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Sex: The power of randomization

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ABSTRACT

In evolutionary biology, randomness has been perceived as a force that, in and of itself, is capable of inventing: mutation creates new genetic information at random across the genome which leads to phenotypic change, which is then subject to selection. However, in science in general and in computer science in particular, the widespread use of randomness takes a different form. Here, randomization allows for the breaking of pattern, as seen for example in its removal of biases (patterns) by random sampling or random assignment to conditions. Combined with various forms of evaluation, this breaking of pattern becomes an extraordinarily powerful tool, as also seen in many randomized algorithms in computer science. Here we show that this power of randomness is harnessed in nature by sex and recombination. In a finite population, and under the assumption of interactions between genetic variants, sex and recombination allow selection to test how well an allele will perform in a sample of combinations of interacting genetic partners drawn at random from all possible such combinations; consequently, even a small number of tests of genotypes such as takes place in a finite population favors alleles that will most likely perform well in a vast number of yet unrealized genetic combinations. This power of randomization is not manifest in asexual populations.

1. Introduction

Sexual reproduction has been intensively studied in evolutionary theory for about a century now: Modifier theory has provided numerous invaluable insights on what factors affect the evolution and maintenance of sex (e.g., Nei, 1967; Feldman, 1972; Feldman et al., 1980; Feldman and Liberman, 1986; Altenberg and Feldman, 1987; Bergman and Feldman, 1990, 1992; Barton, 1995; Charlesworth, 1993; Korol et al., 1994; Otto and Lenormand, 2002; Hadany and Beker, 2003; Otto and Nuismer, 2004; Keightley and Otto, 2006; Hadany and Otto, 2007, 2009), while other work (referred to as "intrinsic theories" by Felsenstein, 1974, and "optimality arguments" by Feldman et al., 1997) has investigated how the existence of sex affects the evolution of other traits and the population mean fitness. Focusing on the latter, the Fisher–Muller theory entails that sex speeds up the increase in population mean fitness by allowing beneficial alleles in different loci to spread in the population in parallel, rather than having to accumulate serially in an asexual clone (Fisher, 1930; Muller, 1932). According to Muller's ratchet, sexual reproduction regenerates mutation-free genotypes from genotypes harboring deleterious mutations in different loci, thus saving a finite population from perpetual accumulation of slightly deleterious mutations (Muller, 1964). The deterministic mutation hypothesis concerns an extension of Muller's ratchet to infinite populations. It proposes that sexual reproduction increases the population mean fitness by speeding up the destruction of deleterious mutations through combining them from different genotypes into particularly unsuccessful genotypes, under the assumption of prevalent synergistic negative epistasis (Kondrashov, 1982). According to the Hill–Robertson effect, selection acting at one locus increases the variance in fitness of an allele at another locus and thus reduces the effectiveness of selection on the latter, the more so the stronger the linkage between these loci, and thus sexual recombination reduces the interference between selection at different loci (Hill and Robertson, 1966) (which also provides a general framework for the Fisher–Muller theory and Muller's ratchet; Felsenstein, 1974). The parasite hypothesis entails that sexual recombination keeps regenerating less common genotypes, which are better at escaping common parasites adapted to the common genotypes (Jaenike, 1978; Hamilton, 1980). Considerations of diploidy show that an advantageous mutation must appear twice in a parthenogenetic species for its establishment and eventual substitution to occur but only once in a sexual species, which provides an advantage to sexuals under incomplete dominance (Kirkpatrick and Jenkins, 1989). As we examine these ideas and others (e.g., Eshel and Feldman, 1970; Zhuchenko and Korol, 1983; Bernstein et al., 1985; Hadany and Beker, 2003), the possibility that sex could enable

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random sampling of combinations of interacting genetic variants from an exponentially large population of possible genotypes by a relatively small, finite population of genetic combinations, and thus allow selection to favor alleles that will perform well across a vast number of yet unseen genetic combinations, seems not to have been a part of the discussion on the effects of sex on evolution. In other words, the possibility that the interaction of sex and natural selection harnesses randomization for predictive power has not been considered in these references.

The power of random sampling is well demonstrated throughout the experimental sciences. When gathering subjects for a controlled trial of a psychology experiment, for example, ideally, subjects are selected at random from the population of interest and then assigned at random to the different study conditions. This helps to avoid patterns in the selection of participants for the study as a whole and for its different conditions. For example, it avoids studying only people who have just had lunch, or only people of a particular gender, etc.; it avoids placing in one condition only the people who arrive early and in another condition only the people who arrive late to the study, etc. Any such difference may potentially be correlated with psychological differences that may not be of interest in the given study but may introduce biases and errors in the interpretation of the results. Randomization, by almost certainly breaking any possible pattern, allows the experimenters to focus the study on the element of interest. Furthermore, it ensures that the results will be, in all likelihood, relevant for the entire population, and not only for the particular, small sample of individuals studied (it makes the small sample representative of the entire population). In other words, thanks to random sampling, even a very small sample can provide an accurate prediction of what would happen in a vast number of unknown individual sample points.

The power of breaking a pattern, or randomness, is also used in a myriad of contexts in computer science (e.g., Motwani and Raghavan, 1995; Goldreich, 1998; Wigderson, 2006; Wigderson, 2019). It is used in algorithms for testing whether an algebraic identity is correct, for encrypting messages, for playing games of strategy, for testing software, for sorting large files, and more. Essentially, one devises algorithms which, while employing chance in a few crucial and well chosen steps, maintain a firm deterministic control on others, a technique often used to explore a distribution with a small sample and make decisions based on the properties of the distribution revealed with high probability by the sample, and widely used, from Monte Carlo simulations to testing for primality. In fact, a fundamental problem in computer science is how to create and amplify randomness (Wigderson, 2019), which shows how useful randomness is — when used properly.

How this power of randomness applies to sex and recombination can be described in a simple and intuitive way. Sex and recombination shuffle the genes. This means that the genetic partners for any given allele within and across loci are being randomized, so that this allele participates in a random sample of genotypes. This randomization ensures that the outcome of selection, representing how well this allele interacted with a variety of combinations of genetic partners in the small, actual population, can be extrapolated to represent how well it will interact with a vast number of yet untried, potential combinations of genetic partners, namely how well it will perform in the vast array of potential genotypes. In a sense, and as counterintuitive as it may first seem, randomization by sex allows the process of selection to predict future performance in yet untested interactive genetic contexts, and not just record past performance.

This point connects with a recent approach to the role of sex in evolution, called mixability theory (Livnat et al., 2008, 2010, 2011). While the leading idea of 20th-century theoretical research on the role of sex in evolution using population-genetic models has been that sex must somehow facilitate the increase in the population mean fitness measure (e.g., Karlin and Mcgregor, 1972; Karlin and McGregor, 1974; Kondrashov, 1982), mixability theory argues that the sexual shuffling of the genes shifts the focus of natural selection from favoring particular genetic combinations of high fitness to favoring alleles that perform well across a wide variety of different genetic contexts — it favors mixable alleles (Livnat et al., 2008, 2010, 2011). Additionally, mixable alleles can be thought of as robust modules (Livnat et al., 2008, 2010; Srivastava et al., 2014), and related approaches in terms of the allele-based vs. genotype-based selection also found a connection between sexual reproduction and the appearance of genetic modules (Misevic et al., 2006; Neher and Shraiman, 2009).[1] So far, however, for finite populations, investigators have focused on phenomena such as hitchhiking and issues related to the theories mentioned earlier (Otto and Barton, 2001; Peck, 1994; Howard and Lively, 1994; Hartfield and Otto, 2011), whereas mixability has only been studied in infinite populations (Livnat et al., 2008, 2010, 2011). It is in the shift from studying mixability in infinite populations to studying it in finite populations that the idea of sex as random sampling immediately presents itself: It is the mixability of an allele in a vast space of *potential* genotypes that is tested by random sampling, which is implemented by the interaction of sex and natural selection in finite populations.

If the fitness of an individual were determined by "beneficial alleles" whose benefits extend across all genetic contexts, as in the Fisher–Muller theory (Fisher, 1930; Muller, 1932; Crow and Kimura, 1965), then there would be no information to be exposed by random sampling about the value of an allele. Once beneficial, always beneficial: No randomization by sex would be needed (sex could only avoid clonal interference). At the same time, if the fitness of an individual were a random function (the most complex function in a Kolmogorov-complexity sense) of the genotype, then again there would be no information to be exposed about the value of an allele by any sampling. It is intriguing, therefore, that if sex implements random sampling, then genetic interactions are important for evolution yet have some structure — they are not overly complex.

At the conceptual level, one may now compare the idea that sex enables random sampling to past ideas on the benefits of sex. Take for example the deterministic mutation hypothesis (DMH, Kondrashov, 1982). Random sampling is a far more widely known and important effect across diverse realms than the effect modeled by DMH. Furthermore, its implication that there must be structured genetic interactions (of any form, but not as complex as random) is a far more plausible *a priori* biological assumption than the requirement of ubiquitous negative synergistic epistasis. Therefore, we believe that the effect of random sampling needs to be considered in trying to expand our understanding of the role of sex in evolution.

Sex is often analyzed in terms of the costs and benefits it may entail to individuals or to populations and how it may have evolved from asex based on them. However, it is neither clear that sex evolved from asex originally[2] nor that substantial adaptive evolution could occur empirically in the long-term in a purely asexual state and serve as a viable point of contrast against which sex could be said to have costs and benefits (Livnat, 2013, p. 5–10). In addition, while modifier theory has been a central tool used to successfully study the evolution of recombination rates, sometimes in connection with perceived benefits of sex (Otto and Lenormand, 2002; Otto and Nuismer, 2004; Keightley and Otto, 2006),

1 For related views on modularity, see Park et al. (2015a,b).

2 An alternative is that advanced sexual mechanisms evolved from a primordial world where natural mixing of materials represented primitive sex; see (Livnat, 2013, p. 5–10).

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it has not been easy to overcome the reduction principle [namely that modifiers for reduced recombination rates are favored (Feldman, 1972; Feldman et al., 1980; Feldman and Liberman, 1986; Altenberg et al., 2017)], nor does it address the emergence of the ability to recombine or the ability to modify recombination rates in the first place. Thus, scientific caution is required when pursuing the question of the evolution of sex including attention to previously implicit assumptions, so that attempts to understand the phenomenon of sex for what it is will not be encumbered by untested hidden assumptions about its own evolution. While an important question, in the current paper we do not consider the question of the emergence of sex, but only attempt to characterize a consequence of sex for evolution, given that it exists.

Since the principle of random sampling is well known, our goal here is not to provide an unexpected mathematical result *per se*, but rather to cast a fundamental biological fact in a new light. We will capture the effect of random sampling by sex with a simple, explicit population genetic model.

2. Model

Evolutionary theoreticians interested in the role of sex in evolution or in the evolution of sex often construe "sex" broadly to mean genetic shuffling, which can take many forms (Barton and Charlesworth, 1998; Livnat, 2013). In eukaryotes, genetic shuffling involves the random assortment of chromosomes, both homologous and non-homologous, as well as recombination within chromosomes, all of which occur during meiosis. In prokaryotes, other events such as conjugation or transformation lead to the shuffling of genes. A one-locus diploid model allows us to examine that part of sexual shuffling which is represented by Mendelian segregation of homologous chromosomes in eukaryotes, and is a mathematically convenient starting point (although later we will comment on the multilocus case, which we expect to show a stronger effect). Consider such a model with many alleles, discrete generations, panmixia and no mutation. We will examine change across one generation only.

Let there be N individuals in the population and n alleles, such that $1 < n \leq 2N$. As we will soon see, for random sampling to be meaningful, N must be substantially smaller than the number of possible genotypes that could be constructed from these alleles, which is $\frac{n(n+1)}{2}$. In other words the number of alleles must not be too small relative to the population size. Closely linked loci, for example nucleotides in a sequence where exchange of segments is rare, would produce a large number of possible alleles with variation at the nucleotide level. Let v_i^t be the number of instances of allele i in the population, and $f_i^t = \frac{v_i^t}{2N}$ be its frequency, at generation t.

To represent Mendelian segregation in the simplest possible way, we will start by considering a diploid population in which random mating occurs by random union of gametes. Under this assumption, the starting population can be represented as a gene pool. Considering cN births in the given generation (c is a parameter representing fertility), we can draw from this gene pool two alleles at random with replacement for each birth. This pair of alleles will form the new genotype, which will then undergo selection. To represent selection, let the fitness of genotype ij, w_{ij}, be its probability of survival (viability, but not fertility, is genetic).

In our model and simulations below, genetic drift is implemented either via the random sampling of gametes (in the gene-pool representation) or via the sampling of individuals for random mating and the random sampling of alleles within individuals due to meiosis (where the initial state consists of individual, diploid genotypes). In addition we allow for further randomness in the change of allele frequencies due to the probabilistic nature of fitness. Note, however, that the effects of genetic drift, though present in the model, are not our focus of interest.

Table 1
Genotype classes and their probabilities of survival.

Genotype class	Number of surviving genotypes	Probability of genotype surviving
$\hat{i}x$	k_1	$p_1 = 2f_{\hat{i}}^t \sum_{l\neq\hat{i},\hat{j}} f_l^t w_{\hat{i}l}$
$\hat{j}x$	k_2	$p_2 = 2f_{\hat{j}}^t \sum_{l\neq\hat{i},\hat{j}} f_l^t w_{\hat{j}l}$
$\hat{i}\hat{j}$	k_3	$p_3 = 2f_{\hat{i}}^t f_{\hat{j}}^t w_{\hat{i}\hat{j}}$
$\hat{i}\hat{i}$	k_4	$p_4 = f_{\hat{i}}^{t\,2} w_{\hat{i}\hat{i}}$
$\hat{j}\hat{j}$	k_5	$p_5 = f_{\hat{j}}^{t\,2} w_{\hat{j}\hat{j}}$

Let us examine a pair of specific alleles, $\hat{i}$ and $\hat{j}$, and let x be any allele other than $\hat{i}$ or $\hat{j}$, $x \neq \hat{i}, \hat{j}$. After random union of gametes, which represents the outcome of sexual reproduction, 5 classes of genotypes may be obtained that include $\hat{i}$ and/or $\hat{j}$, namely $\hat{i}x$, $\hat{j}x$, $\hat{i}\hat{j}$, $\hat{i}\hat{i}$ and $\hat{j}\hat{j}$, as shown in Table 1. Let $k_1, \ldots, k_5$ be the number of surviving genotypes of each class, and let $p_1, \ldots, p_5$ be the probabilities that a genotype in each class survives (see Table 1).

The probabilities $p_1, \ldots, p_5$ do not sum up to 1 because they do not include probabilities of no survival or of genotypes not involving $\hat{i}$ or $\hat{j}$. We let k_6 be the number of genotypes (of cN births) that either did not survive or carried neither allele $\hat{i}$ nor $\hat{j}$, $k_6 = cN - k_1 - k_2 - k_3 - k_4 - k_5$, and let $p_6 = 1 - p_1 - p_2 - p_3 - p_4 - p_5$ be the probability of a genotype in that category.

Effective random sampling exists when two conditions are met: First, the probability of "error" in the inference made regarding the space of potential genotypes must be small, and second, the size of the finite population (the sample size) must be small compared to the space of genotypes being sampled.

Using our one-locus diploid population genetic model, we will examine the first condition with the help of the probability P that allele $\hat{i}$ will fare better (increase relatively more in frequency) than allele $\hat{j}$ in the *finite* population in the current generation, $P\left(\frac{f_{\hat{i}}^{t+1}}{f_{\hat{i}}^t} > \frac{f_{\hat{j}}^{t+1}}{f_{\hat{j}}^t}\right)$, given that it would have fared better in an analogous *infinite* population testing all possible genotypes, a condition described by the following inequality:

$$\frac{p_1 + p_3 + 2p_4}{f_{\hat{i}}^t} > \frac{p_2 + p_3 + 2p_5}{f_{\hat{j}}^t}. \tag{1}$$

In other words, P is the probability of "correct inference" [under condition (1)].[3]

Now, the probability $P\left(\frac{f_{\hat{i}}^{t+1}}{f_{\hat{i}}^t} > \frac{f_{\hat{j}}^{t+1}}{f_{\hat{j}}^t}\right)$ equals $P\left(\frac{v_{\hat{i}}^{t+1}}{v_{\hat{i}}^t} > \frac{v_{\hat{j}}^{t+1}}{v_{\hat{j}}^t}\right)$. Therefore:

$$P = \sum_{k_1+k_2+\cdots+k_6=cN} \binom{cN}{k_1, k_2, \ldots, k_6} p_1^{k_1} p_2^{k_2} p_3^{k_3} p_4^{k_4} p_5^{k_5} p_6^{k_6} \times F(k_1, k_2, k_3, k_4, k_5), \tag{2}$$

where

$$F(k_1, k_2, k_3, k_4, k_5) = \begin{cases} 1 & \text{if } \frac{k_1+k_3+2k_4}{f_{\hat{i}}^t} > \frac{k_2+k_3+2k_5}{f_{\hat{j}}^t} \\ 0 & \text{otherwise.} \end{cases}$$

[3] Of course, we do not use the terms "randomization" and "inference" to imply that the process of natural selection in the presence of sex is a conscious process that is purposefully randomizing genotypes in order to make an inference, but rather to point out that this process is such that its outcome is one that would have been achieved by applying randomization and inference-making.

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Starting from equal frequencies

To satisfy the first condition for random sampling by Mendelian segregation of homologous chromosomes, we must show that the probability P is large, but this goal must be simplified and refined first. In particular, it is pedagogically helpful to start from equal allele frequencies, for two reasons. First, if only few alleles relative to the population size are very common, and the rest are very rare, then overall the finite population must behave very similarly to the infinite population in the sense that all possible combinations of high frequency alleles will be sampled many times (the very rare alleles will be dominated by drift). Assuming $f_i^t = f_j^t \ \forall i, j$ provides a simple way of examining that aspect of the finite population that is of interest here: It allows us to examine allele frequency dynamics when the finite population can test only a small fraction of the genotypes that these alleles could make, in a case where all these genotypes must be considered important because they are all equally likely to appear, even though only a small fraction of them will.

Second, let us define the mixabilities of alleles $\hat{i}$ and $\hat{j}$, $\mu_{\hat{i}}$ and $\mu_{\hat{i}}$ respectively, as the arithmetic means of the fitnesses of the genotypes carrying these alleles, namely $\mu_{\hat{i}} = \frac{1}{n}\sum_l w_{\hat{i}l}$ and $\mu_{\hat{j}} = \frac{1}{n}\sum_l w_{\hat{j}l}$, respectively (since $f_i^t = f_j^t = \frac{1}{n}\ \forall i, j$, in this case, these are the marginal average allele fitnesses, although mixability in general is not equivalent to marginal fitness; see Livnat et al., 2008). Now imagine for example that $\mu_{\hat{j}} > \mu_{\hat{i}}$, allele $\hat{j}$ is very common, allele $\hat{i}$ is very rare, the fitness of genotype $\hat{\hat{i}}\hat{\hat{j}}$ is very high, and all other fitnesses are very low. This case demonstrates that, when the allele frequencies are not all equal, one can choose $f_{\hat{i}}^t, f_{\hat{j}}^t$ and w such that the frequency of allele $\hat{i}$ will jump in the first generation from near 0 to near 50% and the frequency of $\hat{j}$ will jump from near 100% to near 50%, even though allele $\hat{j}$ has higher mixability. By choosing $f_i^t = f_j^t \ \forall i, j$, we exclude such artificial cases and make the interpretation of F and inequality (1) easier, because they can now be understood directly in terms of the mixabilities of alleles $\hat{i}$ and $\hat{j}$, as shown below.

Under the simplification $f_i^t = f_j^t \ \forall i, j$, we now obtain the probabilities in Table 2.

Now,

$$P\left(\frac{f_{\hat{i}}^{t+1}}{f_{\hat{i}}^t} > \frac{f_{\hat{j}}^{t+1}}{f_{\hat{j}}^t}\right) = P\left(v_{\hat{i}x}^{t+1} + 2v_{\hat{\hat{i}}\hat{\hat{i}}}^{t+1} > v_{\hat{j}x}^{t+1} + 2v_{\hat{\hat{j}}\hat{\hat{j}}}^{t+1}\right),$$

where v_{yz} is the count of genotype yz in the population, p_6 and k_6 are defined as before, and therefore:

$$P = \sum_{k_1+k_2+\cdots+k_6=cN} \binom{cN}{k_1, k_2, k_3, k_4, k_5, k_6} p_1^{k_1} p_2^{k_2} p_3^{k_3} p_4^{k_4} p_5^{k_5} p_6^{k_6} \times F(k_1, k_2, k_4, k_5), \tag{3}$$

where

$$F(k_1, k_2, k_4, k_5) = \begin{cases} 1 & \text{if } k_1 + 2k_4 > k_2 + 2k_5 \\ 0 & \text{otherwise.} \end{cases}$$

(Note that p_3 and k_3 drop out because of the assumption of equal allele frequencies.)

As before, we want to show that P is large given that

$$p_1 + 2p_4 > p_2 + 2p_5,$$

or:

$$\sum_l w_{\hat{i}l} > \sum_l w_{\hat{j}l}. \tag{4}$$

Inequality (4) (when multiplied by $\frac{1}{n}$) involves precisely the mixabilities of alleles $\hat{i}$ and $\hat{j}$, respectively. In other words, starting from equal allele frequencies, we want to show that if the mixability of allele $\hat{i}$ in the *infinite* population is sufficiently larger than that of allele $\hat{j}$, then the probability that the frequency of allele $\hat{i}$ will be higher than that of $\hat{j}$ in the next generation in the *finite* population is large.

Table 2
Genotype classes and their probabilities of survival; the simple case.

Genotype class	Number of surviving genotypes	Probability of genotype surviving
$\hat{i}x$	k_1	$p_1 = \frac{2}{n^2}\sum_{l\neq\hat{i},\hat{j}} w_{\hat{i}l}$
$\hat{j}x$	k_2	$p_2 = \frac{2}{n^2}\sum_{l\neq\hat{i},\hat{j}} w_{\hat{j}l}$
$\hat{\hat{i}}\hat{\hat{j}}$	k_3	$p_3 = \frac{2}{n^2} w_{\hat{\hat{i}}\hat{\hat{j}}}$
$\hat{\hat{i}}\hat{\hat{i}}$	k_4	$p_4 = \frac{1}{n^2} w_{\hat{\hat{i}}\hat{\hat{i}}}$
$\hat{\hat{j}}\hat{\hat{j}}$	k_5	$p_5 = \frac{1}{n^2} w_{\hat{\hat{j}}\hat{\hat{j}}}$

To meet the second condition for random sampling by sex, we must check that the number of genotypes actually represented is relatively small compared to the size of the space being sampled. For this purpose, let $G(N, c, n)$ be the expected number of different genotypes tested by the finite population in the span of one generation:

$$G(N, c, n) = \sum_{m_{11}=0}^{cN} \sum_{m_{12}=0}^{cN-m_{11}} \sum_{m_{13}=0}^{cN-m_{11}-m_{12}} \cdots \sum_{m_{22}=0}^{cN-\cdots} \sum_{m_{23}=0}^{\cdots} \cdots \sum_{m_{33}=0}^{\cdots} \cdots \cdot \binom{cN}{m_{11}, m_{12}, m_{13}, \ldots, m_{22}, m_{23}, \ldots, m_{33}, \ldots} \cdot \left(f_1^2\right)^{m_{11}} (2f_1f_2)^{m_{12}} (2f_1f_3)^{m_{13}} \cdots \cdot \left(f_2^2\right)^{m_{22}} (2f_2f_3)^{m_{23}} \cdots \left(f_3^2\right)^{m_{33}} \cdots \cdot H(m_{11}, m_{12}, m_{13}, \ldots, m_{nn}) \tag{5}$$

where H is the number of m terms that are larger than zero. After simplification, the product of f terms becomes $\left(\frac{1}{n^2}\right)^{cN} 2^{\sum_{y\neq z} m_{yz}}$ Now, while G is the expected number of different genotypes tested by the finite population, let $g(N, c, n)$ be the fraction of this number of genotypes tested among all possible genotypes, $g(N, c, n) = \frac{2G(N,c,n)}{n(n+1)}$.

We now have two functions, $g(N, c, n)$ and $P(N, c, n, \mu'_{\hat{i}}, \mu'_{\hat{j}}, w_{\hat{\hat{i}}\hat{\hat{i}}}, w_{\hat{\hat{j}}\hat{\hat{j}}})$, where $\mu'_{\hat{i}} = \frac{1}{n}\sum_{l\neq\hat{i},\hat{j}} w_{\hat{i}l}$ and $\mu'_{\hat{j}} = \frac{1}{n}\sum_{l\neq\hat{i},\hat{j}} w_{\hat{j}l}$. P being large means that the probability of correct inference regarding the alleles' relative performance in the population comprising all possible genotypes is large. g being small means that the genotypes sampled are a small fraction of all possible genotypes. Therefore, if P can be large and g can be small at the same time, then sex can implement random sampling. If so, the conditions where P is large and g is small are the conditions under which sex (in the form of Mendelian segregation of homologous chromosomes) implements random sampling in the one-locus diploid model.

Description of the simulation

While the above calculations give us in principle the exact values of P and g, it is not practical to run these calculations on a computer for all but the smallest populations, because of the large multinomial coefficients. However, it is possible to simulate the calculation above in a very simple way.

For the $\frac{n(n+1)}{2}$ genotypes of the diploid one-locus model with n alleles, for each trial of the simulation, we randomized the fitness values w_{ij} such that the two alleles of interest, $\hat{i}$ and $\hat{j}$ with mixabilities $\mu_{\hat{i}}$ and $\mu_{\hat{j}}$ defined as before, namely $\mu_{\hat{i}} = \frac{1}{n}\sum_l w_{\hat{i}l}$ and $\mu_{\hat{j}} = \frac{1}{n}\sum_l w_{\hat{j}l}$, respectively, had a mixability ratio of $\sum_l w_{\hat{i}l} / \sum_l w_{\hat{j}l}$

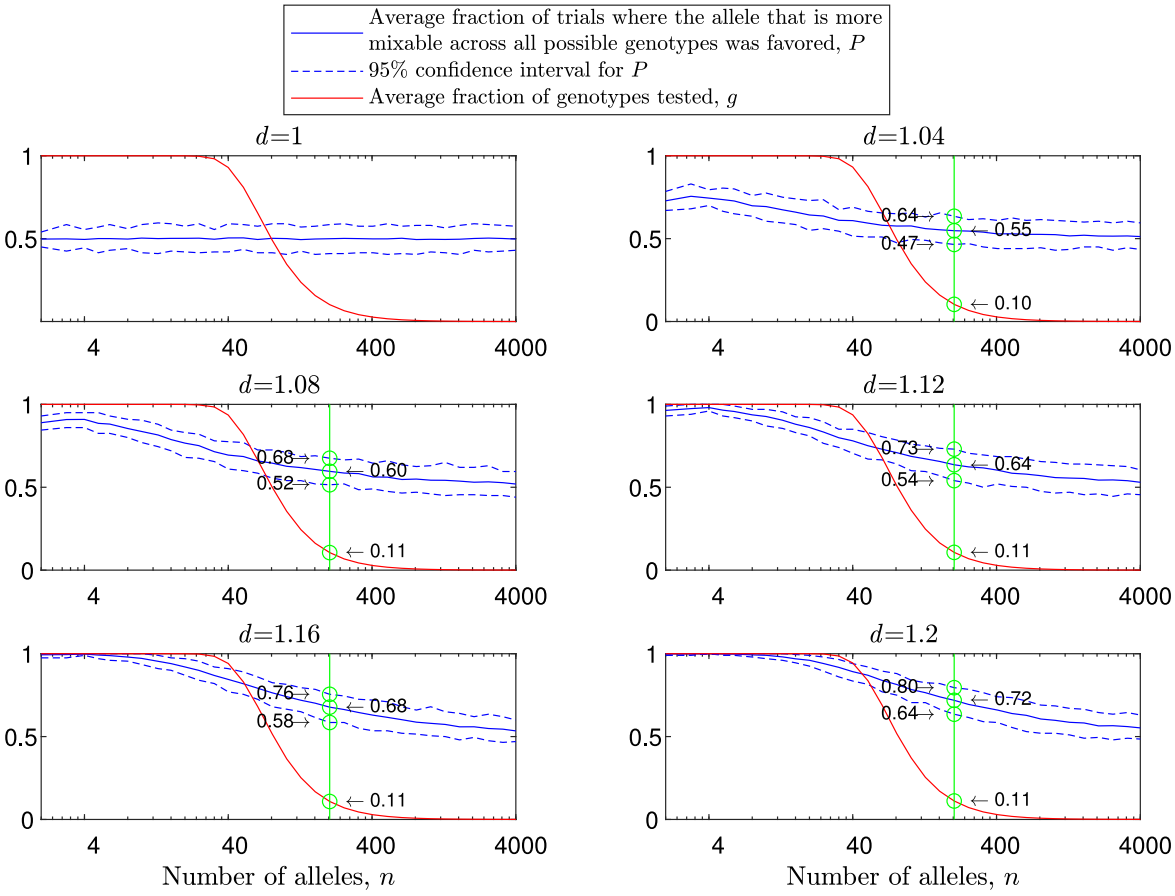

Fig. 1. Sex enables random sampling in a single-locus diploid model. In each panel, results from a mixability-based comparison of two alleles are shown for a population size of 2000 and for a varying number of alleles from 2 to 4000. In each panel, for each number of alleles, based on 200 independent runs of 100 independent trials each, the red line shows the average fraction of all possible genotypes that actually materialized and were tested by the population (for each such genotype, at least one individual was born with that genotype and either survived or did not), the blue solid line shows the average fraction of trials in which the allele that is more mixable across all possible genotypes increased in frequency more than the allele that is less mixable across all possible genotypes, and the blue dashed lines demarcate the 95% confidence interval of the latter, obtained empirically by excluding the top and bottom 2.5% of the runs. Each panel shows the results of this analysis for a different ratio d of mixabilities of the two alleles of interest (see main text for procedure), ranging from 1 to 1.2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

almost equal to a pre-chosen value, $d_{\tilde{ij}}$, as follows. Fitness values were first set as

$$w_{ij} = 1 - h_{ij}s,$$

where the h_{ij} were drawn from the uniform distribution over the interval $[0, 1]$, and s is a parameter representing selection strength. Then, the fitness values of alleles $\hat{i}$ and $\hat{j}$ were adjusted as follows:

$$w_{\hat{i}k} := w_{\hat{i}k}\sqrt{\frac{d_{\tilde{ij}}\sum_{l\neq\hat{i}} w_{\hat{j}l}}{\sum_{l\neq\hat{j}} w_{\hat{i}l}}}$$

and

$$w_{\hat{j}k} := w_{\hat{j}k}\sqrt{\frac{\sum_{l\neq\hat{j}} w_{\hat{i}l}}{d_{\tilde{ij}}\sum_{l\neq\hat{i}} w_{\hat{j}l}}}.$$

These adjusted values have a mixability ratio between $\hat{i}$ and $\hat{j}$ nearly equal to $d_{\tilde{ij}}$.

At each "trial run" of the simulation, a generation was created by repeatedly drawing a pair of alleles ij at random with equal probabilities across the alleles (reflecting the assumption of equal starting allele frequencies) and allowing it to survive with probability w_{ij}, until N surviving individuals were obtained, where N is the population size. At the same time, the number of different genotypes that materialized in the process (namely the number of genotypes that were tested at least once, whether they survived or not) was recorded.

Finally, for each mixability ratio $d_{\tilde{ij}}$, number of alleles n and population size N, multiple independent trials were run. The across-trials average fraction of all possible genotypes that materialized and were tested by the population, $g(N, c, n)$ (where the c value is implicitly defined by the simulation procedure), was then calculated. Then the fraction of trials in which, of the particular allele pair $\hat{i}$ and $\hat{j}$, the allele that was more mixable across all possible genotypes increased in frequency more than the allele that was less mixable across all possible genotypes was recorded (ties in this measure, whether due to equal mixabilities or due to an equal change in frequency, were counted as "half a point" for each allele). For clarity, we note that our results discussed below capture the fact that sex promotes the ability of alleles to perform well in the vast number of yet unseen combinations of existing alleles. They do not, however, capture in and of themselves the ability of alleles to perform well in interaction with alleles that have not yet been created.

3. Results

Fig. 1 shows the results of such a simulation for a population size of $N = 2000$ diploids, $d_{\tilde{ij}}$ values ranging from 1 to 1.2, selection strength s of 0.2 and 100 independent trials for each parameter combination. In the top-left panel, where $d_{\tilde{ij}} = 1$, the alleles are equally mixable by definition, and the blue line shows random

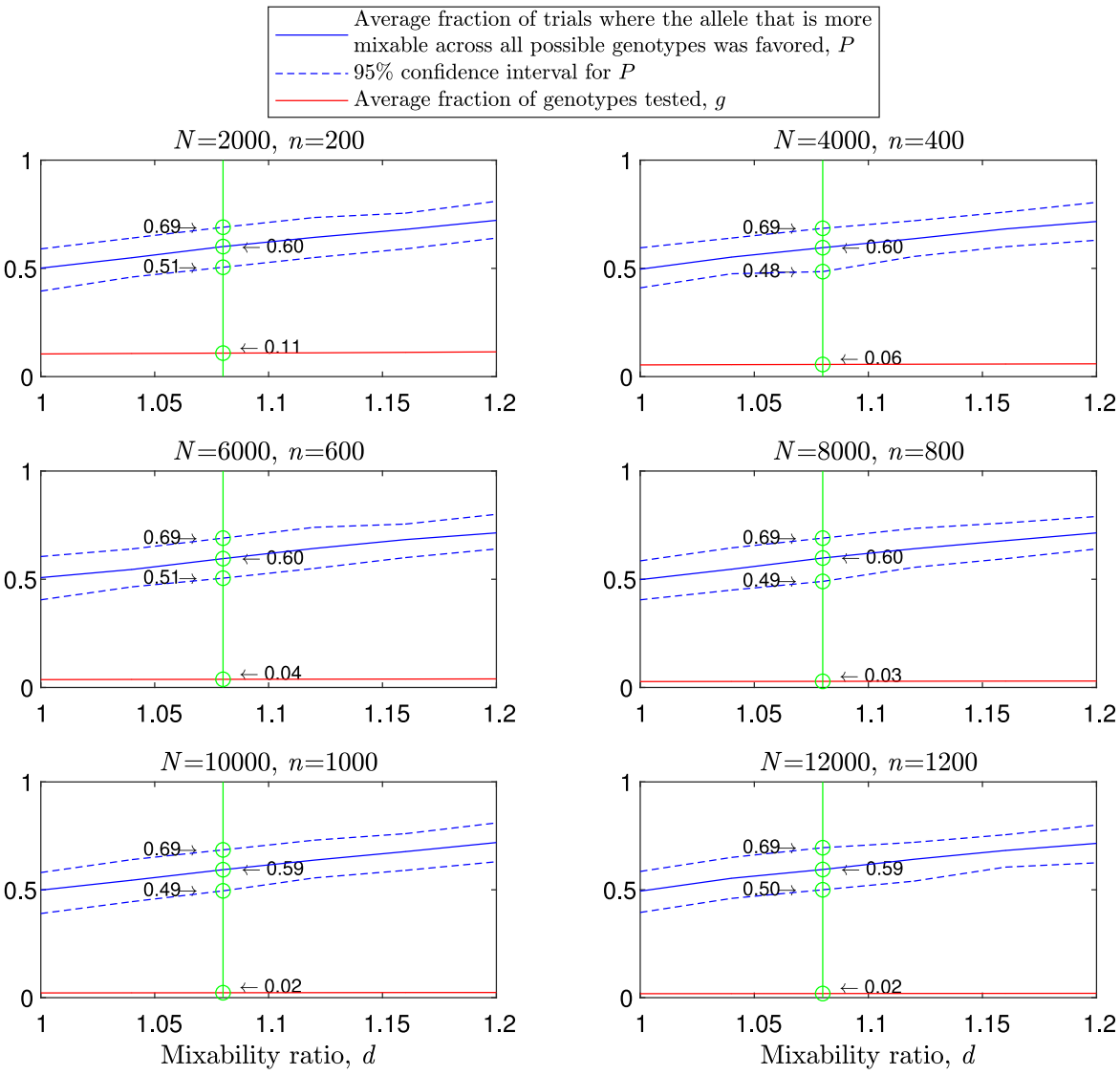

Fig. 2. Random sampling in a single-locus diploid model for different population sizes. The mixability-based comparison of the two focal alleles is shown in each panel for a few mixability ratios d ranging from 1 to 1.2 on the x-axis. For each d value, based on 200 independent runs of 100 independent trials each, the red line shows the average fraction of all possible genotypes that actually materialized and were tested by the population, the blue solid line shows the expected fraction of trials in which the allele that is more mixable across all possible genotypes increased in frequency more than the allele that is less mixable across all possible genotypes, and the blue dashed lines demarcate the 95% confidence interval of the latter. Each panel shows the results of this analysis for a different pair of N and n, which are multiples of 2000 and 200, respectively. The green line shows the particular values of the two measures plotted at $d = 1.08$, for demonstration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

deviations from equal frequencies; this serves as a "control" condition. All other panels can be understood as follows. On the left side of each panel, each allele is represented by many copies (with the extreme at the left end being 2000 instances for each of the 2 alleles), and the number of alleles is small relative to the population size. Therefore, in each of these $d_{\tilde{ij}} > 1$ panels, on the left side, all possible genotypes get tested by the materialized population, and almost always, the more mixable allele wins. On the right side, the number of alleles is large relative to the population size ($2N$ alleles at the right end), each allele is represented by very few copies (a single instance per allele at the right end), and therefore the dynamics of allele frequencies are dominated by drift.

In the middle range, however, the situation becomes interesting. Ranging from a few to a few dozen instances per allele under the given population size, we see that the allele that is more mixable across all possible genotypes is the one more likely to win, even though only a small fraction of all possible genotypes is actually tested. As expected, we see this effect in each panel where $d_{\tilde{ij}} > 1$, and this effect increases with $d_{\tilde{ij}}$. For demonstration, the green line, positioned at $\sim$ 200 alleles, or $\sim$ 20 instances per allele, shows the fraction of times that the allele more mixable across all possible genotypes was favored and the expected fraction of all possible genotypes tested under those parameters; the former fraction is almost always larger than 0.5, while the latter is substantially lower than 0.5. This demonstrates that sex – in this case, Mendelian segregation of homologous chromosomes – enables random sampling in selecting for mixability. Under realistic conditions, the probability of correct evaluation is high while the sample size is low.

Fig. 2 shows the results for the same range of $d_{\tilde{ij}}$ values, now on the x axis, but for different population sizes N and numbers of alleles n, which are multiples of 2000 and 200 respectively. The expected fraction of genotypes tested (red line) increases slightly with $d_{\tilde{ij}}$ because, given the procedure above, larger $d_{\tilde{ij}}$ values force the average of all fitnesses to be lower, and thus more genotypes are lost in generating the next generations' N surviving genotypes.

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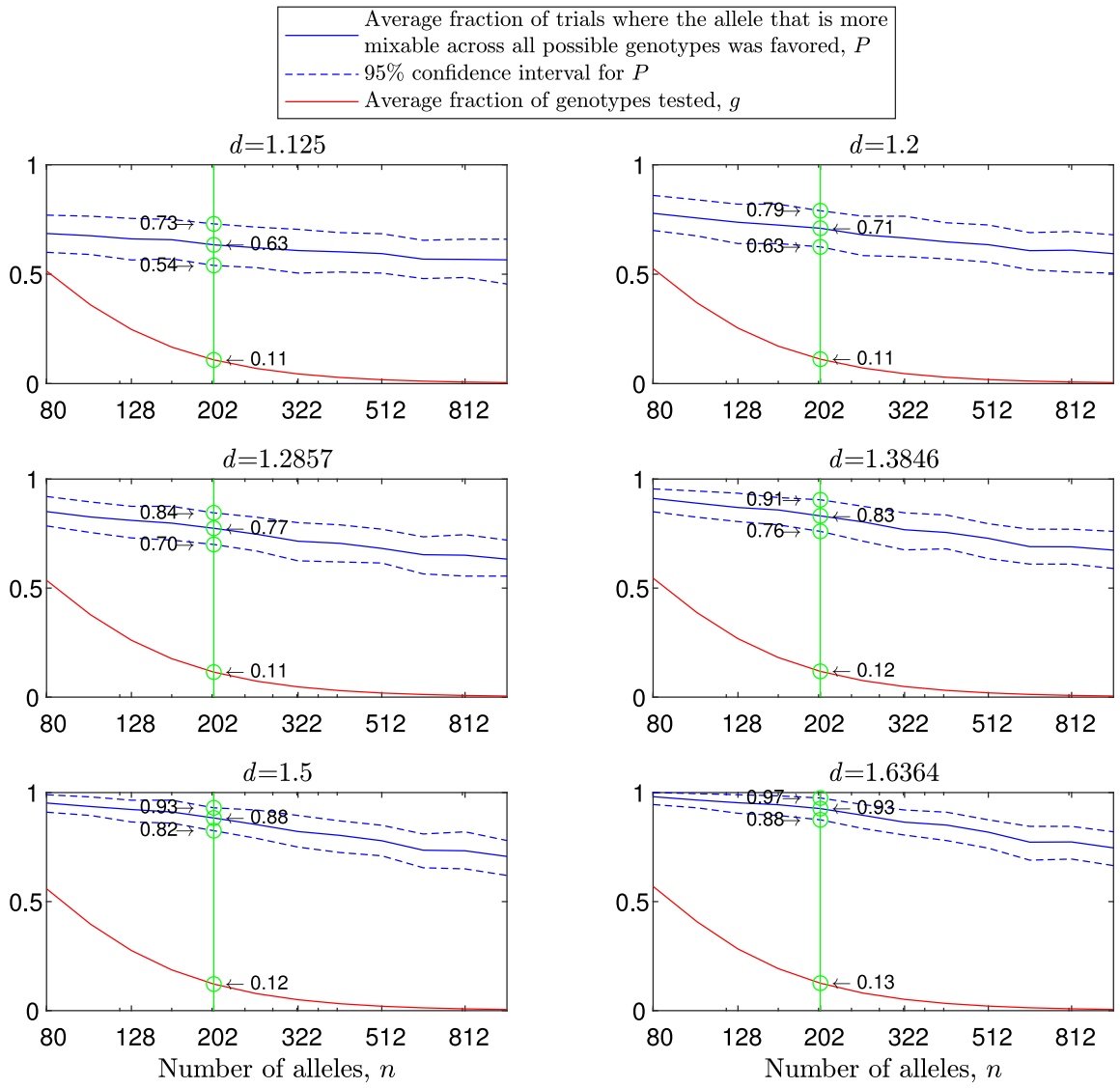

Fig. 3. Random sampling in the single-locus diploid model with fitness values either 0 or 1. In each panel, results are shown for a population size of 2000 and for a varying number of alleles from 80 to 1024. As before, for each number of alleles, based on 200 independent runs of 100 independent trials each, the red line shows the average fraction of all possible genotypes that actually materialized and were tested by the population, the blue solid line shows the average fraction of trials in which the allele that is more mixable across all possible genotypes increased in frequency more than the allele that is less mixable across all possible genotypes, and the blue dashed lines demarcate the 95% confidence interval of the latter. The fraction of genotypes of fitness 1 of all possible genotypes for the more mixable allele is 0.9 for each panel, whereas the fraction of genotypes of fitness 1 of all possible genotypes for the less mixable allele decreases from 0.8 to 0.55, producing a range of d values (the ratio between the fractions of genotypes of fitness 1) from 1.125 to over 1.6. The green line shows the particular values of the two measures for n close to 200, for demonstration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

More importantly, we can see that, as the population size and number of alleles increase, the fraction of all possible genotypes tested decreases substantially, until at $N = 12{,}000$ and $n = 1200$, selection in the presence of sex evaluates the mixability of the full space "correctly" 59% of the times, even though it samples only 2% of all possible genotypes.

Variations of the diploid one-locus case

As noted, one of the causes of random deviations from "correct evaluation" of mixabilities in this model is the probabilistic nature of survival. To study the importance of this source of variance, we have run the same simulations again, but with the fitness of each genotype taking the values of either 0 or 1. The mixability of an allele now can be understood as the fraction of genotypes of fitness 1 that carry this allele, and the parameter $d_{\widetilde{ij}}$ can be understood as the ratio of these fractions for the two alleles of interest. This scenario has a further advantage that now the performance of alleles can be more quickly and intuitively gathered from the numbers. At the same time, we move from representing the starting population with a gene pool to a starting population of concrete, specific genotypes, in order to ensure that no parent of the starting population has fitness 0 (i.e., all parents that survived to replicate have fitness 1).

Note that, at low values of n, the requirement that no parent has fitness 0 conflicts with the pedagogical requirement of equal starting allele frequencies at low values of n. We used a simple procedure to ensure that the starting allele frequencies are equal and that no parent is of fitness zero: we formed parents from an equal number of allele instances for all alleles, and then assigned fitness 0 at random to genotypes that have not been formed, at the rate that would lead to allele mixabilities that closely approximate

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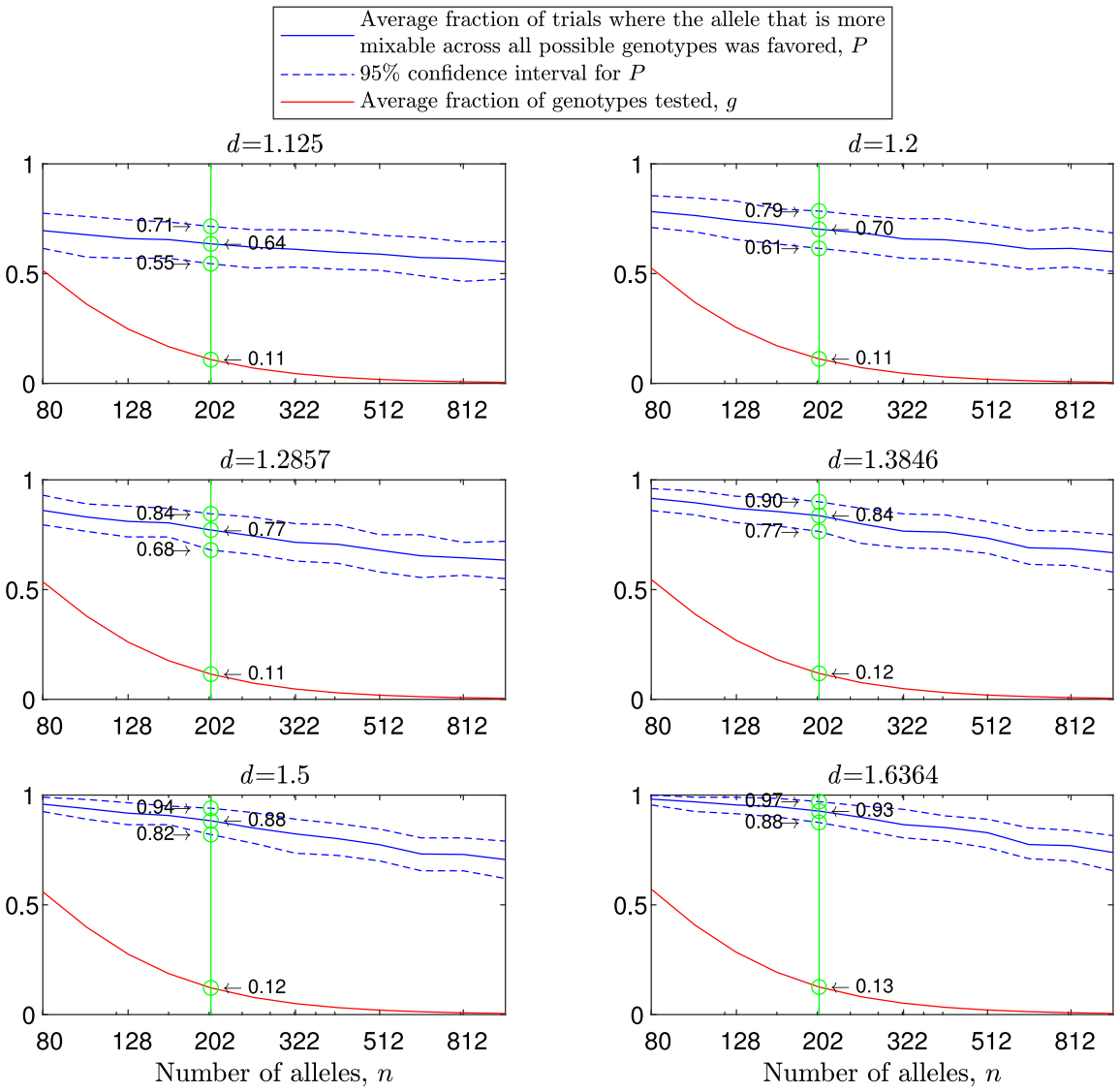

Fig. 4. Random sampling in the single-locus diploid model with fitness values either 0 or 1 and with two mating types. The simulation conditions are as described in Fig. 3, except that now the parents are divided into two mating types, so that mating can occur only between type 1 and type 2 individuals.

the mixability ratio, d_{ij}, chosen for the given simulation. Using this simple procedure, simulations show that, for the given range of parameters, the two requirements mentioned above do not materially conflict at $n \geq 80$. Therefore, we ran the simulations of discrete fitness values for $n \geq 80$.

Fig. 3 shows the results for this scenario, produced in a manner analogous to Fig. 1. For the more mixable allele, the fraction of genotypes with fitness 1 was always fixed at 0.9, and for the less mixable allele this fraction took the values of 0.8, 0.75, 0.7, 0.65, 0.6 and 0.55 across the panels. We see that, for the range of parameters examined before (top two panels), the results remain essentially the same. However, it is now also possible to understand more intuitively the importance of randomization by sex for larger values of d_{ij} (in the previous scenario described by Fig. 1, at values of d_{ij} greater than 1.2, each genotype of the more mixable allele would have had higher fitness than any genotype of the less mixable allele; this is no longer the case here). With the more mixable allele surviving at a rate of 0.9 and the less mixable at the rate of 0.55, with $\sim$ 200 alleles and a population size of 2000, selection makes the "correct" mixability evaluation 93% of the times, even though it tests only 13% of all possible genotypes (Fig. 3, bottom right).

So far, we have examined Mendelian segregation of homologous chromosomes in hermaphrodites capable of selfing. To examine the case of two mating types, we have divided the starting population into two separate types, "type 1" and "type 2," and allowed mating only between types. Results are shown in Fig. 4. Given that the 95% confidence intervals of Figs. 3 and 4 overlap almost entirely, there is no significant difference between the two figures, i.e., no substantial differences appear between hermaphrodites capable of selfing and two mating types — as one might expect.

Besides probabilistic fitness, another, more important cause of random deviations from correct inference of mixabilities is random genetic drift due to the sampling of parents and of alleles within parents with replacement. This sampling creates random variation in the parents' fertilities, as well as random variation in the transmission success of alleles within a parent. To observe the "pure" effect of random sampling by sex for a pedagogical purpose, free of these effects of drift, one can remove these sources of randomness by running the same simulations, while ensuring that each individual appears in exactly two mating events and that each allele is transmitted exactly once.

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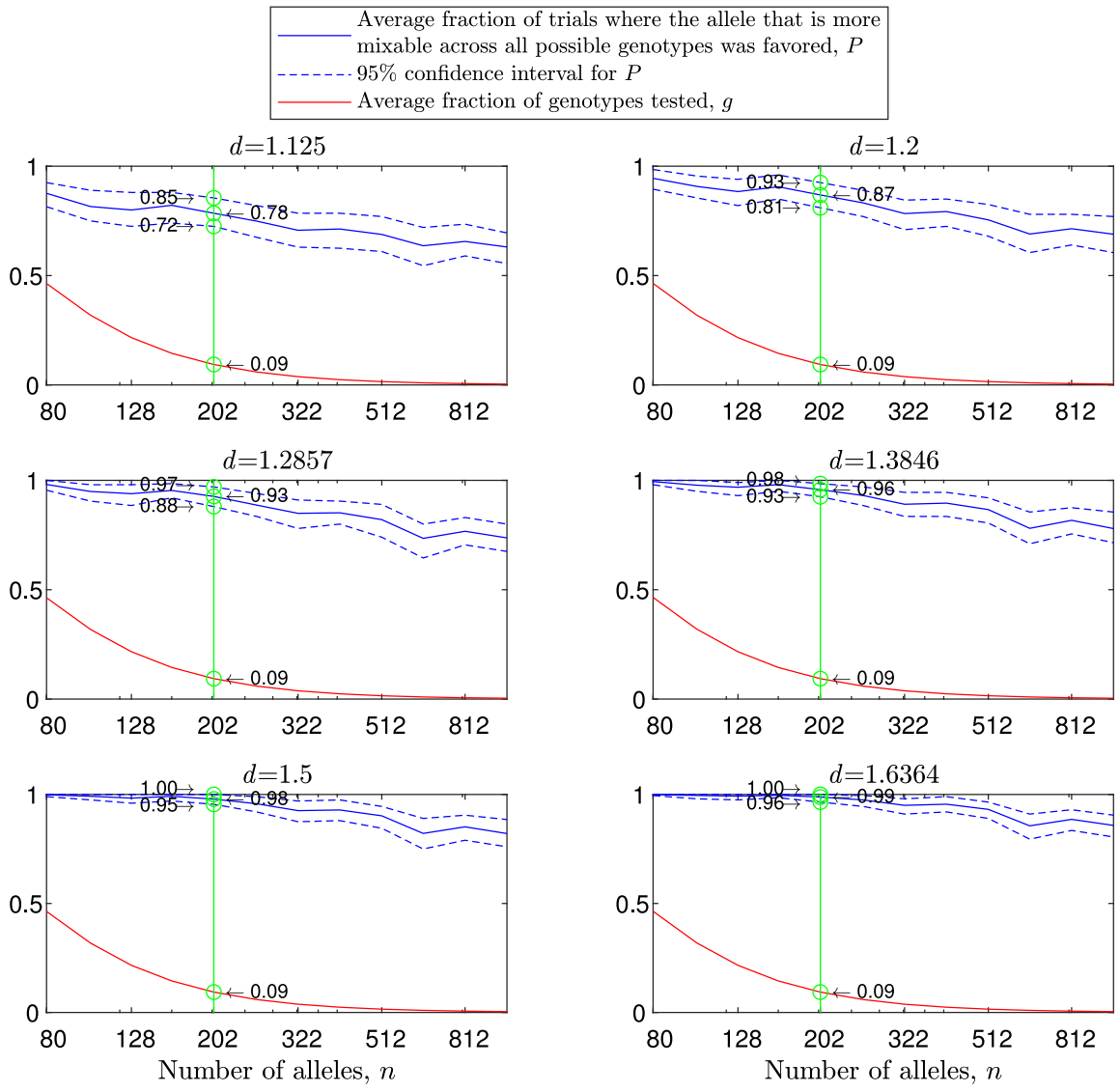

Fig. 5. Random sampling in the single-locus diploid model with fitness values either 0 or 1, two mating types and without replacement of parents and alleles. The simulation conditions are as described in Fig. 4, except that now each parent participates in exactly two reproductive events, and each allele in each parent is transmitted exactly once. The differences between the present figure and Figs. 3 and 4 show the importance of drift due to the sampling of parents and of alleles with replacement. Note furthermore that the number of alleles does not normally divide $2N$. This creates deviations from the assumption of equal frequencies which, given the n values simulated, are strongest at $n = 322$ and $n = 644$, leading to dips at those n values across the 6 panels. If n values are chosen that divide $2N$, the resulting curves would be smooth.

To keep the simulation elegant and simple, this scenario forces us to forgo the constant population size: Instead of generating new individuals until N of them survive, we repeat the simulation now until N parents have appeared in $2N$ mating events. In particular, we have run the simulations with discrete fitness values and with two mating types under this condition.

Fig. 5 shows the results for this scenario in a manner analogous to Fig. 3. With random genetic drift removed, the results are now clearly stronger. Take for example the scenario depicted by the green line in the top-right panel: With a population size of 2000, $\sim$ 200 alleles, and with the more mixable allele surviving at a rate of 0.9 and the less mixable at the rate of 0.75 (top-right panel), selection makes the correct evaluation 87% of the times by testing 9% of all possible genotypes, in contrast to Fig. 3 (drawing parental alleles with replacement), where selection makes the correct mixability evaluation 71% of the times by testing 11% of all possible genotypes under the same conditions. This evaluation reaches a rate of 99% correct with $d_{ij}^{\tilde{\tilde{}}} \approx 1.6$ (bottom-right panel, Fig. 5). Thus, as expected, removing random variation in the fertility of individuals and transmission of alleles increases the accuracy of the evaluation of genetic mixability across all possible genotypes by random sampling due to sex.

The parameter d and the statistical view

It is important to discuss the parameter $d_{ij}^{\tilde{\tilde{}}}$. $d_{ij}^{\tilde{\tilde{}}} \neq 1$ implies that fitness is a non-random function of the alleles in the genotype. It is critical to note, however, that this function need not be additive, and indeed is not additive in our model and simulation. The fact that $d_{ij}^{\tilde{\tilde{}}}$ causes the fitness function to deviate from what would otherwise be a random function is critical. If fitness were a purely random function of the genotype, then no sample would have been informative about the population not sampled, and there would have been no room for random sampling by sex. At the same time, had we defined "beneficial alleles" as alleles that are beneficial across all genetic contexts and simply bound to spread in the

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population once they arise, as in the Fisher–Muller theory of the benefit of sex (Fisher, 1930; Muller, 1932; Crow and Kimura, 1965), then there would have been no room to expose the possible value of an allele in a multigenerational process involving the interaction of sex and natural selection – no room for random sampling by sex – nor for considerations of mixability. Random sampling is only meaningful when the signs of the mixability differences between alleles are *both not known in advance and estimable*. Then, the interaction between sex and natural selection can discover them, which is what we demonstrate here.

Of course, it is possible to look at the above from a basic, statistical point of view. The competition between two alleles in a finite population is equivalent to comparing two samples drawn from two different almost-independent distributions, each sample being a set of genotypes containing one of the alleles. Randomization by sex makes it so that the mixability of each allele in its sample is the best estimate of its mixability in the much larger space of potential genotypes, and that the statistical power of the comparison of mixabilities by selection depends on the difference between the means of the distributions, their variances, and the sample sizes. Statistics textbooks mention randomization as an essential, key element of study design. However, since there is no proper "control group" lacking randomization with which to contrast the randomized group and thus demonstrate the importance of randomization *per se*, we are satisfied with merely pointing out that this randomization is a fundamental idea in statistics and that, once one moves away from the focus on "beneficial alleles" as beneficial across all genetic contexts (Crow and Kimura, 1965) as well as the traditional focus on the population mean fitness measure toward focusing on genetic interactions and mixability, this randomization immediately becomes front and center when examining the question of the role of sex in evolution.

That being said, one way of drawing $2N/n$ genotypes *non*-randomly from the distribution of all potential genotypes with replacement is by drawing the same particular genotype, chosen once at random, $2N/n$ times. It is immediately obvious that, unless the difference in means between two such repetitive samples is large compared to the variances, the probability of "error" in comparing such samples by natural selection is incomparably larger than when drawing genotypes at random $2N/n$ times for each sample[4]. Indeed, an asexual clone is one such repetitive sample.

The multilocus case

The effect demonstrated in the single diploid locus model is not relevant if the number of alleles is too small relative to the population size. N must be substantially smaller than the number of possible genotypes. However, while n alleles per locus give $\frac{n(n+1)}{2}$ genotypes in the single diploid locus model, they give $\left(\frac{n(n+1)}{2}\right)^L$ possible genotypes (under the conservative assumption of no position effects) in the multilocus model with L loci. Therefore, the one-locus diploid model actually gives a severely restricted version of the power of random sampling that sexual reproduction in general provides. With each allele being represented by the same number of instances that overcomes the effects of drift in both kinds of model, the size of the population of potential genotypes being sampled would be vastly greater with multiple loci. Therefore, we predict that the gap between the curve representing the fraction of genotypes tested and the curve representing the probability of correct inference would grow faster with the number of alleles in the multilocus case (and of course much faster as the number of loci increases in the multilocus case), and the results would be much stronger than those of the one-locus diploid model. Indeed, note that any living population can only sample a tiny fraction of the space of possible genotypes that can in principle be created by recombination from the genetic diversity present in it. With a genotype of 100 loci with 2 alleles per locus, for example, the number of possible genetic combinations is 2^{100}, which is incomparably larger than the size of any living population.

Let us now consider L unlinked, interacting loci. In the weak selection regime, where the recombination rate is much larger than fitness differences – a commonly made assumption for unlinked loci (Nagylaki, 1993; Nei, 2005) – the alleles are approximately at linkage equilibrium (Nagylaki et al., 1999). Thus the focal allele will sample partners within and across loci at random from the total space of potential genetic combinations. Selection will then be able to test which alleles will perform better overall in interactions with alleles across loci across a vast space of potential genotypes through only a tiny number of actual tests. In particular, according to an exciting result by Rabani et al. (1995), in a sexual population without selection with multiple loci and two alleles per locus, the mixing time, defined as

$$\tau(\epsilon) = \max_{p_0} \min\{t : \|p_{t'} - p_\infty\| \leq \epsilon \quad \forall t' \geq t\},$$

where p_t is the distribution of genotypes at generation t, $\|\cdot\|$ denotes the variation distance, and $\epsilon \in (0, 1]$, is bounded as follows:

$$\tau(\epsilon) \leq log_{1/(1-r)}\left(\frac{L^2}{\epsilon}\right),$$

where r is the lowest recombination rate in the genome (Rabani et al., 1995). In other words, the mixing time, defined as the shortest time under the worst starting distribution of genotypes to a variation distance between the distribution of genotypes and the stationary distribution, p_∞, that is less than or equal to a constant ϵ is on the order of $\log L$ for free recombination, and on the order of $\frac{\log L}{-\log(1-r)}$ in general. Thus, after only $\log L$ generations in the case of free recombination, each allele will have been removed from its original genetic context, and will be sampling from the full realm of genetic possibilities. By comparison, a Monte Carlo process is said to be *rapidly mixing* if after $\log M$ steps, where M is the total (potential) population, it is sampling from the true distribution (Sinclair, 1993). Rabani et al.'s result shows that recombination creates a kind of "super-rapid" mixing, where true sampling starts after only $\log\log M$ steps (Rabani et al., 1995). Though this result was obtained for recombination without selection, it gives a clear sense of the breadth of sampling of potential genotypes in the multilocus case. Of course, with epistatic selection, the dynamics will depend strongly on the functional form of the epistasis (duPlessis et al., 2016).

4. Discussion

Our model demonstrates an important biological point: Due to the randomization that is due to sex, a small number of tests suffices to find an allele that will perform well as an interacting partner in a large number of unknown and untested genetic combinations — even under the assumption that alleles interact in rather complex, but structured ways. We have demonstrated this in particular for the single locus diploid case (see conceptual figure, Fig. 6) and conjectured that results will only be much stronger for the multilocus case. There is no counterpart for this in asexual populations, in which the same mutation will have to be introduced independently a great number of times into many distinct clones in order to achieve any extensive sampling of genotypes, and the sampling will be constrained to the existing genotypes. Note also that our result could not be achieved assuming an infinite population; there, all possible combinations are immediately tested

[4] $2N/n$ is the maximum number of individuals carrying a given allele in the diploid model when alleles are of equal frequencies.

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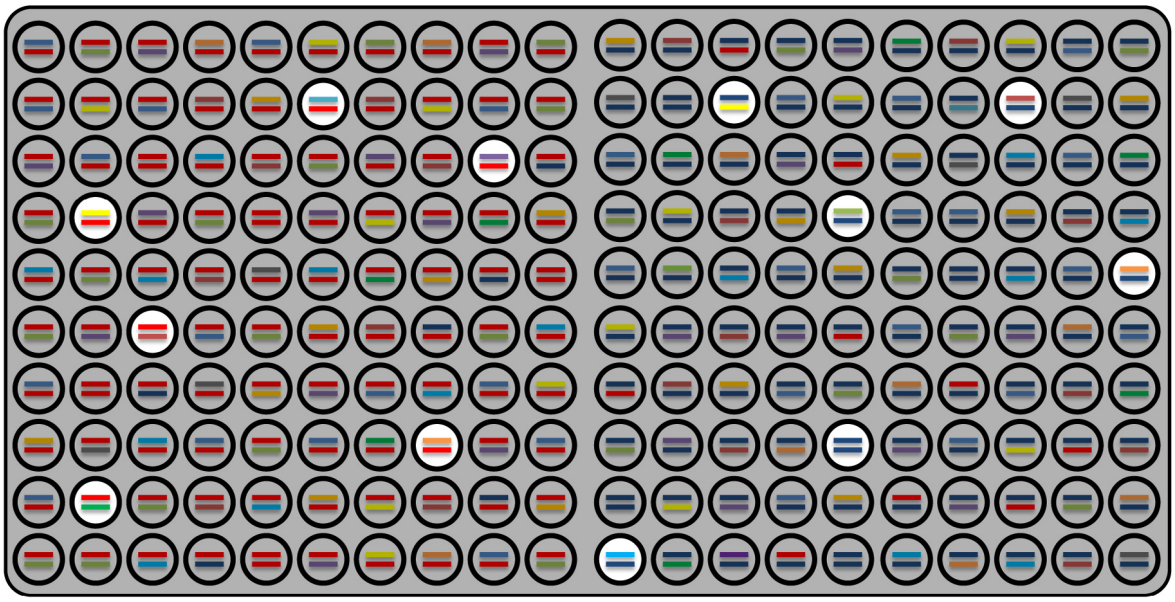

Fig. 6. A schematic figure capturing the meaning of the model. Each circle represents an individual in the 1-locus diploid case. The two lines inside each circle represent the two alleles at the locus under study. The different colors of the lines represent the different alleles that segregate in the population. We are interested neither in the case where "beneficial" alleles are favored across all genetic contexts as in the Fisher–Muller theory (Crow and Kimura, 1965) nor in the case where fitness is a random function of the genotype, but instead in all forms of genetic interactions that have some structure (here, fitness is a function of the *combination* of alleles at the diploid locus). Sexual reproduction entails that the actual genotypes that materialize (white circles) are a random sample drawn from the space of all possible genotypes. These materialized genotypes are then subject to selection, which takes into account the interactions between alleles within each genotype. The alleles that are favored (e.g., red over blue) – the mixable alleles – are ones that have interacted well with their genetic partners overall across the combinations that materialized. However, the alleles thus favored are also, with high probability, ones that will interact well with a far wider variety of existing potential genetic partners in combinations that have not yet materialized (gray circles). This effect is due to randomization. Specifically, it is due to the randomization that sexual reproduction, under the assumption of random mating, entails. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

by selection, and there is no benefit of extrapolation from a small number of tests to a large space of potential possibilities.

Notice that how well an allele performs across genetic contexts is the allele's mixability (Livnat et al., 2008, 2010, 2011; Livnat and Papadimitriou, 2016), defined here as the expected fitness of a genotype carrying this allele in the current mix of potential genotypes. This connects our results to previous theory. However, while previous theory studied mixability in infinite populations (Livnat et al., 2008, 2010, 2011; Livnat and Papadimitriou, 2016), the present effect – sex as random sampling – can be seen as a study of mixability in finite populations (see also Otto and Barton, 2001; Peck, 1994; Howard and Lively, 1994; Hartfield and Otto, 2011, which address the advantage of sex in finite populations). It is interesting that adding a realistic aspect to mixability – i.e., the switch from an infinite to a finite population – adds a new and powerful effect: The ability of natural selection to *act as though* a prediction is made on how an allele will interact with genetic partners in yet unseen combinations.

The present result has an intriguing implication for the nature of genetic interactions. If the fitness of an individual were a random function of its multilocus genotype, the performance of an allele in any finite population would not be indicative of its performance in other genotypes, and there would be no benefit to random sampling. Likewise, if the fitness of an individual were determined by rare additive alleles as assumed by the Fisher–Muller theory for example (Fisher, 1930; Muller, 1932; Crow and Kimura, 1965; Bodmer, 1970), there would be no benefit to random sampling as discussed. Thus, the idea that sex implements random sampling intriguingly implies that alleles across loci interact, but that there is a certain structure to the genetic interactions; fitness is not an entirely random function of them.

Let us now clearly distinguish the present results from past theory. It has already been proposed that the benefit of recombination is that it releases a beneficial mutation from the non-ideal background on which it may have appeared (Fisher, 1930; Muller, 1932; Crow and Kimura, 1965; Hill and Robertson, 1966; Felsenstein, 1974). Based on this, one may try to argue that random sampling is already implicit in such a release, and therefore the random sampling effect of sex is already known and understood. However, those past works asked whether and under what conditions sex enables a faster spread of "beneficial" mutations or a faster destruction of "deleterious" mutations and what the implications are for the population mean fitness measure. They did not concern themselves with exposing the value of a mutation in the first place, or whether sex has consequences that are notable and useful for a more basic process of this sort.

For example, in the classic Fisher–Muller theory, the relevant mutations are defined as "beneficial." Once such a mutation arises, it will spread to fixation deterministically (Crow and Kimura, 1965; Felsenstein, 1974) — in other words, it is conceptualized as beneficial in all genetic contexts, and there is no room for random sampling. This lack of recognition of random sampling can be extended to Muller's ratchet and the Hill–Robertson effect, and Felsenstein has argued that these three are conceptually related (Felsenstein, 1974). Indeed, the fact that previous studies did not draw the implications of random sampling for genetic interactions makes it clear that they did not address the effect of sex as randomization *per se* — randomization in the service of exposing how well alleles will perform in many, yet unseen, genetic combinations.

It is worthwhile to comment on the use of the concept of randomness in evolutionary biology in general. So far, randomness has been perceived as a force that, in and of itself, is capable of directly inventing: Random mutation creates new genetic information and phenotypic change that are subject to selection. This

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notion of mutation, recently criticized by Livnat (2013, 2017), is actually different from its counterpart in evolutionary computation, a field that involves computational problem-solving methods that have been heavily inspired by evolution, such as simulated annealing (Kirkpatrick et al., 1983) or genetic algorithms (Holland, 1975). The difference is that in evolutionary biology, traditional thinking has held that random mutation is ultimately completely uncontrolled – it can disrupt the genome anywhere (but see discussions of evolvability, Sterelny, 2007; Koonin, 2011, and Livnat, 2013, 2017) – whereas in evolutionary computation, it is controlled: Prior knowledge is used to restrict the parameter space to be sampled by mutation in a useful way, the core part of the algorithm does not mutate, and mutation can be further controlled, for example by the gradual lowering of the temperature parameter in simulated annealing. However, moving beyond evolutionary computation to examine not only computer science but science in general and other realms like polling, we have noted that randomization is used there in a way that is very different from randomization as encapsulated in the traditional notion of "random mutation," yet one that is very powerful: It is used to break patterns (to destroy — almost the opposite of invent); and sometimes, breaking a pattern, in conjunction with other elements, is an extraordinarily powerful tool. What if, when randomization is harnessed by biological evolution, it is harnessed in this way? Here, we have argued that sex could be a prime example of this point.

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