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ORIGINAL ARTICLE

Relative effects of segregation and recombination on the evolution of sex in finite diploid populations

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The mechanism of reproducing more viable offspring in response to selection is a major factor influencing the advantages of sex. In diploids, sexual reproduction combines genotype by recombination and segregation. Theoretical studies of sexual reproduction have investigated the advantage of recombination in haploids. However, the potential advantage of segregation in diploids is less studied. This study aimed to quantify the relative contribution of recombination and segregation to the evolution of sex in finite diploids by using multilocus simulations. The mean fitness of a sexually or asexually reproduced population was calculated to describe the long-term effects of sex. The evolutionary fate of a sex or recombination modifier was also monitored to investigate the short-term effects of sex. Two different scenarios of mutations were considered: (1) only deleterious mutations were present and (2) a combination of deleterious and beneficial mutations. Results showed that the combined effects of segregation and recombination strongly contributed to the evolution of sex in diploids. If deleterious mutations were only present, segregation efficiently slowed down the speed of Muller's ratchet. As the recombination level was increased, the accumulation of deleterious mutations was totally inhibited and recombination substantially contributed to the evolution of sex. The presence of beneficial mutations evidently increased the fixation rate of a recombination modifier. We also observed that the twofold cost of sex was easily to overcome in diploids if a sex modifier caused a moderate frequency of sex.
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Keywords: linkage disequilibrium; segregation; recombination; beneficial mutations; modifier model

INTRODUCTION

Sexual reproduction is a costly and risky activity, but it widely occurs in most eukaryotes. This indicates that there is a general advantage for its evolutionary success (Smith, 1978; Barton and Charlesworth, 1998; Otto and Lenormand, 2002). Although previous studies explained the ubiquity of sex, studies are yet to determine why sex evolves and this question remains one of the most difficult questions in modern evolutionary biology (Agrawal, 2006; De Visser and Elena, 2007). Considering genetics, one main consequence of sex is that it tends to mix genotypes, thereby improving the efficiency of natural selection in the presence of negative genetic associations. Negative genetic associations arise when beneficial mutations combine with deleterious alleles at the same or different loci. As a result, the intermediate fitness phenotype increases and the variance in fitness decreases (Roze, 2009). In sexual diploids, two important components can alter genetic associations that accumulate over time. Recombination breaks down associations between alleles among different loci, thereby eliminating negative linkage disequilibrium (LD). Segregation breaks down associations between alleles at the same locus, thereby helping to re-establish Hardy–Weinberg equilibrium (Hadany and Comeron, 2008). In this study, 'modifier' models were used, in which one tracks the fate of a gene that alters reproductive mode (Feldman *et al.*, 1996). We investigate the conditions under which sex evolves as a consequence of recombination or segregation in finite diploids.

The interference between genetic drift and selection could create negative LD. Recent theoretical studies have mainly focused on how the negative LD drives the evolution of sex in haploids (Barton and Otto, 2005; Otto, 2009). Empirical studies have focused on the effects of negative epistasis rather than drift on the evolution of sex for a long time because recombination can eliminate negative LD caused by epistasis (Barton, 1995; Otto and Feldman, 1997). However, if the population is finite or subdivided, Hill–Robertson interference among deleterious mutations at multiple loci favors the evolution of recombination without the requirement of negative epistasis (Otto and Barton, 2001; Iles *et al.*, 2003; Keightley and Otto, 2006; Martin *et al.*, 2006). Hill–Robertson interference states that selection at one locus affects the efficacy of selection at other linked loci (Hill and Robertson, 1966; Felsenstein, 1974; Charlesworth *et al.*, 2009).

In haploid models, the advantages of sex arise as a consequence of recombination because sex is comparable to recombination (Agrawal and Otto, 2006; Agrawal, 2009a, b). However, in diploids, segregation also affects the evolution of sex by changing associations within a locus on homologous chromosomes, and such associations are absent in haploids. Given that most of the arguments are based on recombination modifiers in haploids, the effects of segregation in diploids have not been fully investigated. Using a deterministic mutation–balance model, Otto (2003) first investigated the possible conditions affecting the evolution of sex as a consequence of

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segregation rather than recombination. Otto (2003) further showed that the conditions favoring segregation require that deleterious mutations are partially recessive. Low levels of inbreeding among individuals tend to widen the conditions that favor segregation. Segregation also provides more benefits to the evolution of sex than recombination. However, Otto (2003) did not investigate the effects of finite population size on the evolution of sex, which is a potentially important factor that affects selection for segregation. In finite populations, the interaction between drift and selection strongly favors a recombination modifier (Keightley and Otto, 2006; Gordo and Campos, 2008). Nevertheless, the mechanism by which drift influences the conditions favoring segregation remains elusive. Recently, Roze and Michod (2010) investigated the effects of recurrent deleterious mutations on the evolution of sex in finite diploids. The results have shown that excessive heterozygosity generated by a finite population size is the key component of selection to favor segregation when deleterious mutations are dominant (Roze and Michod, 2010). However, beneficial mutations are not involved in their simulations. In a finite diploid population subjected to deleterious and beneficial mutations, whether or not genetic drift combined with selection provides a greater advantage of segregation than recombination is unclear. This study primarily aimed to provide a direct comparison of the relative contribution of segregation and recombination to the evolution of sex in finite diploids, in which deleterious and beneficial mutations are present.

This study involved two steps to investigate the conditions that favor sex by using computer simulations. First, we investigated the long-term effect of segregation and recombination by determining the mean fitness of a single asexual/sexual population after thousands of generations evolved. Second, we investigated the short-term effect of segregation and recombination by introducing a sex (or recombination) modifier that could spread or fix in an asexual (or a sexual but without recombination) population and measuring the fixation probability of this modifier. In this study, 'segregation' refers to the process by which homologous chromosomes separate, resulting in the segregation of genes into different gametes; gametes from two different individuals then fuse. 'Recombination' refers to the exchange of alleles in different loci of homologous chromosomes in the same individual. Sexual reproduction involves recombination and segregation to produce an offspring (Supplementary Figure S1). By contrast, asexual reproduction produces offspring that directly inherits the same genome of the parent (clone). To quantify the relative strength of these two processes, we assumed that the genome only contained one pair of chromosome. The predictions from the simulations showed that both modifiers of segregation and recombination were strongly favored when mutations occurred in multilocus. In particular, low extent of beneficial mutations remarkably enhanced the effects of recombination.

MATERIALS AND METHODS

General settings of the program

The simulation programs used in this study (written in C++ and available upon request) were somewhat similar to those in haploid models used by Hartfield *et al.* (2010), but our simulations were newly established. In both studies, an infinite number of possible alleles at each locus, the absence of epistasis and no dominance in mutations were considered. This study was based on diploids undergoing recombination and segregation. A homogeneous population consisted of N diploid individuals at the start of a generation. Each individual contained a pair of independently segregating chromosomes with 200 equally spaced loci affecting fitness. N in this study was set at 10 000 and kept constant. This value was relatively small so that the simulation time was acceptable and appeared reasonable at least for some species.

Each individual in the population was initially mutation free and assigned an identical fitness value of 1.0. The number of mutations per generation occurring in each individual was sampled from a Poisson distribution with a mean of U, and the fraction of beneficial mutations was p_b. Hence, the rate of beneficial mutations was equal to Up_b, and the deleterious mutation rate was expressed as $U(1-p_b)$ ($\approx U$ if p_b was small). The genome mutation rate was set at $U=0.5$, which was in the range of U of model organisms (Keightley and Eyre-Walker, 2000; Denver *et al.*, 2004; Halligan and Keightley, 2006; Haag-Liautard *et al.*, 2007). The position of each mutation was randomly assigned in the genome. Fitness effects were multiplicative among loci, where deleterious mutations and beneficial mutations resulted in constant selective coefficients s_d and s_b, respectively. s_d was set from 0.001 to 0.2 because small and high s_d have been observed in eukaryotes (Garcia-Dorado *et al.*, 1999; Loewe and Charlesworth, 2006). s_b was set at 0.02, which was slightly higher than the estimated s_b in *Drosophila* but with some overlaps (Sella *et al.*, 2009). All of the mutations were maintained in the population to estimate the average population fitness. Epistasis among loci was considered absent because epistasis among deleterious mutations is possibly not important to the evolution of sex in finite populations (Keightley and Otto, 2006). Therefore, the fitness w_i of an individual i with k_d deleterious mutations and k_b beneficial mutations was expressed as follows: $w_i=(1-s_d)^{k_d}(1+s_b)^{k_d}$.

Simulation of a fully asexual/sexual population

In this section, each individual in the population produced either fully sexual or fully asexual offspring. For an asexual population, the probability of generating offspring was proportional to the individual's fitness, in which the offspring inherited all of the mutations that the parent carried. However, sexual individuals should form a mating pair to produce an offspring. Both parents were sampled by replacing the proportion with their corresponding fitness. Once chosen as a parent, recombination occurred between homologous chromosomes with a mean value of L, and uniformly distributed among the 200 loci. One of each parent's chromatins was randomly chosen and contributed to half of the chromosome of the offspring.

The aforementioned life cycle was repeated until the simulation reached a defined generation. The mean log average fitness of the population ($\ln W$), the coefficient of variation in fitness (CV) and the numbers of fixed deleterious (N_d) and beneficial (N_b) mutations were recorded at the end of the simulation. $\ln W$ is an appropriate parameter to compare the rate of adaptation of a sexual/asexual population over time. CV measures whether or not sexually produced offspring are more variable in fitness than asexually produced offspring. The runs were repeated 10 times for each parameter combination.

Simulation of a sex modifier

To simulate the fate of a sex modifier, we first allowed an asexual population to evolve N generations based on its life cycle. After this burn-in period, the population could reach an approximate mutation–selection balance, and the status of the population was saved. We then introduced only one sex modifier to a randomly selected position in a randomly chosen individual in this saved population. An individual carrying this modifier did not initially have a sexual partner except itself. We thus allowed this individual to reproduce asexually at the beginning. The number of its offspring may increase because of drift or selection. In each generation, the number of available sexual individuals was counted. If more than one sexual partner were available ($n_{sex}>1$), sexual mode could be possibly spread. If an individual A with a sex modifier was chosen, another individual B was randomly selected from the available sexual individuals based on its fitness to form a mating pair. This pair sexually produced an offspring with a probability p_{sex}. The modifier was assumed dominant, and thus p_{sex} was constant for both heterozygous and homozygous modifier alleles. Recombination events occurred with a mean value of L between homologous chromosomes in both A and B. If the offspring was produced asexually (with a probability of $1-p_{sex}$), its genome was exactly the same as the genome of individual A. This process was repeated until N offspring were created. We also ran simulations based on two different partially sexual saved populations (with a sexual reproducing probability $p_{init}=0.01$ or 0.1) to investigate whether or not sex can invade a population that has already undergone sex at a low rate.

The cost of sex increased with p_{sex}. w_i of the sexual individual was reduced before selection by a factor $C = 1/(1+p_{sex})$, where $w_i = C(1-s_d)^{k_d}(1+s_b)^{k_b}$. C is directly determined by p_{sex}, where $C = 1.0$ corresponds to $p_{sex} = 0$ (for an asexual individual, no cost) and $C = 0.5$ corresponds to $p_{sex} = 1.0$ (for a fully sexual individual, twofold cost of sex). Given that selection is relevant to individual's fitness, C allows us to introduce a direct cost of sex. For instance, in a random mating system of hermaphroditic organisms, sexual female provides all her resources in the same extent as an asexual female, whereas male subjects invest gametes but no resources to the next generation. As a result, the sexual female only produces 50% offspring compared with the sexual female when all else are equal (in this case, $C = 0.5$).

The fate of the modifier was tracked until it was fixed or lost in the population, and we recorded the fixation probability of the modifier u. For each saved population, single modifier was introduced N repetitions to estimate u. This fixation probability u was compared with the fixation probability of a neutral allele $u^\star$ ($u^\star = 1/2N$), to calculate the relative probability of the modifier, $u/u^\star$. We repeated the whole simulation process by using five different 'saved populations' for each parameter combination to calculate average $u/u^\star$.

Simulation of a recombination modifier

The simulation of a recombination modifier is slightly different from that of a sex modifier as follows. A sexual burn-in population without recombination events was simulated and saved. A recombination modifier was then introduced to a randomly selected individual. The modifier increased the expected number of recombination events (L) of its carrier from 0 to 0.5, 1.0 or 1.5. The simulation continued at most N generations or until the modifier was fixed or lost in the population. The fixation probability of the recombination modifier was recorded. A recombination modifier was introduced at least N repetitions in five different saved populations to estimate the average $u/u^\star$.

Estimation of N_e in asexual populations

In this study, the method used to estimate N_e in asexuals here was similar to that of Keightley and Otto (2006). A neutrally linked locus with an initial value of 0 was inserted into the genome of each individual. After a burn in of N generations, the value in each individual was altered in each generation by adding Gaussian noise with a mean value of 0 and a variance of $V = 1.0$. The equilibrium variance is VN for this neutral locus (Lynch and Hill, 1986). The simulation continued for N generations to determine N_e. Ten independent runs were preformed in different saved populations to estimate the average N_e.

RESULTS

Evaluating mean population fitness and variation in fitness

To understand the evolution of sex, we should answer one basic question regarding the effects of sex on fitness: do sexually produced offspring exhibit a higher mean fitness or more variable in fitness than asexually produced offspring? We calculated the mean fitness $\ln W$ after the population evolved 3000 generations. Different selective coefficients of deleterious mutations (s_d) were investigated in cases with only deleterious mutations or with both deleterious and beneficial mutations (Figure 1). In both cases, sexual populations exhibited higher values of $\ln W$ than asexual populations. With solely deleterious mutations ($U = 0.5$, $p_b = 0$), Muller's ratchet was performed in an asexual population, resulting in a continuously decreasing fitness over generations. Segregation removed deleterious mutations more efficiently, thereby slowing down the rate of Muller's ratchet. The occurrence of recombination with all the considered levels ($L \geqslant 0.5$) completely terminated the operation of Muller's ratchet, resulting in a balanced value of $\ln W$ (Figure 1a). In the presence of a small fraction of beneficial mutations ($p_b = 0.02$), recombination resulted in higher $\ln W$ than segregation alone, and $\ln W$ increased with L (Figure 1b). Moreover, $\ln W$ was minimized for some intermediate values of $s_d \approx s_b$ in both sexual and asexual

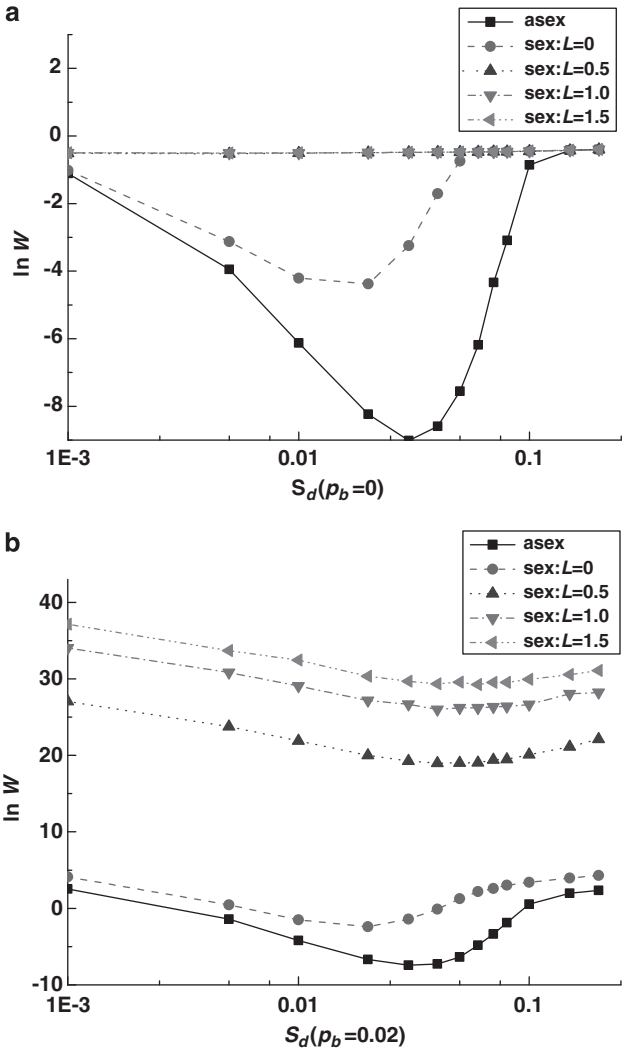

Figure 1 Log fitness $\ln W$ vs coefficient of deleterious mutations s_d. (**a**) $p_b = 0$; (**b**) $p_b = 0.02$. The measurements were taken after the populations evolved 3000 generations. Other parameters used: $U = 0.5$, $s_b = 0.02$.

populations, and this result has been confirmed in asexuals (Bachtrog and Gordo, 2004; Jiang *et al.*, 2011).

Segregation alone ($L = 0$) markedly decreased the fixation number of deleterious mutations N_d, whereas almost no deleterious mutations could be fixed with recombination (Figure 2a). This result was consistent with that observed in the changes of fitness. In the presence of beneficial mutations, more deleterious mutations were fixed by hitchhiking effects (Figure 2b). However, beneficial mutations could offset such negative effects on fitness. In this case, sexual reproduction provided a dual advantage by eliminating deleterious mutations more efficiently and by fixing beneficial mutations more rapidly than asexual reproduction. We also observed that recombination evidently aided the fixation of beneficial mutations compared with the moderate increase caused by segregation (Figure 2c). Furthermore, in the absence of beneficial mutations, the coefficient of variation of fitness (CV) in sexual populations was slightly higher than that in asexuals (Figure 3a). By contrast, in the presence of beneficial mutations, recombination significantly increased CV (Figure 3b). This result indicated that beneficial mutations resulted in sexually

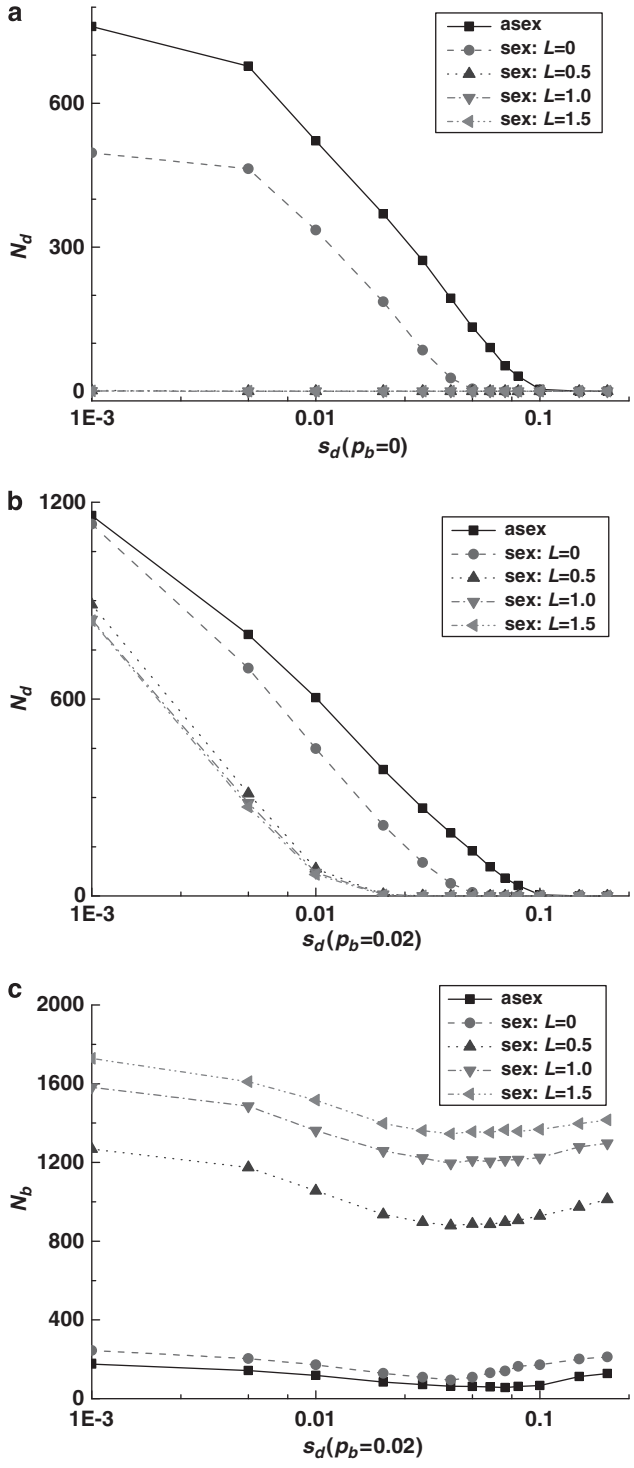

Figure 2 Number of the fixed deleterious (beneficial) mutations N_d (N_b) vs coefficient of deleterious mutations s_d. (**a**) $p_b=0$; (**b**, **c**) $p_b=0.02$. Parameters used were the same as those used in Figure 1.

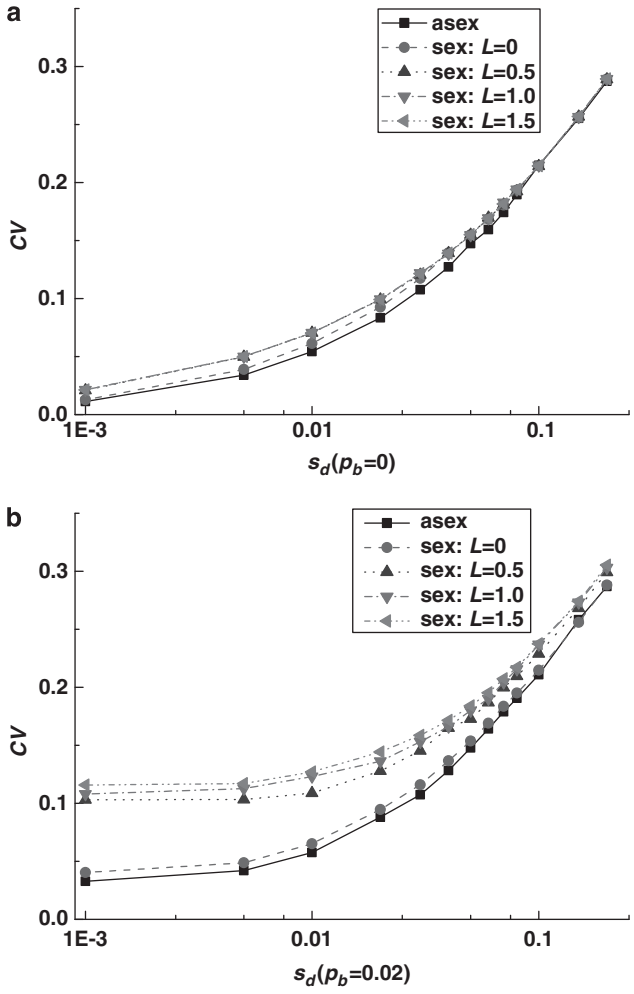

Figure 3 Coefficient of variation of the mean population fitness CV vs coefficient of deleterious mutations s_d. (**a**) $p_b=0$; (**b**) $p_b=0.02$. Parameters used were the same as those used in Figure 1.

produced offspring exhibiting more variable in fitness than asexually produced offspring.

Selection on a sex modifier

We investigated whether or not segregation and recombination can allow sex to invade an asexual population by tracking the fate of a sex modifier that was introduced to an asexual population. The relative fixation probabilities of a sex modifier, u/u^*, were obtained under two mutational scenarios with or without beneficial mutations (Figure 4). $u^*=1/2N$ were checked in the simulations, and $u/u^*>1.0$ indicated that a sex modifier was favored. The sex modifier in diploids was strongly selected, except the case in which only strong deleterious mutations were present ($s_d>0.1$).

Three principal tendencies were observed from this result. First, the strength of selection on a sex modifier that promotes segregation was high ($L=0$). This finding suggested that segregation provided substantial benefits to drive the evolution of sex in diploids. In finite asexual haploid, Hill–Robertson interference occurs between loci. In finite diploids, drift also creates an alternative interference within a locus. Without segregation, mutation that occurs in one of the homologous chromosomes is possibly restricted to this chromosome unless another mutation arises in the same locus of the second chromosome, thereby creating excessive heterozygotes (Charlesworth and Charlesworth, 1997). With segregation, mating between heterozygotes quickly produces new homozygotes, which can be efficiently eliminated by selection. Second, the fixation probabilities of the sex modifier continued to increase as L varied from 0 to 1.5. This increase indicated that recombination provided additional benefits to help the

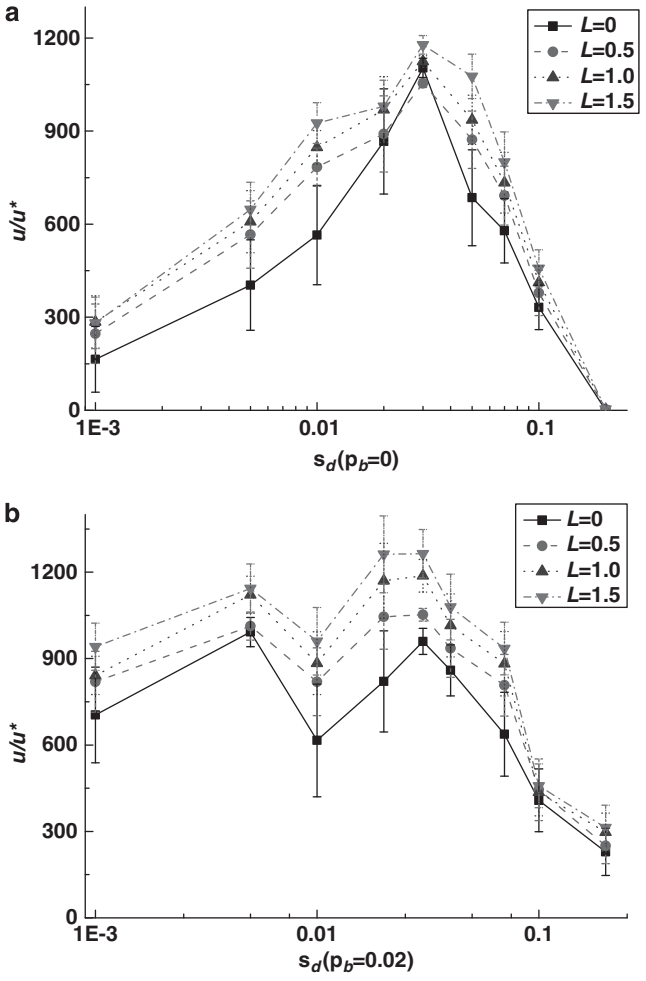

Figure 4 Selective advantage of a sex modifier u/u^* vs coefficient of deleterious mutations s_d. (**a**) $p_b = 0$; (**b**) $p_b = 0.02$. A modifier caused the carrier to produce offspring sexually with probability $p_{sex} = 0.1$. Other parameters used: $U = 0.5$, $s_b = 0.02$. Error bars through the paper were ±s.e.m. The differences between different L values were significant (Friedman rank sum test: $\chi^2 = 31.6$, df = 8, P-value = 0.0001098 for $p_b = 0$; $\chi^2 = 30.2$, df = 8, P-value = 0.0001948 for $p_b = 0.02$). The presence of beneficial mutations had significant effects on the fixation probability of the sex modifier with different recombination levels (one-sided Wilcoxon signed-rank tests: $V = 6$, P-value = 0.027345 for $L = 0$; $V = 1$, P-value = 0.003906 for $L = 0.5$; $V = 0$, P-value = 0.001953 for $L = 1.0$; $V = 0$, P-value = 0.001953 for $L = 1.5$). All statistical analyses in this article were completed in R 2.15.1.

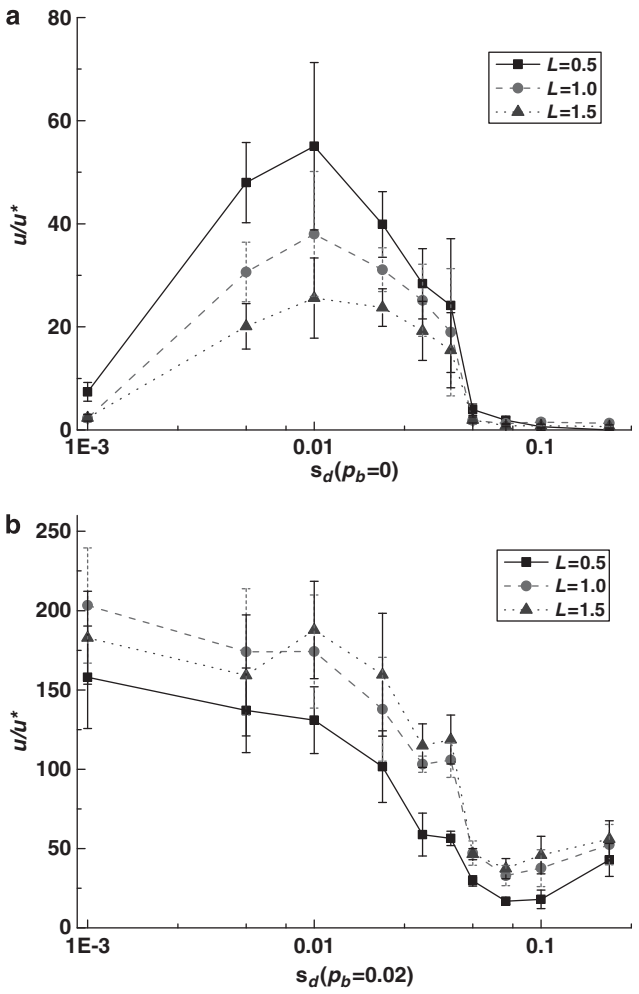

Figure 5 Selective advantage of a recombination modifier u/u^* vs coefficient of deleterious mutations s_d. (**a**) $p_b = 0$; (**b**) $p_b = 0.02$. Other parameters used: $U = 0.5$, $s_b = 0.02$. The differences between different L values were significant (Friedman rank sum test: $\chi^2 = 26.4182$, df = 9, P-value = 0.001745 for $p_b = 0$; $\chi^2 = 26.2727$, df = 9, P-value = 0.001843 for $p_b = 0.02$). The presence of beneficial mutations had significant effects on the advantage of the recombination level (one-sided Wilcoxon signed-rank tests: $V = 0$, P-value = 0.0009765 for $L = 0.5$; $V = 0$, P-value = 0.0009765 for $L = 1.0$; $V = 0$, P-value = 0.0009765 for $L = 1.5$).

fixation of a sex modifier ($P \approx 1.1 \times 10^{-4}$ with $p_b = 0$, $P \approx 1.9 \times 10^{-4}$ with $p_b = 0.02$; both values showed a significant difference based on Friedman rank-sum test). Third, the presence of beneficial mutations resulted in a significantly higher fixation rate of a sex modifier (Figure 4b) than the cases with solely deleterious mutations (Figure 4a) (at all different recombination levels, $P < 0.05$ using one-sided Wilcoxon's signed-rank tests). For the cases with very strong deleterious mutations that did not have a chance to be fixed in asexuals ($s_d \geqslant 0.1$), a sex modifier was still favored (For example, $u/u^* \approx 230$ with $s_d = 0.2$, $L = 0$; Figure 4b). We observed that the effective population size N_e in asexual populations was markedly reduced compared with the actual population size N (Supplementary Figure S2). The decrease in N_e was considered as an important signature of Hill–Robertson interference (Comeron *et al.*, 2007). For instance, N_e reduced to approximately 0.8% ($p_b = 0.02$) of the actual population size with $s_d = 0.05$, demonstrating that Hill–Robertson interference was very strong. The presence of beneficial mutations caused an even larger reduction in N_e than solely deleterious mutations in most cases. This result indicated that the increasing strength of Hill–Robertson interference improved the fixation rate of a sex modifier.

We also investigated the spread rate of a sex modifier in a saved population, which underwent sex at $p_{init} = 0.01$ (Supplementary Figure S3) or $p_{init} = 0.1$ (Supplementary Figure S4). The relative fixation probability of the sex modifier u/u^* was evidently decreased compared with that in a fully sexual population, in which the highest u/u^* was < 100 in both cases. In purely asexual populations, the main advantages of sex included the following: N_e was increased and the operation of Muller's ratchet was slowed down (or terminated). Therefore, a high fixation probability of a sex modifier was observed

with segregation alone ($L=0$). By contrast, this phenomenon unlikely occurred in a population that underwent sex at a low rate. More polymorphisms were possibly maintained in the partial sexual population. This mechanism could explain why the relative advantage of recombination ($L=1.0$) was significantly enhanced compared with that of segregation ($L=0$) ($P\leq 0.05$, one-sided Wilcoxon's signed-rank tests). With solely segregation ($L=0$), significant differences in u/u^* was not observed when beneficial mutations were added ($p_b=0.02$) ($P=0.16015$ in Supplementary Figure S3 and $P=0.0615$ in Supplementary Figure S4, one-sided Wilcoxon's signed-rank tests). Nevertheless, recombination also provided additional advantages to the evolution of sex in these partially sexual saved populations. In addition, the presence of beneficial mutations still resulted in a larger advantage of recombination.

Selection on a recombination modifier

Given that recombination increased the advantage of sex by speeding up the fixation rate of beneficial mutations (Figure 2c), the fixation probability of a recombination modifier in sexuals was expected to be higher in the presence of beneficial mutations than that in the presence of solely deleterious mutations. We showed the fate of a modifier with different recombination levels in sexual populations for different s_d (Figure 9). The modifier introduced recombination events to its non-recombinant carrier with a mean value of L. In the presence of beneficial mutations, u/u^* was much greater than 1.0 in our simulations, and this result is consistent with our expectation. The highest u/u^* (≈ 200) was observed in the case in which the effects of deleterious mutations were weak ($s_d=0.001$), indicating that recombination was strongly favored. A higher fixation probability of a recombination modifier was obtained by adding beneficial mutations ($p_b=0.02$; Figure 5b). Mann–Whitney U-test showed that u/u^* significantly differed between $p_b=0$ and $p_b=0.02$ groups at the three different recombination levels ($P\approx 1.0\times 10^{-3}$, one-sided test).

The different recombination levels exhibited significant differences in u/u^* in $p_b=0$ and $p_b=0.02$ groups (Friedman's rank-sum test, $P\approx 1.7\times 10^{-3}$ for $p_b=0$; $P\approx 1.8\times 10^{-3}$ for $p_b=0.02$). However, we noticed that a higher recombination level resulted in decreasing rather than increasing fixation probabilities of the modifier if mutations were solely deleterious (Figure 5a). In such a sexual population that has undergone segregation, slight increase in the recombination rate could terminate the operation of Muller's ratchet. Further recombination disrupted the balanced gene combination, which was possibly the reason why further recombination provided a decreasing advantage. By contrast, additional beneficial mutations created additional negative associations between loci, thereby enhancing Hill–Robertson interference. In this case, further recombination could liberate beneficial mutations from their deleterious background and thus was strongly favored.

Influence of p_{sex}, n_{sex}, U and C on u/u^*

We investigated the effects of changing the probability of an individual undergoing sexual reproduction (p_{sex}) on the relative fixation probability of a sex modifier, u/u^*. An increasing p_{sex} evidently increased the fixation probability of the sex modifier (Figure 6). A low probability of sex has been proven to provide substantial benefits in terms of sex rate (Pamilo *et al.*, 1987; Charlesworth *et al.*, 1993; Green and Noakes, 1995; Barton and Charlesworth, 1998). Strong modifiers that substantially increased the sex rate exhibited a higher advantage than weak modifiers. This result was the same as in haploids, in which the advantage of a sex

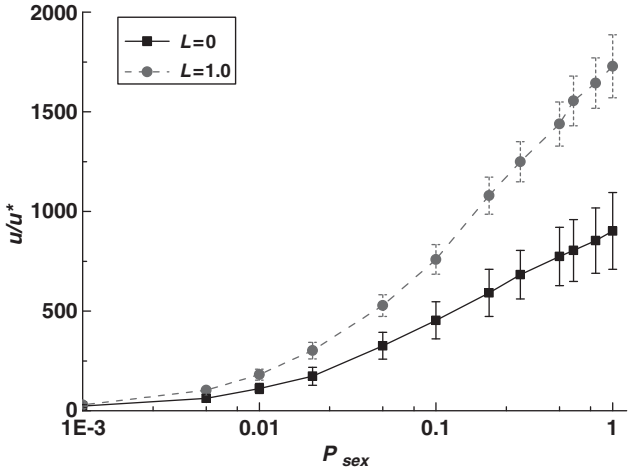

Figure 6 Selective advantage of a sex modifier u/u^* vs probabilities of it undergoing sexual productive ways, p_{sex}. Other parameters were used: $U=0.5$, $p_b=0.02$, $s_d=0.05$, $s_b=0.02$.

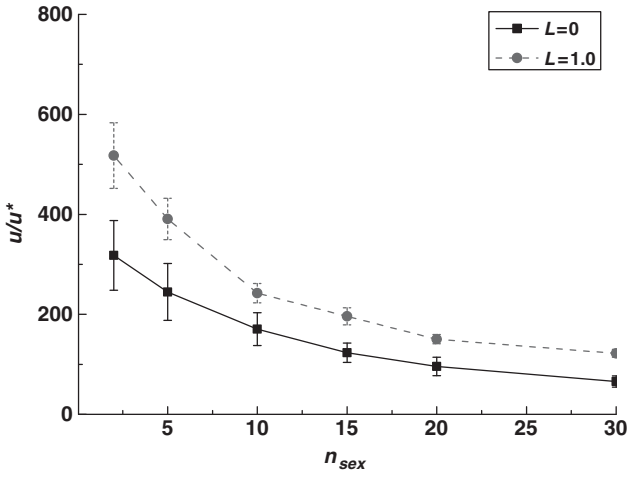

Figure 7 Selective advantage of a sex modifier u/u^* vs the available sexual partners, n_{sex}. Other parameters used: $U=0.5$, $p_{sex}=0.05$, $p_b=0.02$, $s_d=0.05$, $s_b=0.02$.

(recombination) modifier begins to increase as its strength increases at $p_{sex}\approx 0.01$ (Gordo and Campos, 2008).

Considering that all of the other factors were constant, the fixation rate of the sex modifier decreased with the available number of sexual partners, n_{sex} (Figure 7). Two opposite effects may appear when n_{sex} was increased. The number of available sex individuals was increased to produce more feasible sexual offspring at one generation, but a longer time is needed at first to reach a relatively larger n_{sex}. Therefore, the decrease in u/u^* with n_{sex} occurred possibly because the sexual reproduction of offspring immediately provided additional advantages to the population than to wait for n_{sex} to increase as caused by drift.

The fixation probability of a sex modifier u/u^* does not always increase as the mutation rate U increase (Figure 8). Very high mutation rates ($U>0.8$) caused a decrease in u/u^*. More (beneficial) mutations were expected to produce more negative associations to favor more sex. This unexpected result was possibly because a higher mutation rate can also reduce the effective population size N_e; by

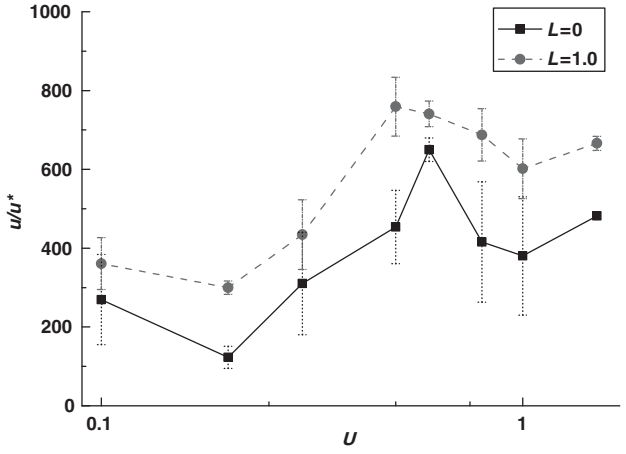

Figure 8 Selective advantage of a sex modifier u/u^* vs mutation rate, U. Other parameters were used: $p_{sex}=0.05$, $p_b=0.02$, $s_d=0.05$, $s_b=0.02$.

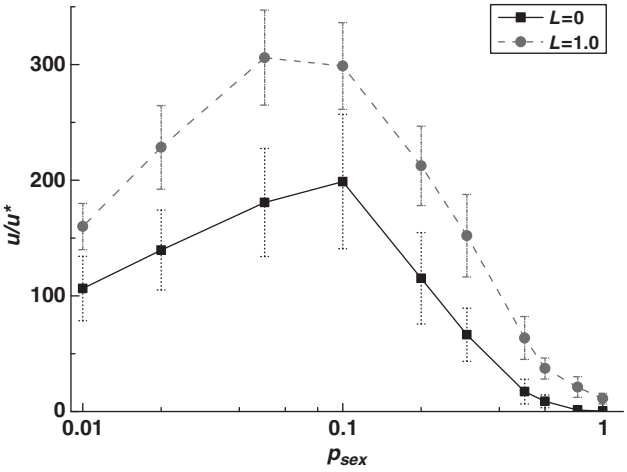

Figure 9 Selective advantage of a sex modifier u/u^* vs cost of sex, C. Other parameters used: $U=0.5$, $p_b=0.02$, $s_d=0.05$, $s_b=0.02$.

contrast, smaller N_e impedes the spread rate of the sex modifier (Hartfield *et al.*, 2010). The decrease in $u/u*$ was attributed to the dominance of the opposite effects of delaying the spread rate of the modifier exceeding the effects of increasing interference.

We presented the fixation rate of a sex modifier as a function of the cost of sex to determine whether or not sex can invade an asexual population with a substantial cost (Figure 9). C was directly determined by p_{sex}, where C ranging from 0.99 to 0.5 corresponded with p_{sex} varying from 0.01 to 1.0. We observed that $u/u*$ was >1.0 in most cases. This result indicated that the selection on a sex modifier was very strong. Therefore, the cost of sex could be easily overcome in diploids, confirming that sex frequently evolves in diploid organisms (Otto, 2003). The maximum advantage of sex occurred when the modifier caused a moderate increase in the probability of sexual reproduction ($p_{sex}\approx 0.1$). In particular, costly sex was more likely to spread with both segregation and recombination.

DISCUSSION

We used two models in this study to perform a detailed investigation on the relative contribution of segregation and recombination to the evolution of sex in diploids: the model based on purely asexual/sexual population and the modifier model. The sex modifier model was introduced to investigate the mechanism by which sex initially evolves from an asexual population that has accumulated deleterious (or beneficial) mutations. However, whether or not sex evolves originally from such a degenerating asexual population is unknown. In a study on accumulated deleterious mutation in *Aspergillus nidulans*, the fitness of sexual spores decreases at a slower rate than the equivalent asexual lineages (Bruggeman *et al.*, 2003). Studies on several organisms have also shown that individuals likely engage in sexual reproduction when conditions become stressful (Grishkan *et al.*, 2003; Goddard *et al.*, 2005). For example, experimental yeast sexual populations evolved faster than the asexual populations when environmental temperature or osmolarity is increased, but this evolution does not occur under benign conditions (Goddard *et al.*, 2005). Considering the observations in these experiments and our simulations, we expected that the relationship between the evolution of sex and the stressful condition under which deleterious mutations are accumulated also evolved. We also showed that a sex modifier was still favored, although an evidently decreased fixation rate was observed in a population that already underwent a low rate of sex.

Moreover, the spread rate of the recombination modifier was directly related to beneficial mutations. As an essential process in sexual diploids, segregation could effectively reduce the accumulation of deleterious mutations, thereby decreasing the relative contribution of recombination to the evolution of sex (Figure 5a). Nevertheless, rare beneficial mutations provided the driving force of adaptive evolution. Recombination could provide more advantages in fixing beneficial mutation than segregation alone and thus was strongly selected (Figure 5b). This observation in diploids that already underwent segregation indicated that recombination functions in the potential adaptive process in the presence of beneficial mutations.

The fate of the sex modifier depended strongly on the first available sexual number, n_{sex} (Figure 7). A smaller n_{sex} indicated a higher level of inbreeding because only one modifier was introduced in the population. All of the individuals with a sex modifier were descendents of the initial parent individual. Inbreeding is important in selection related to segregation and recombination (Otto, 2003; Roze and Lenormand, 2005; Agrawal and Otto, 2006; Agrawal, 2009b). Many populations have exhibited some degrees of inbreeding. Therefore, this model could be used to predict the relative advantage of segregation and recombination in most diploids. Nevertheless, if we allow mating to occur randomly between sexual and asexual individuals when the modifier was initially introduced without waiting for the presence of several available sexual partners, different results may be obtained. These random mating systems should be studied in the future to understand the mechanism by which such differences in mating affect the evolution of sex.

Our model also exhibits limitations. For instance, dominance within loci was not considered. Dominance of deleterious mutations in diploids has been investigated in other studies (Haag and Roze, 2007; Roze and Michod, 2010). However, little is known about the dominance of beneficial mutations, particularly the mode of interaction between deleterious and beneficial mutations (that is, beneficial and deleterious mutations coexist in the same locus). We will discuss the mechanism by which the dominance of beneficial mutations affects the advantages of sex in diploids in a future study based on infinite loci.

DATA ARCHIVING

Data deposited in the Dryad repository: doi:10.5061/dryad.82hk6.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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Agrawal AF (2006). Evolution of sex: why do organisms shuffle their genotypes? *Curr Biol* **16**: R696–R704.
Agrawal AF (2009a). Differences between selection on sex versus recombination in red queen models with diploid hosts. *Evolution* **63**: 2131–2141.
Agrawal AF (2009b). Spatial heterogeneity and the evolution of sex in diploids. *Am Natural* **174**: S54–S70.
Agrawal AF, Otto SP (2006). Host–parasite coevolution and selection on sex through the effects of segregation. *Am Natural* **168**: 617–629.
Bachtrog D, Gordo I (2004). Adaptive evolution of asexual populations under Muller's ratchet. *Evolution* **58**: 1403–1413.
Barton NH (1995). Linkage and the limits to natural selection. *Genetics* **140**: 821–841.
Barton NH, Charlesworth B (1998). Why sex and recombination? *Science* **281**: 1986–1990.
Barton NH, Otto SP (2005). Evolution of recombination due to random drift. *Genetics* **169**: 2353–2370.
Bruggeman J, Debets AJ, Wijngaarden PJ, DeVisser JA, Hoekstra RF (2003). Sex slows down the accumulation of deleterious mutations in the homothallic fungus *Aspergillus Nidulans*. *Genetics* **164**: 479–485.
Charlesworth B, Betancourt AJ, Kaiser VB, Gordo I (2009). Genetic recombination and molecular evolution. *Cold Spring Harb Symp Quant Biol* **74**: 177–186.
Charlesworth B, Charlesworth D (1997). Rapid fixation of deleterious alleles can be caused by Muller's ratchet. *Genet Res* **70**: 63–73.
Charlesworth D, Morgan MT, Charlesworth B (1993). Mutation accumulation in finite outbreeding and inbreeding populations. *Genet Res* **61**: 39–56.
Comeron JM, Williford A, Kliman RM (2007). The Hill–Robertson effect: evolutionary consequences of weak selection and linkage in finite populations. *Heredity* **100**: 19–31.
De Visser JA, Elena SF (2007). The evolution of sex: empirical insights into the roles of epistasis and drift. *Nat Rev Genet* **8**: 139–150.
Denver DR, Morris K, Lynch M, Thomas WK (2004). High mutation rate and predominance of insertions in the *Caenorhabditis elegans* nuclear genome. *Nature* **430**: 679–682.
Feldman MW, Otto SP, Christiansen FB (1996). Population genetic perspectives on the evolution of recombination. *Annu Rev Genet* **30**: 261–295.
Felsenstein J (1974). The evolutionary advantage of recombination. *Genetics* **78**: 737–756.
Garcia-Dorado A, Lopez-Fanjul C, Caballero A (1999). Properties of spontaneous mutations affecting quantitative traits. *Genet Res* **74**: 341–350.
Goddard MR, Godfray HC, Burt A (2005). Sex increases the efficacy of natural selection in experimental yeast populations. *Nature* **434**: 636–640.
Gordo I, Campos PRA (2008). Sex and deleterious mutations. *Genetics* **179**: 621–626.
Green RF, Noakes DLG (1995). Is a little bit of sex as good as a lot? *J Theor Biol* **174**: 87–96.
Grishkan I, Korol AB, Nevo E, Wasser SP (2003). Ecological stress and sex evolution in soil microfungi. *Proc Biol Sci* **270**: 13–18.
Haag CR, Roze D (2007). Genetic load in sexual and asexual diploids: segregation, dominance and genetic drift. *Genetics* **176**: 1663–1678.
Haag-Liautard C, Dorris M, Maside X, Macaskill S, Halligan DL, Houle D *et al*. (2007). Direct estimation of per nucleotide and genomic deleterious mutation rates in *Drosophila*. *Nature* **445**: 82–85.
Hadany L, Comeron JM (2008). Why are sex and recombination so common? *Ann NY Acad Sci* **1133**: 26–43.
Halligan DL, Keightley PD (2006). Ubiquitous selective constraints in the *Drosophila* genome revealed by a genome-wide interspecies comparison. *Genome Res* **16**: 875–884.
Hartfield M, Otto SP, Keightley PD (2010). The role of advantageous mutations in enhancing the evolution of a recombination modifier. *Genetics* **184**: 1153–1164.
Hill WG, Robertson A (1966). The effect of linkage on limits to artificial selection. *Genet Res* **8**: 269–294.
Iles MM, Walters K, Cannings C (2003). Recombination can evolve in large finite populations given selection on sufficient loci. *Genetics* **165**: 2249–2258.
Jiang X, Xu Z, Li J, Shi Y, Wu W, Tao S (2011). The influence of deleterious mutations on adaptation in asexual populations. *PLoS One* **6**: e27757.
Keightley PD, Eyre-Walker A (2000). Deleterious mutations and the evolution of sex. *Science* **290**: 331–333.
Keightley PD, Otto SP (2006). Interference among deleterious mutations favours sex and recombination in finite populations. *Nature* **443**: 89–92.
Loewe L, Charlesworth B (2006). Inferring the distribution of mutational effects on fitness in *Drosophila*. *Biol Lett* **2**: 426–430.
Lynch M, Hill WG (1986). Phenotypic evolution by neutral mutation. *Evolution* 915–935.
Martin G, Otto SP, Lenormand T (2006). Selection for recombination in structured populations. *Genetics* **172**: 593–609.
Otto SP (2003). The advantages of segregation and the evolution of sex. *Genetics* **164**: 1099–1118.
Otto SP (2009). The evolutionary enigma of sex. *Am Natural* **174**: S1–S14.
Otto SP, Barton NH (2001). Selection for recombination in small populations. *Evolution* **55**: 1921–1931.
Otto SP, Feldman MW (1997). Deleterious mutations, variable epistatic interactions, and the evolution of recombination. *Theor Popul Biol* **51**: 134–147.
Otto SP, Lenormand T (2002). Resolving the paradox of sex and recombination. *Nat Rev Genet* **3**: 252–261.
Pamilo P, Nei M, Li WH: and others (1987). Accumulation of mutations in sexual and asexual populations. *Genet Res* **49**: 135–146.
Roze D (2009). Diploidy, population structure, and the evolution of recombination. *Am Natural* **174**: S79–S94.
Roze D, Lenormand T (2005). Self-fertilization and the evolution of recombination. *Genetics* **170**: 841–857.
Roze D, Michod RE (2010). Deleterious mutations and selection for sex in finite diploid populations. *Genetics* **184**: 1095–1112.
Sella G, Petrov DA, Przeworski M, Andolfatto P (2009). Pervasive natural selection in the *Drosophila* genome? *PLoS Genet* **5**: e1000495.
Smith JM (1978). *The Evolution of Sex*. Cambridge University Press: Cambridge.

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