Rate of fixation of beneficial mutations in sexual populations

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(Received 16 February 2009; revised manuscript received 15 May 2009; published 11 June 2009)

We have investigated the rate of substitution of advantageous mutations in populations of haploid organisms where the rate of recombination can be controlled. We have verified that in all the situations recombination speeds up adaptation through recombination of beneficial mutations from distinct lineages in a single individual, and so reducing the intensity of clonal interference. The advantage of sex for adaptation is even stronger when deleterious mutations occur since now recombination can also restore genetic background free of deleterious mutations. However, our simulation results demonstrate that evidence of clonal interference, as increased mean selective effect of fixed mutations and reduced likelihood of fixation of small-effect mutations, are also present in sexual populations. What we see is that this evidence is delayed when compared to asexual populations.

DOI: 10.1103/PhysRevE.79.061915 PACS number(s): 87.23.Kg, 87.10.Mn, 02.50.Ey

I. INTRODUCTION

The rate at which natural populations evolve has been a matter of intense study in the recent evolutionary biology literature [1–7]. The gradual development of this issue has enabled us to acquire the knowledge of the several processes driving the evolution of these populations. From these recent achievements in experimental evolutionary biology, today we know that the rate of production of new beneficial variants in natural populations is much larger than previously supposed [2,6,8].

This fact has several important consequences, especially for asexual populations, where this large supply of beneficial mutations can actually slow down the rate at which these advantageous mutations fix in the populations, a process which is known as clonal interference [1,9]. On the other hand, if the rate of beneficial mutations is extremely large then clonal interference can be alleviated [6], giving rise to the multiple-mutation regime, where now more than one segregating beneficial mutation can reach fixation simultaneously. Empirical evidence of this regime has been demonstrated in yeast [8] and bacteriophage [6].

Most of the recent analysis of speed of adaptation in populations has considered asexual populations. All these previous works have helped us to understand how different mechanisms contribute to increase or decrease the strength of clonal interference. Among these mechanisms we mention deleterious mutations [3,10,11], population structure [12–14], environmental heterogeneity [15,16] and population bottlenecks [4].

Here we want to quantify how sex and recombination can alter the strength of clonal interference and the occurrence of the multiple-mutation regime. Sex and recombination is one of the evolutionary mechanisms pointed out to speed up adaptation by combining beneficial mutations on different backgrounds to form better adapted organisms. This is one of the possible explanations for the spreading of the sexual mode of reproduction. In addition, sex has also a crucial role on eliminating deleterious mutations and restoring best adapted classes of organisms, and in a broad range of parameters can even stop Muller's ratchet [17,18], which is the continuous loss of the most adapted organisms and that can even lead the population to extinction [19,20].

Our main goal is to understand this transition, in terms of rate of adaptation, from a completely asexual population to one where the mode of reproduction is sexual. Additionally, we want to check whether signatures of clonal interference persist in a population where recombination occurs. In order to do that, we perform a statistical analysis on the rate of fixation of advantageous mutations as well as on the distribution and mean values of selective effects of mutations that have reached fixation.

Our paper is organized as follows. In the next section we describe the computer simulation model we employ in our investigation. In Sec. III we present our simulation results together with some analytical predictions. And finally, in the last section we discuss our conclusions.

II. MODEL

We consider a sexual population of haploid organisms of constant size N. The population evolves with nonoverlapping generations and those individuals which are most adapted are most likely to contribute with more offsprings to the next generation (Wright-Fisher model). Every individual is represented by a genome consisting of L genes, where each gene is assumed to be infinitely long, i.e., it behaves as an infinite

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sites model. The model assumes the occurrence of both beneficial and deleterious mutations. There are on average U_b beneficial and U_d deleterious mutations per genome per reproduction. Thus during replication, the offspring inherits the mutations (beneficial and deleterious) carried on by its parent genome plus additional mutations taken from a Poisson distribution of mean U_b (beneficial mutations) and U_d (deleterious mutations). Each mutation changes a new site in a randomly chosen locus. The effect on fitness of each deleterious mutations is assumed to be constant with value s_d, whereas beneficial mutations have their effects drawn from an exponential distribution of mean $1/\alpha$,

$$P(s_b) = \alpha \exp(-\alpha s_b). \tag{1}$$

The choice of this particular distribution for beneficial effects of advantageous mutations is supported on empirical evidence [21–24], and also based on theoretical grounds which makes use of extreme value theory arguments [25,26,29], though other distributions must not be rejected [24,27,28]. Actually, this is a current issue of great importance in the population genetics and evolutionary biology literature with consequences on several adaptive scenarios. The great challenge in inferring directly the distribution of effects of newly arising mutations is that most of the mutations appear in very low frequency in the populations and are rapidly lost due to drift or interference with other mutations. So, the idea is to infer $P(s_b)$ from the distribution of fixed mutations, which is usually bell shaped.

Since we assume that each gene behaves as an infinite site model and in this case we neglect the occurrence of back mutations, an individual's genome is represented as a sequence of size L, where each site is characterized by the number of deleterious and beneficial mutations it carries $\mathbf{S} = \{n_b^1, n_d^1; n_b^2, n_d^2; \ldots; n_b^L, n_d^L\}$, where n_b^i and n_d^i correspond to the numbers of beneficial and deleterious mutations in site i, respectively. For a multiplicative fitness landscape, as considered here, the fitness value of each individual is estimated as

$$\omega = \left[\prod_{i=1}^{L} (1 - s_d)^{n_d^i}\right]\left[\prod_{i=1}^{L}\prod_{j=1}^{n_b^i} (1 + s_b^j)\right], \tag{2}$$

where s_b^j is the selective advantage conferred by the j-nth mutation in gene i.

We consider the following life cycle: recombination, mutation, and selection. During recombination, $N/2$ pairs of individuals are randomly formed and then they recombine with probability r. If they recombine the position for the genetic exchange, L_{exc}, is randomly determined. Whether we represent the given pair of individuals as $\mathbf{S}_1 = \{n_{1b}^1, n_{1d}^1; n_{1b}^2, n_{1d}^2; \ldots; n_{1b}^L, n_{1d}^L\}$ and $\mathbf{S}_2 = \{n_{2b}^1, n_{2d}^1; n_{2b}^2, n_{2d}^2; \ldots; n_{2b}^L, n_{2d}^L\}$, then after the recombination event individuals 1 and 2 become $\mathbf{S}_1 = \{n_{1b}^1, n_{1d}^1; n_{1b}^2, n_{1d}^2; \ldots; n_{2b}^{L_{exc}}, n_{2d}^{L_{exc}}; \ldots; n_{2b}^L, n_{2d}^L\}$ and $\mathbf{S}_2 = \{n_{2b}^1, n_{2d}^1; n_{2b}^2, n_{2d}^2; \ldots; n_{1b}^{L_{exc}}, n_{1d}^{L_{exc}}; \ldots; n_{1b}^L, n_{1d}^L\}$, respectively, and of course their adaptation values are re-evaluated. Our model is closely related to that proposed by Keightley and Otto [30], except that they do not assume the occurrence of advantageous mutations. Additionally, in their model the number of recombination events for each mating pair is not necessarily equal to one as assumed here, but it is taken from a Poisson distribution.

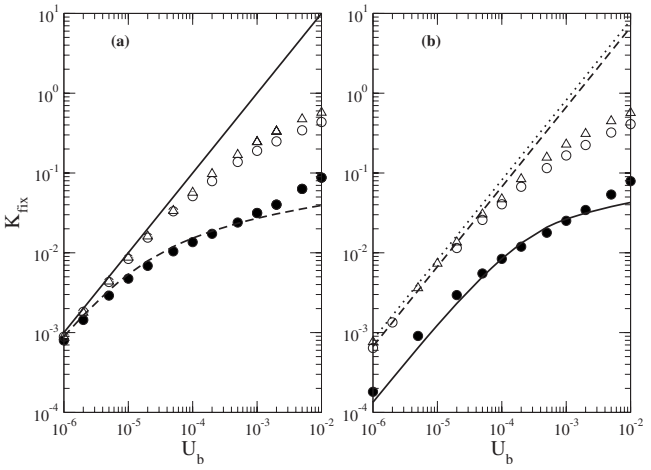

FIG. 1. Rate of fixation of advantageous mutations, K_{fix}, as a function of the rate of beneficial mutations, U_b. In this plot we have considered population size $N=10\,000$, $\alpha=20$, and rates of recombination $r=0$ (filled circles), $r=0.5$ (empty circles) and $r=1.0$ (triangles up). The rate and selective effects of deleterious mutations are: part (a) $U_d=0$; part (b) $U_d=0.2$ and $s_d=0.1$. The solid line in part (a) denotes the strong-selection weak-mutation approximation according to Eq. (3), whereas the dashed-line refers to the theoretical prediction according to Eq. (4). In part (b) the solid line refers to the numerical solution of Eq. (6), whereas the dashed-lines represent an upper bound for the rate of fixation when recombination occurs, $K_{fix}^{upper} = 2NU_b f_r/\alpha$.

In our simulations we first let the population evolve in such way to reach an equilibrium regime, and after that we start to track the fate of all newly arisen beneficial mutations. The time to achieve an equilibrium distribution of deleterious mutations is proportional to $1/s_d$ [14]. In most of our simulations the time to equilibrium was set to 1000 generations. For all the simulations, we have considered a much longer time in order to ensure equilibrium was reached. Fixation of a particular mutation at a site corresponds to its presence in every individual in the population. One measures the rate of fixation of advantageous mutations as the number of fixation events in a given time interval divided by its length. In most of our simulations, the population evolved until 50 fixation events were found, except for very small rates of beneficial mutations where the time required for such threshold was extremely large.

III. RESULTS AND DISCUSSIONS

From now, we will present our results from extensive computer simulations together with some theoretical predictions. In Fig. 1 we show the rate of substitution of beneficial mutations, K_{fix}, as a function of the rate of beneficial mutations U_b. As expected, K_{fix} is a monotonically increasingly function of U_b in all situations. Part (a) displays K_{fix} for different rates of recombination in the simplest scenario

where there are no deleterious mutations ($U_d=0$). In the plot we already perceive that the sexual mode of reproduction provides a higher rate of adaptation for $U_b \simeq 1\times 10^{-5}$. From this point, coexistence of segregating beneficial mutations is possible, and so in an asexual population ($r=0$) this coexistence leads to the competition among beneficial mutations in a way to reach fixation. This process, named clonal interference, slows down the rate of fixation of advantageous mutations [3,4,9,10,14]. For small U_b values, K_{fix} is well predicted by

$$K_{fix} = NU_b \int_0^\infty 2s_b \alpha e^{-\alpha s_b} ds_b = 2NU_b/\alpha, \tag{3}$$

where NU_b is the expected number of newly arising beneficial mutations per generation, and $2s_b$ is the probability of fixation of a given mutation of selective effect s_b [31]. This approximation is expected to work in the strong-selection weak-mutation regime, where the rate of adaptation is bounded by the availability of beneficial mutations [25]. For sexual reproduction, Eq. (3) fits well the simulation results for a wider range of U_b, and deviations from theoretical expectations starts to occur only when NU_b is close to one, which corresponds to a regime of very strong competition, involving several segregating beneficial mutations in the same lineage.

In order to predict the rate of fixation of mutations in the clonal interference regime, Gerrish and Lenski [1] have proposed that the rate K_{fix} can be estimated by

$$K_{fix} = NU_b \int_0^\infty 2s_b \alpha e^{-\alpha s_b} e^{-I(s_b)} ds_b, \tag{4}$$

where

$$I(s_b) = \frac{1}{2} T_{fix} NU_b \int_{s_b}^\infty 2s\alpha e^{-\alpha s} ds. \tag{5}$$

$I(s_b)$ corresponds to the expected number of interfering mutations that a beneficial mutation of selective effect s_b finds en route for fixation. Assuming that the number of interfering mutations is Poisson distributed, the term e^{-I} is just the probability of not finding any interfering mutation during the process. According to the theory, interfering mutations are mutations that have escaped drift and also confer a larger benefit effect than that provided by the focal mutation. As soon as such mutation appears the focal mutation is outcompeted by clonal interference. In Eq. (5) T_{fix} refers to the time of fixation of beneficial mutations of effect s_b, which according to Kimura is $T_{fix}=2/s_b \ln N$ [32]. In Fig. 1(a), we compare the theoretical prediction in Eq. (4) to the simulation results for the asexual population. We see that agreement is quite satisfactory for small and intermediate values of U_b, failing only in the regime of very large $U_b(NU_b>1)$, where the theory underestimates K_{fix}. In this phase, named multiple-mutation regime [8,27], more than one segregating beneficial mutation can simultaneously take place in the same individual, a fact that is neglected in Gerrish-Lenski's theory.

In part (b) of Fig. 1 we again present K_{fix} as a function of U_b but now additionally considering the occurrence of deleterious mutations at rate $U_d=0.1$ and selective effect $s_d=0.1$. Qualitatively the scenario is similar to that shown in part (a), where an increased rate of recombination provides larger rates of substitution of advantageous mutations. However, the ratio between the rates of fixation for sexual and asexual populations is considerably large already for very small of U_b. In this case, recombination has two distinct consequences: combining beneficial mutations from distinct lineages and restoring genetic background free of deleterious mutations.

Since deleterious mutations promote a reduction in the effective population size, its occurrence is expected to reduce severely the rate of adaptation [3,5,10,14]. When s_d is larger than the benefit effects of beneficial mutations, as considered in Fig. 1(b), one can simply assume that only beneficial mutations arising in a genetic background free of deleterious mutations contribute to adaptation. Therefore, in order to account for the presence of deleterious mutations we estimate the expected rate of fixation for the asexual population replacing N by f_0N in Eqs. (4) and (5), where $f_0=\exp(-U_d/s_d)$ is the frequency of mutation-free individuals [33,34]. Thus, for an asexual population K_{fix} equals

$$K_{fix} = Nf_0U_b \int_0^\infty 2s_b \alpha e^{-\alpha s_b} e^{-I(s_b)} ds_b, \tag{6}$$

where

$$I(s_b) = \frac{1}{2} T_{fix} Nf_0 U_b \int_{s_b}^\infty 2s\alpha e^{-\alpha s} ds. \tag{7}$$

For sexual populations, one can find an upper bound for the rate of adaptation by disregarding the competition among the beneficial mutations. The combined effects of background deleterious mutations and recombination promotes a reduction in the population effective size which is given by $f_r=\exp(-U/r)$ [34–37], when $r \gg s_d$. In this case we write the rate of fixation of advantageous mutations as $K_{fix}^{upper}=2NU_bf_r/\alpha$. We observe from Fig. 1(b) that there is an agreement between simulations and the predicted K_{fix}^{upper} for a broad range of U_b. As expected for very large U_b, the theory overestimates the expected rate since it neglects competition among distinct mutations.

An important measurement to identify signatures of clonal interference is the mean selective effect of those beneficial mutations that have reached fixation, which here we denote by s_{fix}. So far, the most important evidence of clonal interference is that it slows down the rate of substitution of advantageous mutations together with the occurrence of larger selective effects of the fixed mutations.

Figure 2 displays our computer simulations data for s_{fix} as a function of the mutation rate U_b. The two panels in the figure correspond to the same set of parameters used in the corresponding panels of Fig. 1. For null rate of deleterious mutation [panel (a)], the asexual population experiences a continuous growth of s_{fix} as we augment U_b. When $U_b=1\times 10^{-6}$ we obtain $s_{fix}\simeq 0.1$, which is the expected value of benefit effects of mutations when there is no clonal interfer-

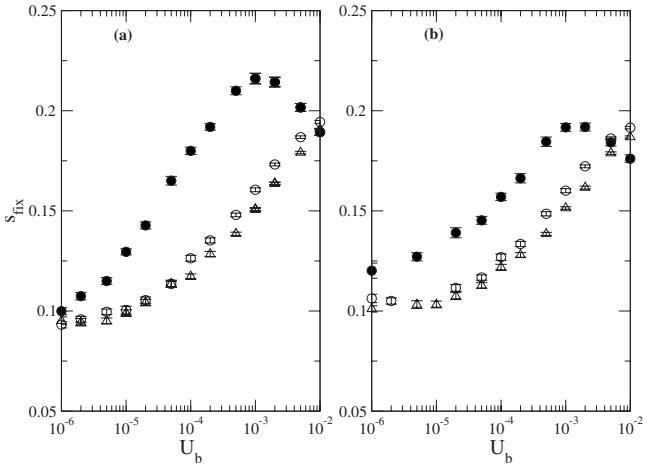

FIG. 2. Mean selective effect of beneficial mutations that have reached fixation, s_{fix}, as a function of the rate of beneficial mutations, U_b. In this plot we have considered population size $N=10\,000$, $\alpha=20$, and rates of recombination $r=0$ (filled circles), $r=0.5$ (empty circles), and $r=1.0$ (triangles up). The rate and selective effects of deleterious mutations are: part (a) $U_d=0$; part (b) $U_d=0.2$, and $s_d=0.1$.

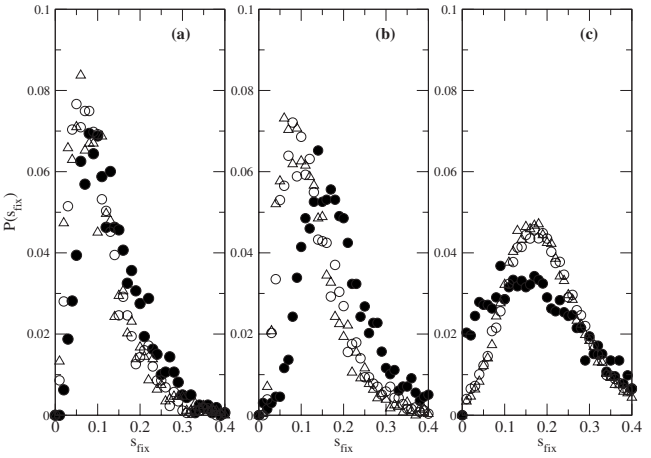

FIG. 3. Probability distribution of the selective effects of beneficial mutations that have reached fixation, $P(s_{fix})$. The parameter values are $N=10\,000$, $U_d=0$, $\alpha=20$ and rate of advantageous mutations $U_b=1\times10^{-5}$ [panel (a)], $U_b=1\times10^{-3}$ [panel (b)] and $U_b=0.01$ [panel (c)]. The solid circles correspond to recombination rate $r=0$ (asexual populations), empty circles correspond to $r=0.5$, and triangles up denote $r=1$.

ence and also assuming the exponential form of the probability density of newly arising beneficial mutations [5]. From this point, s_{fix} grows with the increment of U_b, meaning that the strength of clonal interference becomes more intense. When $U_b=1\times10^{-3}$, s_{fix} reaches a maximum and then drops with a further increase of U_b. This comes to corroborate our previous finding that in this regime mutations of small-effect hitchhike to big-effect mutations in order to reach fixation. This corresponds to the multiple-mutation regime [8]. For non-null rate of recombination, we see that the increase in s_{fix} with U_b also occurs, although this growth phase is shifted toward higher values of U_b. This is evidence that even with recombination competition among advantageous mutations is present. Though in this case competition takes place not only among single mutations in distinct lineages, but competition among multiple beneficial mutations in distinct segregating lineages.

The picture for non-null rate of deleterious mutations is qualitatively similar to that shown in part (a), however as deleterious mutations have a severe effect on the probability of fixation of advantageous mutations, only big-effect mutations have a reasonable likelihood of being successful, and this is perceived for small and intermediate values of U_b. For very high U_b, we notice that s_{fix} becomes independent of both the recombination rate r and the deleterious mutation rate U_d.

In Fig. 3 we plot the distribution of selective effects of the beneficial mutations that have reached fixation, $P(s_{fix})$. From the plot we can notice the role of recombination on the adaptive process. All the results correspond to $U_d=0$. In panel (a), where a small mutation rate $U_b=1\times10^{-5}$ has been considered, small-effect mutations in sexual population ($r>0$) have a slightly higher chance of fixing compared to the asexual case. On the other hand, when $U_b=0.001$ we clearly notice that the peak of the distribution $P(s_{fix})$ in the asexual population is shifted toward larger values of s_{fix}, whereas for the sexual case no prominent change is observed. For sexual populations, the displacement of the position of the peak of $P(s_{fix})$ is tightly related to clonal interference since it reduces the chance of success of small-effect mutations. For instance, we see that mutations with effect smaller than 5% ($s_{fix}<0.05$) have almost no chance of fixating, whereas mutations of large effect become overrepresented. In panel (c) we show the simulation results for $U_b=0.01$, and now the population has evolved in the multiple-mutation regime. From this panel, we can really ascertain that the drop of s_{fix} in this regime is clearly associated with the fixation of mutation of very small effect. As explained before, these mutations are promoted for fixation by hitchhiking with mutations of large effect.

Surprisingly, we see that in this regime recombination prevents the fixation of small-effect mutations, and at the same time enhances the likelihood of fixation of mutations with intermediate and large effects. This means that during the adaptive process the linkage between small-effect and large-effect mutations is broken in such way to enable the combination of large-effect mutations in the same lineage.

Two restrictive assumptions made in our model deserve special attention: (1) that all deleterious mutations have the same effect and (2) that the number of recombination events is set to one for each mating pair. The first assumption will most likely be incorrect, although we are still far from having a correct description on the distribution of selective effects s_d in natural populations [38]. Nevertheless, we can tell from direct observation of computer simulations (results not shown here) that the effect of variable s_d on the estimates of K_{fix} is pretty small. We have tried different shapes for the distribution of selective effects s_d. More specifically, we have considered a gamma distribution, where we can tune its shape by tuning the shape parameter. In any case, we have not observed any noticeable deviation from the results obtained when assuming constant s_d. Regarding the second as-

sumption, our previous investigation on the advantage of sex and recombination [17] does not present any qualitative difference between this model and the model proposed by Keightley and Otto [30], where multiple recombination events are allowed. So, we do not expect that the possibility of multiple recombination events will change the scenarios we show here.

IV. CONCLUSIONS

In the current work we have examined the rate of adaptation in populations subjected to sex and recombination. For such purpose, we have proposed a finite population model of haploid individuals which are allowed to recombine at a given rate r, which tunes the amount of sex in the model.

The comparison between sexual and asexual populations demonstrates that sexual populations always adapt faster since recombination permits the combination of beneficial mutations originally from distinct lineages in the population. The advantage of sexual populations over the asexual ones is even larger when deleterious mutations occur, since now recombination has an important role in restoring the least loaded classes of deleterious mutations.

However, we were able to identify clear signatures of clonal interference phenomenon in sexual populations. What we have observed is that compared to asexual populations, in sexual populations clonal interference is delayed to higher values of mutation rate U_b. A clear drop on the slope of K_{fix} together with augment of S_{fix} as U_b increases is noticed. More surprising is the observation of a bell-shaped distribution for the distribution of beneficial effects of those mutations that have reached fixation. As in strictly asexual populations, clonal interference also reduces the chance of fixation of small-effect mutations.

ACKNOWLEDGMENTS

This work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), program PRONEX/MCT-CNPq-FACEPE and Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco. J.F.G. is supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). The authors acknowledge Isabel Gordo for helpful suggestions.

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