

A mixability theory of the role of sex in evolution

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Submitted to Proceedings of the National Academy of Sciences of the United States of America

The question of what role sex plays in evolution is still open despite decades of research. It has often been assumed that sex should facilitate the increase in fitness, hence the fact that it may break down highly favorable genetic combinations has been seen as a problem. Here we consider an alternative to this problematic assumption. We define a new measure that represents the ability of alleles to perform well across different combinations and, using numerical iterations within a classical population-genetic framework, show that selection in the presence of sex favors this ability in a highly robust manner. We also show that the mechanism responsible for this effect has been out of the purview of previous theory, because it operates during the evolutionary transient, and that the breaking down of highly favorable genetic combinations is an integral part of it. Implications of these results and more to evolutionary theory are discussed.

sex | recombination | mixability | epistasis | robustness | modularity

Theories on the role of sex in evolution have often been led by the assumption that sex should facilitate the increase in population mean fitness, \bar{w} [1]. At the same time, it has been recognized that sex may break down highly favorable combinations of genes, which impedes the increase in fitness [2, 3]. Thus, in a prominent review of sex theory, Barton and Charlesworth wrote to the effect that the breaking down of highly favorable gene combinations has been one of the most obvious difficulties in understanding sex [4].

Here we examine the role of sex in evolution from a different angle. We develop a new measure, \bar{M} , which represents the genome-wide ability of alleles to perform well across different combinations. Using numerical iterations within a classical population-genetic framework, we find that sex favors the increase in \bar{M} in a highly robust manner. Furthermore, we expose the mechanism underlying this effect, and find that it operates during the evolutionary transient, which has been relatively little studied. We also find that the breaking down of highly favorable gene combinations is an integral part of this mechanism. Therefore, if the role of sex involves selection not for the best combinations of genes, as would be registered by \bar{w} , but for genes that are favorable in many different combinations, as is registered by \bar{M} , then the breaking down of highly favorable combinations may be understood.

A precedent to our work can be found in the work of Crow and Kimura [5], who suggested briefly, based on intuition, that sex favored “good mixers.” However, they did not develop this intuition, and in fact considered the breaking down of highly favorable gene combinations to be a disadvantage of sex. In line with their choice of words, we call \bar{M} the “average mixability” of alleles in the genome.

Theoretical treatments normally assume that genes make semi-independent contributions to fitness. For example, in the case of two loci, the fitness w_{ij} of a genotype consisting of allele i in the first locus and allele j in the second locus

is often represented as $w_{ij} = 1 + s_i + t_j + \epsilon_{ij}$, where s_i and t_j are the semi-independent, additive contributions of alleles i and j respectively and ϵ_{ij} is an interaction or “epistasis” term. In our models, there is no a priori assumption of semi-independent contributions to fitness. However, sex favors the increase in \bar{M} and, as a result of that increase, as we shall see, it becomes natural and important to use forms that feature semi-independent contributions to fitness such as the above. These forms have been used in population genetics since its inception [6], but how sex relates to them is captured here.

Our results may help to bridge between sex theory and modularity theory [7, 8, 9, 10, 11]. In recent simulations, Misesvic et al. [10] found that, as compared to asex, sex favored a genomic organization where genetic elements that coded for the same trait were physically closer to each other and farther from other such elements. In their interpretation, this organization was modular [10, 11] and, accordingly, the groups of linked elements featured in it were modules. However, the ideal module in this sense is one whose elements are absolutely linked, and this ideal module is also a “good mixer” in the sense that it is transferred as a whole by recombination and is therefore more likely to maintain its individual contribution to fitness across different backgrounds. Hence, the theory to be given here may help to explain these simulation results on a conceptual level.

Throughout this paper, and in the tradition of evolutionary theory, we use the words “gene” and “allele” to refer not only to a genetic sequence that codes for a protein or a set of proteins related by alternative splicing, but to any contiguous stretch of the genome that may be represented by a locus in our models and informed by our results [12].

Theory and results

Consider the haploid 2-locus fitness landscape in Fig. 1. While genotype A_1B_3 has maximum fitness, there is a sense in which allele A_2 performs best overall among the A alleles across different genetic contexts (same for B_2). Let $P_{ij,t}$ be the frequency of genotype A_iB_j at generation t , r be the recombination rate ($0 \leq r \leq \frac{1}{2}$) and w_{ij} be the fitness of A_iB_j , with $\bar{w}_t = \sum_{k,l} P_{kl,t} w_{kl}$ and $\tilde{P}_{ij,t} = P_{ij,t} w_{ij} / \bar{w}_t$. The discrete time evolutionary dynamics of a large panmictic population without mutation can be written as:

$$P_{ij,t+1} = (1-r)\tilde{P}_{ij,t} + r \sum_l \tilde{P}_{il,t} \sum_k \tilde{P}_{kj,t}. \quad [1]$$

This paper was submitted directly to the PNAS office.

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Iterating this equation numerically from many different initial genotypic frequencies we find that, for $r = 0$ (asex), genotype A_1B_3 outcompetes all other genotypes, whereas for many values of r with $0 < r \leq \frac{1}{2}$ (sex), alleles A_2 and B_2 most often outcompete all other alleles (Fig. 2).

To formalize this observation, let M_i be the average fitness of allele i , i.e.: $M_i = \frac{\sum_{g \in G} w_g i_g}{\sum_{g \in G} i_g}$, where G is the set of all genotypes with ordering (i.e., for the case of diploid genomes, symmetric genotypes are considered distinct), w_g is the fitness of genotype $g \in G$, and i_g is the number of times that allele i appears in genotype g (assuming 0 or 1 times in haploid genomes and 0, 1 or 2 times in diploid genomes). For example, in Fig. 1, $M_{A_2} = \frac{1}{3}(w_{21} + w_{22} + w_{23})$ and, with the values of w_{ij} specified, $M_{A_2} > M_{A_1}, M_{A_3}$ and $M_{B_2} > M_{B_1}, M_{B_3}$. Now, M_i can be taken to represent the ability of allele i to perform well across different combinations; and in the given example, while asex favors the most fit genotype, sex favors the alleles that are highest on this ability, henceforth called “mixability.”

As another example, consider the diploid 1-locus model with genotypes A_iA_j having fitnesses $w_{ij} = w_{ji}$, with w_{ij} for all $i, j \geq i$ taking the same values as the corresponding w_{ij} in the previous example (*Supporting Information*, SI 1). Iterating the appropriate equation (Methods 1), again we see that sex favors the alleles of highest mixability (SI 1), this time via segregation rather than recombination. In these examples the alleles of highest mixability fix, but the selection for alleles of high mixability occurs during the evolutionary transient rather than near equilibrium, as we shall see.

To obtain a unified picture of many different cases from three fundamental models of sex: haploid 2-locus (recombination), diploid 1-locus (segregation) and diploid 2-locus (both), we use a robust means of comparison between sex and asex based on a population-wide measure of mixability, \bar{M}_t , which we define as: $\bar{M}_t = (\sum_{\ell \in L} \sum_{i \in \ell} P_{i,t} M_i) / \langle L \rangle$, where L is the set of loci, $\langle L \rangle$ is the cardinality of that set, at each locus $\ell \in L$ there is a set of alleles indexed by i , and $P_{i,t}$ is the frequency of allele i at generation t . For example, in the haploid 2-locus model, $\bar{M}_t = \frac{1}{2}(\sum_i P_{i,t} M_i + \sum_j P_{j,t} M_j)$. \bar{M} , which is the average mixability in the population, can be contrasted with a fundamental measure in population genetics, namely \bar{w} , average (genotypic) fitness.

We iterated the three models (Methods 1) in four cases, namely 2, 3, 4, or 5 alleles per locus, three r values (in the sex cases of the 2-locus models; $r \in \{0.5, 0.2, 0.05\}$) and three values of a parameter (f) which determined the range of fitness values (Methods 2). In each condition (one model, one allele number, one r and one f value), we chose a random set of n fitness matrices, $\{W^1, \dots, W^n\}$ and a random set of n initial genotypic frequency matrices, $\{P^1, \dots, P^n\}$, $n = 25$ (Methods 2), and for each of the n^2 pairs of P and W matrices, iterated the corresponding equations for a certain number of generations (e.g., $2^{15} \approx 32,000$ generations) both with and without sex; each such iteration was called a “trial.” At a representative set of generations (e.g., $\{0, 1, 2, 4, \dots, 2^{15}\}$), we recorded the percentage of trials in which the sexual population had a higher \bar{M} than the asexual one ($\% \bar{M}^{sex} > \bar{M}^{asex}$) and vice versa ($\% \bar{M}^{asex} > \bar{M}^{sex}$) and the percentage of trials in which the asexual population had a higher \bar{w} than the sexual one ($\% \bar{w}^{asex} > \bar{w}^{sex}$) and vice versa ($\% \bar{w}^{sex} > \bar{w}^{asex}$).

These pairs of percentages do not necessarily sum up to 100 since frequency differences between sex and asex below a very small threshold were taken to mean that these measures were essentially the same (Methods 3). Hence we call the difference (easily inferred by eye) between the percentage of trials in which one population was higher in \bar{M} and the percentage of trials in which the other population was higher in \bar{M} the “advantage” to the former population in \bar{M} (and similarly for \bar{w}).

Typical evolutionary dynamics are given for the 2-locus diploid model in Fig. 3 and for other conditions in SI 2. The main result is that while the asexual population has a decisive advantage in \bar{w} , the sexual population has a decisive transient advantage in \bar{M} . This result holds remarkably well under all conditions investigated and in all three models (SI 2).

A verbal explanation of the results

That \bar{w} is maximized under asex is clear, since in that case the geometric growth of genotypic frequencies according to their fitnesses leads to the eventual extinction of all but the most fit genotypes. But how does sex favor mixability? Consider the haploid 2-locus model in Eq. 1. The second term in this equation shows that recombination and independent assortment of non-homologous chromosomes act to reduce the variance in the frequencies of genotypes that carry a given allele. This reduction of variance shifts the growth rate of this allele in the long term from being associated with the performance of the most fit genotype that carries it toward being associated with how well it performs on average with its various genetic partners. Consequently, alleles of the same gene compete with each other based on how well they perform on average rather than how well they perform in any one specific combination. Examination of the diploid 1-locus equation shows that segregation of homologous chromosomes has the same effect (SI 3.1).

Why the reduction in variance has this effect can be understood intuitively by analogy to finance. In order to diversify a portfolio [13] among various investments and thus average its growth rate over time, an investor must keep rebalancing the portfolio at regular intervals [14]. Otherwise, the portfolio will soon be biased toward the investments that had the best individual returns so far. The investments here correspond to the genotypes that share an allele, the portfolio corresponds to that allele, and by analogy, it is the persistent re-homogenization by sex of frequencies of genotypes carrying each allele that shifts the focus of natural selection over the generations from the individual performance of genotypes to the average performance of alleles.

Since this average performance of alleles can only be registered on the intergenerational time scale, it is essentially different from the average performance of alleles discussed by Fisher [15]. Indeed, population genetics normally focuses on allele frequency changes that occur in one generation only and on the equilibria that could be calculated from them, and the effect just mentioned is not amenable to this approach (SI 3.2).

We can now see the benefit of M_i , which is an average of genotypic fitnesses unweighted by genotypic frequencies, as compared to a familiar measure such as $\phi_{i,t} = \frac{\sum_{g \in G} P_{g,t} w_g i_g}{\sum_{g \in G} i_g}$, which is an average of genotypic fitnesses weighted by the

genotypic frequencies at generation t , $P_{g,t}$ (particularly in the diploid 1-locus model, $\phi_{i,t}$ is related to the marginal fitness). Due to the intergenerational nature of the effect, the “instantaneous” $P_{g,t}$ ’s, which refer to generation t only, would make for inappropriate weights for the w_g ’s. This benefit, however, comes with a cost. By noting that $M_i = \phi_i$ when all $P_{g,t}$ are equal, we see that M_i is fundamentally a proxy that becomes less informative the further the genotypic frequencies are from uniform distribution. Thus, as genetic variation is lost during the numerical iterations due to selection and the genotypic frequency distribution becomes less uniform, the M_i proxy loses power, and the advantage to sex in mixability as seen through M_i decreases.

We can now see why the advantage to sex in \bar{M} peaks in the transients and is less than 100%. On the one hand, either the decrease in the power of M_i begins immediately or M_i is inaccurate from the beginning (SI 3.3). On the other hand, it takes multiple generations for the advantage to sex in \bar{M} to accumulate (SI 3.4). The superposition of these two effects cuts the observed advantage to sex in mixability on both left and right to create the peak mentioned above. Importantly, this is a limitation on our ability to observe selection for mixability through \bar{M} , not a limitation on the selection for mixability itself.

Another limitation on observability is the lack of mutation in our models. While selection for increased \bar{w} under asex cannot continue indefinitely without mutation due to the depletion of genetic variation, selection for increased \bar{M} under sex is even more sensitive to that depletion, since it requires not only variation in the genetic material that is being selected (as in Fisher’s fundamental theorem [15]) but also variation of genetic material tolerance of which is being selected. With respect to these limitations our results are conservative (SI 3.5). In actuality, variation is continually replenished by mutation, selection continues beyond what is shown here, and the difference in mixability between sexual and asexual populations should grow indefinitely (SI 3.6).

Semi-independent effects on fitness

As a corollary to the increase in \bar{M} in our models, sex also gives rise to semi-independent genetic contributions to fitness. To see this, consider a haploid 2-locus model with fitness values w_{ij} , $i \in \{1, \dots, n_A\}$, $j \in \{1, \dots, n_B\}$ with a mean $\frac{1}{n_A n_B} \sum_{ij} w_{ij} = 1$. Each w_{ij} could be represented as a deviation from the mean: $w_{ij} = 1 + x_{ij}$, where x_{ij} can be positive, negative or zero. However, suppose that the set of fitness values belonging to a certain allele i , $w_{i\cdot}$, has a high average; that is, $M_i = \frac{1}{n_B} \sum_j w_{ij}$ is significantly larger than 1. In this case it is statistically meaningful to represent each w_{ij} as a deviation from the mean of that set: $w_{ij} = 1 + s'_i + \epsilon'_{ij}$, where s'_i is positive. Furthermore, suppose that allele j also has a high M_j ; then it is statistically meaningful to use a form such as $w_{ij} = 1 + s_i + t_j + \epsilon_{ij}$. Thus, as the set of alleles of interest in our models becomes restricted through the selection for mixability from the original set of alleles to the subset of alleles that have high M values, it becomes appropriate to describe the fitnesses of genotypes with forms such as the above, which features additive, semi-independent contributions to fitness in the s and t terms.

Note that, first, by using the additive form just mentioned we do not mean to exclude other forms that sig-

nify semi-independent contributions to fitness, such as $w_{ij} = (1 + s_i)(1 + t_j) + \epsilon_{ij}$ (this form is also “additive” in the sense of Fisher, who referred in his formulations to additivity in the exponent). Second, even if alleles A_i and B_j make semi-independent contributions to fitness, the organism may still have to have some allele in locus A and some allele in locus B to be viable at all and, accordingly, semi-independence says nothing about the strength of the interaction between loci A and B that is common to all pairs of alleles A_i and B_j . Additivity, then, is only a part of the concept of interaction.

Discussion

It has long been suggested that sex breaks down highly favorable combinations of genes [2, 3]. This has been seen as a problem due to the assumption that sex should facilitate the increase in population mean fitness, \bar{w} [16, 17]. Specific conditions have been sought under which sex might facilitate that increase [1, 4], but these conditions were found to be restrictive [1, 18, 19, 20]). However, our analysis has shown an advantage to sex in average mixability, \bar{M} , and furthermore it appears that dissociation of gene combinations, in which the breaking down of highly favorable combinations is featured prominently, is needed in order to cause that advantage. Hence we suggest that the role of sex is to enable selection not for highly favorable specific combinations of genes but for genes that are favorable in many different combinations (SI 3.7).

The mechanism enabling the selection for mixability operates on the intergenerational timescale. It has been out of the purview of previous theory, which often focused on single-generational changes in allele frequencies and on the equilibria that could be calculated from them. This mechanism shows that, while at any one generation natural selection operates on genotypic fitnesses, over the generations and in the presence of sex it is particularly efficient not in increasing population mean fitness but in increasing the ability of alleles to perform well across different combinations. Thus, in this mechanism, natural selection and sex operate interdependently and need to be understood in the context of each other.

Our iterations start with random genotypic fitness values that do not depend in any meaningful way on their constituent alleles. In the haploid 2-locus model, for example, the genotypic fitnesses w_{ij} can be written at this stage as $w_{ij} = 1 + x_{ij}$, where where i and j refer to alleles in the first and second locus respectively and x_{ij} can be positive, negative or zero. Then, during the iterations, in the presence of sex, alleles are selected that have high M values. However, when alleles have high M values it becomes statistically meaningful to represent the fitnesses of genotypes symbolically with forms that feature semi-independent contributions to fitness, such as $w_{ij} = 1 + s_i + t_j + \epsilon_{ij}$, where s_i and t_j represent the additive contributions to fitness of alleles i and j respectively, and ϵ_{ij} is an interaction or “epistasis” term. Thus, we start with genetic elements that have no meaning except for the fact that they recombine, and end up with genes that make semi-independent contributions to fitness. Forms such as the above have been used in population genetics since Fisher’s reconciliation of Mendelism and biometry [6], and in that sense can be said to have been inferred from observation. But now we see that, within the confines of our framework, sex provides causal justification to them.

Our work confirms the intuition held by Crow and Kimura [5] that sex favors good mixers, which they described verbally as alleles that made large additive contributions to fitness. It is also consistent with empirical evidence they provided on this point. They noted that analysis of variance of the contribution of different chromosomes to drug resistance that evolved under sexual reproduction in *Drosophila* showed strong additivity [5, 21], whereas drug resistance that evolved under asexual reproduction in *Escherichia coli* was diminished by subsequent recombination in a manner that implied strong interactions [22]. Along the same line, Malmberg [23] showed that contributions of different genomic regions to drug resistance in bacteriophage T4 showed stronger additivity and weaker interactions in populations evolving under higher recombination rates. However, while our work agrees with this evidence, it also suggests that mixability needs to be attended to as a focal issue.

Recently, interest has increased in the evolution of phenotypic robustness to genetic changes [24, 11]. It has been suggested that either this robustness evolves to keep a trait at its optimum [24] (directly as a response to genetic variance or as a correlated response to environmental variance [25]) or this robustness is a byproduct of being near an optimum [24], and that conditions for the former may be more pronounced in sexual than in asexual populations [26, 24, 27, 11]. Fitness is a phenotypic trait of special interest in this context [24], and indeed, recent simulations found higher fitness robustness to recombinational [28] and mutational [28, 10] genetic changes in sexual populations. Since alleles of high mixability maintain high fitness despite recombination, our iterations also show higher fitness robustness to recombinational changes in sexual populations, and on this point they are in agreement with the above. However, our iterations demonstrate an additional route by which this fitness robustness may evolve, since here it evolves as the immediate consequence of sex and natural selection (by the mechanism we described), and not as a result of pressure to stay near a fitness optimum.

Importantly, although selection for mixability in our models favored a genetic variant if it maintained high fitness with multiple genetic partners that it encountered through recombination, such a variant may also be more likely to interact well with genetic partners that it has not yet encountered, including newly mutated ones, since those are likely to differ from the ones that it has encountered by only a small amount. This possibility would accord with recent simulations [28], which showed that recombinational fitness robustness led to mutational fitness robustness [28]. Now, according to de Visser et al. [24], fitness robustness may enhance evolvability [24], and in particular, the ability of loci to tolerate changes in other loci as just mentioned may allow evolution to advance by local changes rather than necessitate a coordinated change across the genome [24]. Accordingly, we conjecture that mixability enhances evolvability.

The possibility that mixability enhances evolvability may provide an answer to the question “what is mixability good for?” It is commonly believed that, among higher organisms, sexual species (obligate and facultative) are more evolvable than asexual ones [29, 30, 31], since they are the founders of wide taxa [29, 12] and are vastly more common [32, 4], while obligate asexuals are mostly recent derivations from sexual ancestors (referred to as “evolutionary dead-ends;” but see

[33]) and are phylogenetically sparse [29, 12]. If mixability enhances evolvability, then (since it is favored under sex) it may have been contributing to the proliferation of sexual species and of sexuality itself. In addition, the tolerance to genetic changes that mixability entails may explain why the same or similar genes often appear in different combinations within and across species [9]. Kirschner and Gerhart attribute this to the components of life being appropriate for “versatility and modification rather than for dedicated single use” [9].

Our analysis shows that sex favors compatibility between alleles. The inverse is that lack of sex allows alleles to develop incompatibility as they evolve. This connects to the Dobzhansky-Muller model [34] of hybrid fitness reduction. In the basic case of this model, a population of diploid genotypes $A_1B_1A_1B_1$ splits into two separate demes, one in which $A_1B_2A_1B_2$ evolves and one in which $A_2B_1A_2B_1$ evolves; and after these demes come back into contact, negative epistatic interactions are said to occur in the hybrid $A_1B_1A_2B_2$ between alleles A_2 and B_2 . The question arises, however, as to why alleles A_2 and B_1 are compatible, alleles A_1 and B_2 are compatible, but alleles A_2 and B_2 are incompatible. The answer, in terms of our theory, is that sex selects for alleles with an additive effect that rises above epistasis. Without sex, epistasis between alleles in non-breeding individuals is free to increase before resulting in a hybrid. Thus, evidence for the Dobzhansky-Muller effect [35] (and the fact that hybrids are less functional in species that are further along the process of speciation [19]) is consistent with our work.

The causal effect of sex on additivity and epistasis described here ties also to the Fisher-Wright debate, where Fisher advocated additive genetic contributions to fitness with weak epistasis [15] and Wright advocated strong epistasis [36], since it suggests that both were partly correct. That is, since mating occurs more often within a deme, it reduces epistasis in crosses within a deme; and since it occurs less frequently between demes, it allows epistasis in crosses between demes to increase with the accumulation of mutations. By a similar argument, genetic linkage [5] and the local rates of recombination across the genome may be expected to affect the extent of epistasis.

Finally, our results may speak to a connection between sex and modularity [10, 11]. According to Schlosser, evolutionary modules are defined partly by the fact that they make semi-independent contributions to fitness [37]. In the presence of sex, the loci in our models acquire this characteristic of evolutionary modules. Furthermore, in simulation experiments with digital organisms [10], Misevic et al. found that genetic elements that coded for the same trait were physically closer to each other and farther from other such elements in sexual than in asexual organisms [10]. In their interpretation, this result showed that sex favored a modular organization of the genome [10, 11], and accordingly, the groups of linked elements featured in sexual genomes were modules. However, the ideal module in this interpretation is one whose elements are absolutely linked, and this ideal module is also a “good mixer” in that it is more likely to be transferred as a whole by recombination and therefore to maintain its individual contribution to fitness across different backgrounds. Thus, the mechanism of selection for mixability described here may contribute to the understanding of the results of Misevic et al. [10] on a conceptual level.

Our analysis does not address the origin of sex and does not attempt to relate the evolution of sex to increase or decrease of mean fitness. Instead, we have observed an interesting relationship between the presence of sex and the temporal pattern of mixability. The ways in which mixability and modularity in response to sex relate to evolvability promise to provide an interesting area for future work.

Methods

1. The three models. The haploid 2-locus model was given in Eq. 1. For alleles $i \in \{1, \dots, n_A\}$ in locus A and alleles $j \in \{1, \dots, n_B\}$ in locus B , $M_i = M_i^o = \frac{1}{n_B} \sum_j w_{ij}$.

In the diploid 2-locus model, asex case, we keep track of genotypes $P_{ijkl,t}$ with fitnesses w_{ijkl} , where $i, k \in \{1, \dots, n_A\}$ refer to alleles in locus A and $j, l \in \{1, \dots, n_B\}$ refer to alleles in locus B , such that ij constitutes one haplotype and kl constitutes the other haplotype. In the sex case, assuming panmixis, we need only keep track of the haplotype frequencies (i.e., chromosomes), $P_{ij,t}$. Position effects entail only $w_{ijkl} = w_{kl ij}$, whereas lack thereof entails $w_{ijkl} = w_{kjil} = w_{ilkj} = w_{kl ij}$ for all i, j, k, l . The next generation frequencies $P_{ijkl,t+1}^{asex}$ and $P_{ij,t+1}^{sex}$ in the asexual and sexual populations respectively are given by:

$$\bar{w}_t'' P_{ijkl,t+1}^{asex} = P_{ijkl,t} w_{ijkl}, \quad [2]$$

$$\begin{aligned} \bar{w}_t'' P_{ij,t+1}^{sex} &= (1-r) P_{ij,t} \sum_{kl} P_{kl,t} w_{ijkl} \\ &+ r \sum_{kl} P_{il,t} P_{kj,t} w_{ilkj}, \end{aligned} \quad [3]$$

where \bar{w}'' is the sum of the right hand sides of the equation where it appears (for all $ijkl$ in Eq. 2 and for all ij in Eq. 3). Here, $M_i = M_i'' = \frac{1}{n_A n_B} \sum_{j,k,l} w_{ijkl}$.

The diploid 1-locus model is obtained from the diploid 2-locus model by setting $r = 0$ and collapsing what was haplotype ij before into allele i and what was haplotype kl before

into allele j . Then:

$$\bar{w}_t' P_{ij,t+1}^{asex} = P_{ij,t} w_{ij} \quad [4]$$

$$\bar{w}_t' P_{i,t+1}^{sex} = P_{i,t} \sum_j P_{j,t} w_{ij}, \quad [5]$$

where \bar{w}_t' is defined as \bar{w}_t'' was. M_i now takes a form similar to M_i^o , except that now i and j refer to the same set of alleles in the same locus: $M_i = M_i' = \frac{1}{n_A} \sum_j w_{ij}$ ($P_{ij,t}$ in Eq. 4 differs from $P_{ij,t}$ in Eq. 1 in the same way).

2. Iterations. The values in each fitness matrix were drawn independently at random from a uniform distribution on the interval $[1-f, 1+f]$.

To construct the frequency matrices, initial allelic frequencies (e.g., $P_{i,0}$, $P_{j,0}$ in the haploid 2-locus model) were first drawn independently at random from the uniform distribution over the interval $[0, 1]$ and normalized for each locus, then genotypic frequencies were obtained by multiplying the allelic frequencies (e.g., $P_{ij,0} = P_{i,0} P_{j,0}$).

3. Comparison. Since “larger than” comparisons are overly sensitive to the least significant decimal digits, we only compared the sexual and asexual populations’ \bar{w} ’s when genotypic frequencies, $P_{g,t}$ ’s, differed beyond a very small threshold ($\sum_{g \in G} (P_{g,t}^{sex} - P_{g,t}^{asex})^2 > \epsilon$, $\epsilon = 10^{-16}$, where genotypes of identical fitness were grouped together as one), and only compared their \bar{M} ’s when both genotypic (previous condition) and allelic frequencies differed beyond a very small threshold (e.g., in the haploid 2-locus model, $((\sum_i P_{i,t}^{sex} - P_{i,t}^{asex})^2 + (\sum_j P_{j,t}^{sex} - P_{j,t}^{asex})^2) / (n_A + n_B) > \epsilon$); otherwise, the \bar{w} ’s (respectively, \bar{M} ’s) were taken to be essentially identical.

We thank Nick Pippenger and Kim Weaver for invaluable conversations during the course of the work, Leiguang Ren for technical assistance, and three anonymous referees for comments on previous versions of this manuscript. AL acknowledges financial support from the Burroughs-Wellcome Fund, the Pew Charitable Trust, and the Miller Institute for Basic Research in Science. Research was supported in part by NSF Grant CCF-0635319 to CP, a Discovery grant from the National Science and Engineering Research Council of Canada to JD, and NIH grant GM28016 to MWF.

- Feldman, MW, Otto, SP, Christiansen, FB (1997) Population genetic perspectives on the evolution of recombination. *Annual Review of Genetics* 30:261–295.
- Eshel, I, Feldman, MW (1970) On the evolutionary effect of recombination. *Theoretical Population Biology* 1:88–100.
- Lewontin, RC (1971) The effect of genetic linkage on the mean fitness of a population. *Proceedings of the National Academy of Sciences* 68:984–986.
- Barton, NH, Charlesworth, B (1998) Why sex and recombination? *Science* 281:1986–1990.
- Crow, JF, Kimura, M (1965) Evolution in sexual and asexual populations. *The American Naturalist* 99:439–450.
- Fisher, RA (1918) The correlation between relatives on the supposition of mendelian inheritance. *Transactions of the Royal Society of Edinburgh* 52:399–433.
- Wagner, GP (1996) Homologues, natural kinds and the evolution of modularity. *American Zoologist* 36:36–43.
- Schlosser, G, Wagner, GP, eds (2004) *Modularity in Development and Evolution* (University Of Chicago Press, Chicago).
- Kirschner, MW, Gerhart, JC (2005) *The Plausibility of Life* (Yale University Press, New Haven).
- Misevic, D, Ofria, C, Lenski, RE (2006) Sexual reproduction reshapes the genetic architecture of digital organisms. *Proceedings of the Royal Society of London Series B* 273:457–464.
- de Visser, JAGM, Elena, SF (2007) The evolution of sex: empirical insights into the roles of epistasis and drift. *Nature Reviews Genetics* 8:139–149.
- Williams, GC (1996) *Adaptation and Natural Selection* (Cambridge University Press, New York), Princeton Science Library edition.
- Samuelson, PA (1967) General proof that diversification pays. *The Journal of Financial and Quantitative Analysis* 2:1–13.
- Evans, JL (1968) The random walk hypothesis, portfolio analysis and the buy-and-hold criterion. *The journal of Financial and Quantitative Analysis* 3:327–342.
- Fisher, RA (1930) *The Genetical Theory of Natural Selection* (Clarendon Press, Oxford).
- Karlin, S, McGregor, J (1972) The evolutionary development of modifier genes. *Proceedings of the National Academy of Sciences* 69:3611–3614.
- Karlin, S, McGregor, J (1974) Towards a theory of the evolution of modifier genes. *Theoretical Population Biology* 5:59–103.
- West, SA, Lively, CM, Read, AF (1999) A pluralistic approach to sex and recombination. *Journal of Evolutionary Biology* 12:1003–1012.
- Stearns, SC, Hoekstra, RF (2005) *Evolution: An Introduction* (Oxford University Press, NY), second edition.
- Kouyos, RD, Silander, OK, Bonhoeffer, S (2007) Epistasis between deleterious mutations and the evolution of recombination. *Trends in Ecology and Evolution* 22:308–315.
- King, JC, Somme, L (1958) Chromosomal analysis of the genetic factors for resistance to ddt in two resistant lines of *drosophila melanogaster*. *Genetics* 43:577–593.

22. Cavalli, LL, Maccacaro, GA (1952) Polygenic inheritance of drug-resistance in the bacterium *escherichia coli*. *Heredity* 6:311–331.
23. Malmberg, RL (1977) The evolution of epistasis and the advantage of recombination in populations of bacteriophage T4. *Genetics* 86:607–621.
24. de Visser, JAGM et al. (2003) Evolution and detection of genetic robustness. *Evolution* 57:1959–1972.
25. Wagner, GP, Booth, G, Bagheri-Chaichian, H (1997) A population genetic theory of canalization. *Evolution* 51:329–347.
26. Stearns, SC (1994) The evolutionary links between fixed and variable traits. *Acta Paleontologica Polonica* 38:215–232.
27. Gardner, A, Kalinka, AT (2006) Recombination and the evolution of mutational robustness. *Journal of Theoretical Biology* 241:707–715.
28. Azevedo, RBR, Lohaus, R, Srinivasan, S, Dang, KK, Burch, CL (2006) Sexual reproduction selects for robustness and negative epistasis in artificial gene networks. *Nature* 440:87–90.
29. Stebbins, GL (1957) Self fertilization and population variability in the higher plants. *American Naturalist* 91:337–354.
30. Levin, DA (1975) Pest pressure and recombination systems in plants. *The American Naturalist* 109:437–451.
31. Glesener, RR, Tilman, D (1978) Sexuality and the components of environmental uncertainty: Clues from geographic parthenogenesis in terrestrial animals. *The American Naturalist* 112:659–673.
32. Vrijenhoek, RC (1989) *Ecology and Evolution of Unisexual Vertebrates*, eds Dawley, R, Bogart, J.
33. Judson, OP, Normark, BB (1996) Ancient asexual scandals. *Trends in Ecology and Evolution* 11:41–46.
34. Coyne, JA, Orr, HA (2004) *Speciation* (Sinauer Associates, Sunderland).
35. Johnson, NA (2000) *Epistasis and the Evolutionary Process*, eds Wolf, JB, Brodie, EDI, Wade, MJ (Oxford University Press, Oxford), pp 197–211.
36. Wright, S (1931) Evolution in mendelian populations. *Genetics* 16:97–159.
37. Schlosser, G (2004) *Modularity in Development and Evolution*, eds Schlosser, G, Wagner, GP (The University of Chicago Press, Chicago), pp 519–582.

Fig. 1. A haploid 2-locus fitness landscape with 3 alleles per locus.

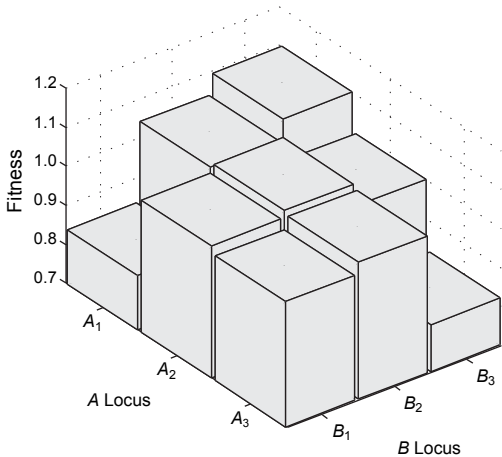
Alleles A_1 , A_2 and A_3 in locus A and B_1 , B_2 and B_3 in locus B give 9 genotypes A_iB_j with fitnesses w_{ij} , represented by the heights of the bars ($w_{11} = 0.840$, $w_{12} = 1.046$, $w_{13} = 1.100$, $w_{21} = 1.040$, $w_{22} = 1.060$, $w_{23} = 1.000$, $w_{31} = 1.020$, $w_{32} = 1.050$, $w_{33} = 0.820$).

Fig. 2. Typical evolutionary dynamics of the haploid 2-locus example.

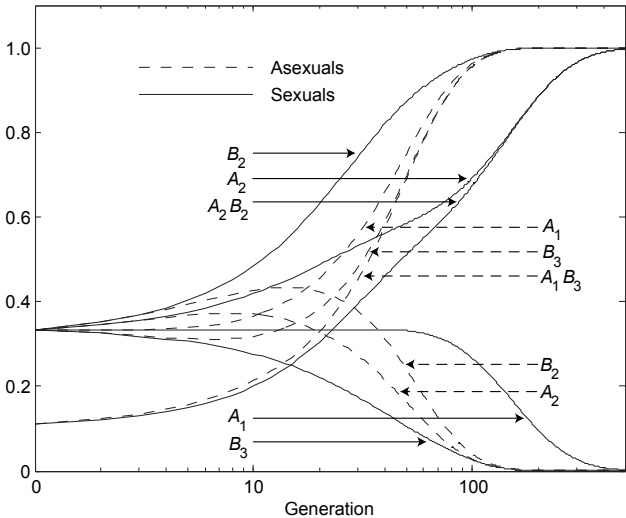
Here we start with equal genotypic frequencies ($\frac{1}{9}$ for each of 9 genotypes) at generation 0 and calculate the genotypic frequencies for generations 1-500 based on Eq. 1 for both $r = \frac{1}{2}$ (sexual, solid lines) and $r = 0$ (asexual, dotted lines). The w_{ij} are as in Fig. 1.

Fig. 3. \bar{M} and \bar{w} comparisons between sex and asex for the 2-locus diploid model without position effects (Methods 1), for $r = 0.5$, $f = 0.5$.

See text for how the parameters and variables were chosen.



Genotype and Allele Frequencies



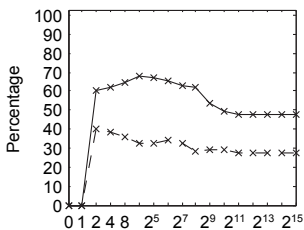
x — x — x — x — x $\% \bar{M}^{sex} > \bar{M}^{asex}$

x * — x — x $\% \bar{M}^{asex} > \bar{M}^{sex}$

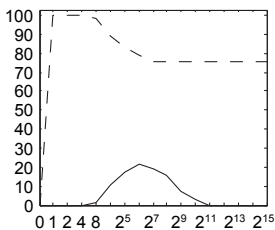
— $\% \bar{W}^{sex} > \bar{W}^{asex}$

- - - $\% \bar{W}^{asex} > \bar{W}^{sex}$

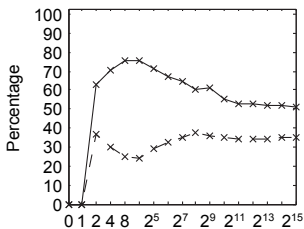
\bar{M} , 2 alleles per locus



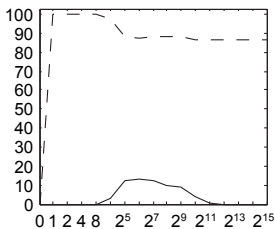
\bar{w} , 2 alleles per locus



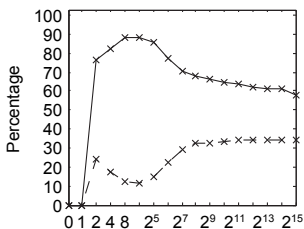
\bar{M} , 3 alleles per locus



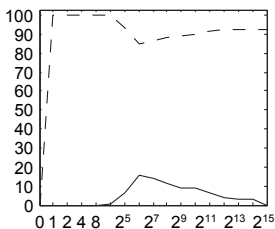
\bar{w} , 3 alleles per locus



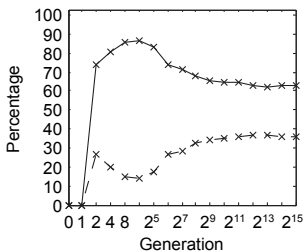
\bar{M} , 4 alleles per locus



\bar{w} , 4 alleles per locus



\bar{M} , 5 alleles per locus



\bar{w} , 5 alleles per locus

