recent theory has also considered the intersection of recombination theory and aspects of genomic architecture, such as the form and extent of epistasis, as well the global and local properties of fitness landscapes. As genomic data become more readily available, both for organisms undergoing recombination and for those lineages that have apparently evolved alternative ways to both generate genetic diversity and avoid the buildup of deleterious mutations in the absence of recombination, we are seeing ways in which existing theory is supported. But there are also indications that a simple explanation is unlikely for this "queen of problems." For example, the use of computer simulations and genetic algorithms highlights the importance of considering both the details of genomic modularity and the timescale under which evolution is considered. The presence of sex across the evolutionary tree of life, in organisms with populations both large and small, and in genomes with widely disparate architectures, argues for a view that the reality of sex, much like the theory needed to fully explain its evolution and persistence, is multifaceted and complex.

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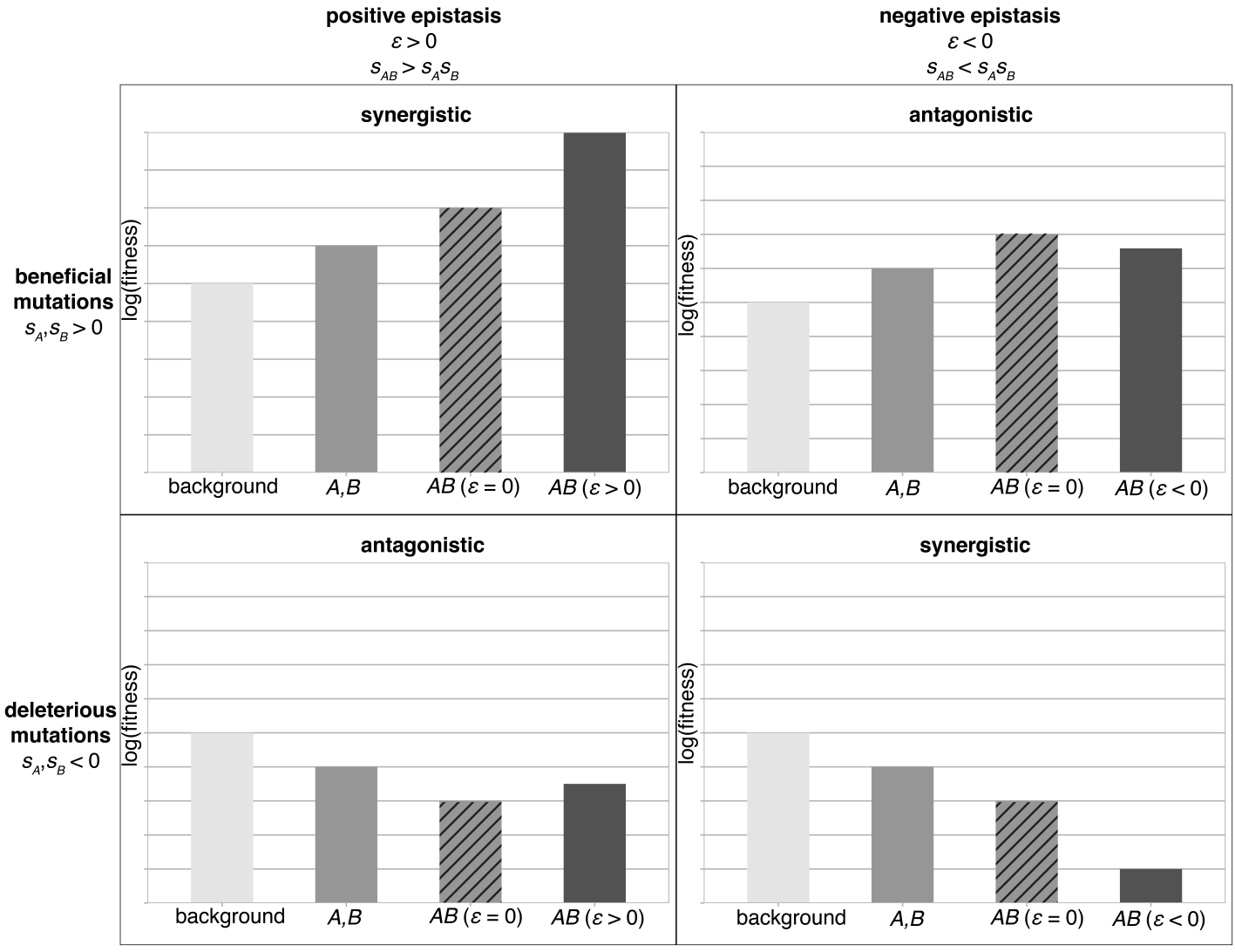
positive epistasis
$\varepsilon > 0$
$s_{AB} > s_A s_B$
negative epistasis
$\varepsilon < 0$
$s_{AB} < s_A s_B$
beneficial mutations
$s_A, s_B > 0$
deleterious mutations
$s_A, s_B < 0$
synergistic
antagonistic
antagonistic
synergistic
log(fitness)
background
A,B
AB (ε = 0)
AB (ε > 0)
AB (ε < 0)

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