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Fixation of advantageous mutations in an off-equilibrium population

O.F.F. Raposo[1], A.W.S. de Almeida[2], A.J.F. Souza[2], and P.R.A. Campos[2,a]

[1] Departamento de Estatística e Informática, Universidade Federal Rural de Pernambuco, Dois Irmãos 52171-900, Recife-PE, Brazil
[2] Departamento de Física e Matemática, Universidade Federal Rural de Pernambuco, Dois Irmãos 52171-900, Recife-PE, Brazil

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Abstract. We investigate the evolution of asexual populations subject to a large supply of deleterious mutations such that Muller's ratchet operates. In this regime, the accumulation of deleterious mutations takes place continuously with the resulting loss of the least-loaded class of individuals. In the current work, we study the effect of the supply of beneficial mutations on the ratchet's speed. We also examine how the rate of substitution of favorable mutations as well as the mean selective effect of favorable mutations that reach fixation is compared to those assuming a population at equilibrium. We observe that under Muller's ratchet, the rate of fixation of advantageous mutations is higher than that predicted for an equilibrium population. The difference between the rate supposing an equilibrium regime and that for the non-equilibrium case becomes larger as we increase the rate of deleterious mutations. On the other hand, the mean selective effect of beneficial mutations that reach fixation is smaller than the expected value for the equilibrium situation.

PACS. 87.10.+e General theory and mathematical aspects – 87.23.Kg Dynamics of evolution – 87.15.Aa Theory and modeling; computer simulation

1 Introduction

The rate at which populations evolve depends on the incoming flux of favorable mutations as well as on their probability of fixation. The probability of fixation of a given mutation is proportional to the selective advantage it confers to the individuals that acquire the mutation. In the most simple instance, the two-allele model, where an advantageous mutations of fitness $1 + s_b$ arises in a pool of individuals with fitness 1, the chance that the beneficial mutations will reach fixation is $2s_b$ [1]. Most of the advantageous mutations are lost by drift in the earlier stages of their appearance [2], on account of genetic drift — random fluctuations due to finiteness of populations. But not only genetic drift can affect the ultimate fate of favorable mutations. It is also known that deleterious mutations, which are expected to be more common in real populations, reduce drastically the likelihood of fixation of favorable mutations because of the chance of its occurrence in an individual already carrying a given amount of deleterious mutations [3–8]. This effect is very pronounced in asexual populations. When the rate of advantageous mutations is high, competition among mutations arising in different lineages also takes place, and this competition also reduces the chance of a given beneficial mutation being sucessful and outcompete the other competitors. This process is referred to as clonal interference [8–10]

Although recent studies have investigated the effect of deleterious mutations on the process of fixation of advantageous mutations [3,4,8], most of them have focused their investigation on the assumption that the population has attained an equilibrium regime. Under this assumption, the frequency of individuals free of deleterious alleles is $\exp(-U_d/s_d)$, where U_d denotes the rate of deleterious mutations and s_d is the selective disadvantage of each deleterious mutation [12,14,15]. Those individuals carrying deleterious mutations are continuously removed by purifying selection and generated by the mutational pressure. However, when we consider finite populations and large values of mutation rate U_d, asexual populations can suffer from an effectively irreversible accumulation of deleterious mutations, which also results in a continuous decline of the fitness population, a process which is known as Muller's ratchet [11–13]. Opposed to that, sexual reproduction can

[a] e-mail: prac@ufrpe.br

circumvent the process of accumulation of deleterious and for that reason Muller's ratchet has been pointed out as an explanation for the advantage of sex [11,15] and the evolution of sex chromosomes [17,18].

In the current work, we study the adaptive process on asexual populations undergoing accumulation of deleterious mutations due to Muller's ratchet. In our model, we assume the occurrence of both deleterious, which are more common, and beneficial mutations. We study the situation at which Muller's ratchet operates and so the equilibrium regime is never attained. We are mostly interested on how the supply of beneficial mutations can affect the speed of the ratchet, defined as the inverse of the mean time between its successive clicks. A click corresponds to the loss of the least-loaded class of individuals in the population. In addition, we examine how the rate of substitution of favorable mutations changes in the non-equilibrium regime compared to its behavior for the equilibrium case.

The paper is organized in the following way: in Section 2 we introduce the model. In Section 3 we show the results and discussions. And finally, in Section 4 we present our conclusions.

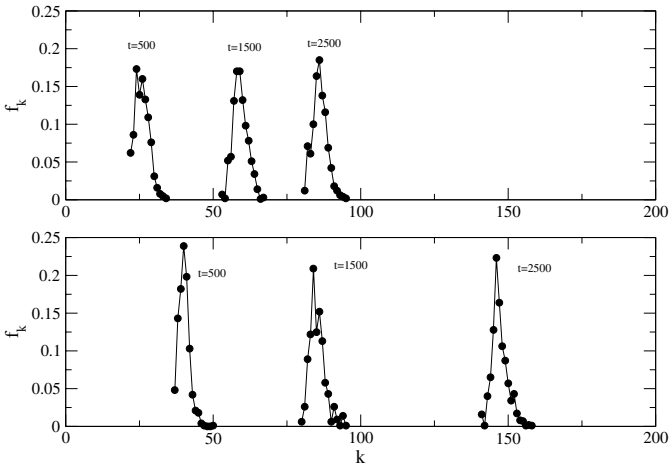

Fig. 1. The frequency distribution of deleterious mutations, f_k, in the whole population for a single run. The figure shows the distribution f_k at generations (from left to right): $t = 500$, $t = 1500$, and $t = 2500$. The parameters are $N = 1000$, $s_d = 0.01$, $U_d = 0.1$ and $\beta = 20$. In part (a) $U_b = 0$ and (b) $U_b = 1 \times 10^{-3}$.

2 The model

The population is composed of N asexual haploid individuals that evolves according to the Wright-Fisher model, i.e., the model assumes non-overlapping generations and the number of offsprings that a given individual generates is proportional to its relative fitness. Each individual is represented by an infinitely large sequence which means that once a mutation has hit a given nucleotide the likelihood of a reversible mutation is negligible, and so the genome is better characterized by the number of deleterious mutations k_d and beneficial mutations k_b it carries. Deleterious mutations take place at a constant rate U_d, and beneficial mutations occur at rate U_b. The fitness is multiplicative across loci, and so an individual carrying (k_b, k_d) mutations has fitness

$$\omega_k = \prod_{i=1}^{k_b} (1 + s_b(i))(1 - s_d)^{k_d}. \quad (1)$$

The deleterious effect of mutations is a constant, which means that they reduce the fitness by the same factor $(1 - s_d)$. On the other hand, the selective effects of the favorable mutations are not the same and their values are distributed according to an exponential distribution of mean $1/\beta$, i.e.,

$$g(s_b) = \beta \exp(-\beta s_b). \quad (2)$$

The fixation of a given mutation happens at the moment it becomes the most recent common ancestor of the population, which means that every individual shares that mutation. During simulations, we keep track of the following quantities: the minimum number of deleterious mutations in the whole population, k_{min}, which corresponds to the least loaded class of individuals; the average number of deleterious mutations, k_{av}; and the number of deleterious mutations that have reached fixation, k_{fix}. Regarding the favorable mutations, we also keep track of the quantities: the number of beneficial mutations that have reached fixation, k_b, and also the mean selective effect of those mutations, which we represent by s_{med}. The mean selective effect s_{med} is estimated as the sum of the selective effects of beneficial mutations that have reached fixation divided by the total number of fixation events. Because k_{min}, k_{av} and k_{fix} behave qualitatively in the same way, we choose to show k_{min} instead of reporting the three quantities.

3 Results and discussion

In Figure 1 we plot the distributions of the number of deleterious mutations for a single simulation in three distinct generations: $t = 500$, $t = 1500$ and $t = 2500$. In part (a) the rate of beneficial mutations U_b is null, whereas in part (b) $U_b = 10^{-3}$. In both situations we observe the loss of the least loaded classes of individuals as the time goes on, which clearly demonstrates that Muller's ratchet is operating. However, the ratchet's speed, that is, the rate at which the least-loaded class of individuals gets lost, is noticeably higher in the second situation, in which beneficial mutations take place. Therefore, the influx of beneficial mutations enhances the chance of fixation of deleterious mutations.

Figure 2 displays the minimum number of mutations in a population as a function of time for several values of the rate of advantageous mutations U_b. The data are averages over 1000 independent simulations. In part (a) we have the mean selective effect of beneficial mutations $1/\beta = 0.05$, whereas in part (b) $1/\beta = 0.0067$. In the former $1/\beta$ is larger than s_d, while in the second $1/\beta$ is

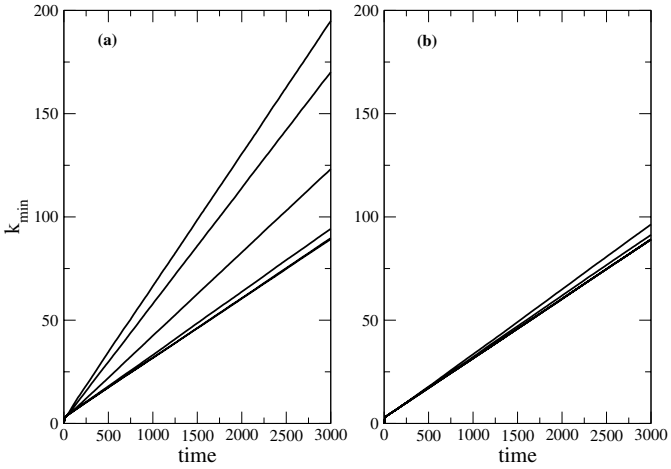

Fig. 2. The least-loaded class of individuals (minimum number of deleterious mutations) in the population as a function of time. The parameters are $N = 1000$, $U_d = 0.1$, $s_d = 0.01$ and from bottom to top $U_b = 1{\times}10^{-7}$, $U_b = 1{\times}10^{-6}$, $U_b = 1{\times}10^{-5}$, $U_b = 1 \times 10^{-4}$, $U_b = 1 \times 10^{-3}$ and $U_b = 5 \times 10^{-3}$. In part (a) we have $\beta = 20$, whereas in part (b) $\beta = 150$.

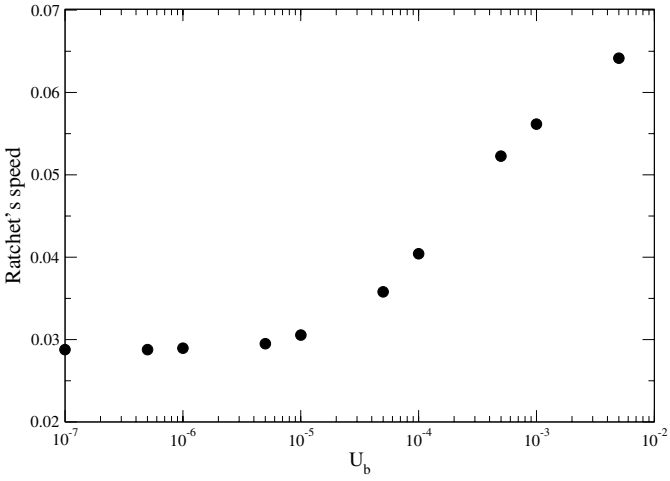

Fig. 3. Ratchet's speed as a function of the mutation rate U_b. The parameters are $N = 1000$, $s_d = 0.01$, $U_d = 0.1$ and $\beta = 20$.

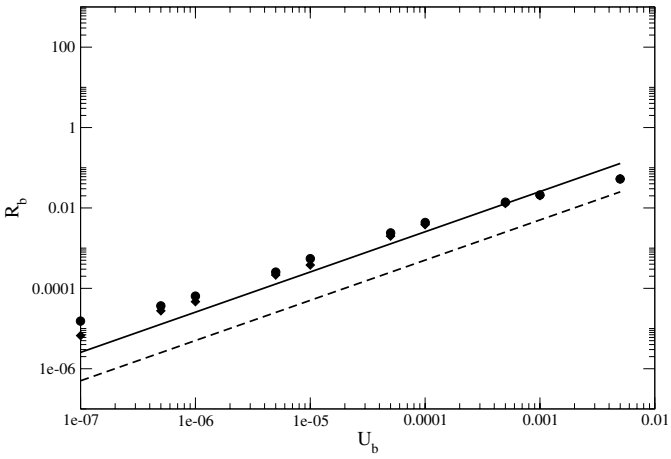

Fig. 4. The rate of fixation of advantageous mutations as a function of the mutation rate U_b. The parameters are $N = 1000$, $s_d = 0.01$, $\beta = 20$ and $U_d = 0.1$ (circles) and $U_d = 0.2$ (diamonds). The lines are the theoretical predictions $R_b = NU_bP_{fix}(U_d, s_d, \beta)$, where the probability P_{fix} is obtained by means of the branching process formulation. The thick line corresponds to $U_d = 0.1$ and the dashed-line corresponds to $U_d = 0.2$.

smaller than s_d. The distinct lines denote different rates of advantageous mutations. In any situation, k_{min} is well described by a straight line. From part (a) we see that as we increase the rate U_b the slope of the lines increases for a larger mutation rate U_b. The slope of the lines corresponds to the ratchet's speed, and so a higher influx of favorable mutations means a faster accumulation of deleterious mutations. Under these circumstances, deleterious mutations can also be carried out to fixation by linkage with those beneficial mutations which reach fixation, and this process is referred to as hitchhiking effect [6,16]. In part (b), where the mean selective effect of advantageous mutations is smaller than the cost associated to each deleterious mutations, we see that the effect of increasing U_b is only noticeable when U_b is extremely high. For small and intermediate U_b, the ratchet's speed is not sensitive to the influx of beneficial mutations, and the hitchhiking effect is not strong. When U_b is very large, there is some chance that more than one beneficial mutation happens in the same genome, increasing the net benefit effect of favorable mutations. Figure 3 shows the speed of the ratchet as a function of U_b. The data points are the slopes of the straight lines in Figure 2a. The transition region in the figure (10^{-6}–10^{-3}) covers the range of realistic values for mutation rates in actual populations, for instance bacteria populations [19] and viruses populations [20].

In Figure 4 we show the rate of beneficial mutations as a function of U_b for $U_d = 0.1$ and $U_d = 0.2$. The data points correspond to simulation results averaged over 1000 independent runs. In the figure we compare the data points, which correspond to a non-equilibrium regime where Muller's ratchet effectively works, to the theoretical prediction (thick and dashed lines) of the rate of substitution of beneficial mutations assuming a population at equilibrium. In order to obtain the theoretical curve, we have used the branching process approximation [3,4] and the rate R_b is estimated as $R_b = NU_bP_{fix}(U_d, s_d, \beta)$, where P_{fix} is the probability of fixation of a single beneficial mutation of selective effect s_b and it is estimated by the set of equations (12) and (13) in reference [3]. Because the selective effects of favorable mutations are exponentially distributed, we have numerically integrated the solution provided in the previous step over all possible values of selective effects (see Ref. [4] for a detailed explanation). Apart from assuming a population at equilibrium, the theoretical prediction for the rate of adaptation does not take into account competition amongst beneficial mutations, and so should overestimate the rate of fixation for large

U_b, where clonal interference becomes a major force. As we can check, the simulation results show that the rate of fixation R_b is higher in a population where Muller's ratchet operates than the expected value in a population at mutation-selection balance for most values of the parameter U_b. However, when $NU_b \simeq 1$ and clonal interference is relevant, the rate R_b now tends to its maximum value, and the rate of increase of R_b decreases with the augment of U_b. Around $NU_b = 1$ beneficial mutations in distinct lineages arises and, in asexual populations, they must compete in order to reach fixation with the ultimate loss of their competitors. This competition amongst favorable mutations puts a limit in the speed of adaptation [5,8], and also increases the time between fixation events. These results demonstrate that clonal interference is still relevant even in a non-equilibrium regime. From the figure, we see that the simulational data is not very sensitive to an increase of the rate of deleterious mutations. The data points for $U_d = 0.1$ and $U_d = 0.2$ nearly collapse onto the same curve. On the other hand, the expected rate of substitutions in an equilibrium population presents a considerably large decrease as we augment U_d. However, the theoretical line still continues to grow without bound with U_b because clonal interference is not considered in the approximation. These results demontrate that the disagreement between the expected rate of fixation R_b in an off-equilibrium and equilibrium populations increases with the increment of the rate of deleterious mutations U_d. Increasing U_d also means a larger speed of the ratchet.

In Figure 5 we show the mean selective effect of those favorable mutations that have reached fixation, s_{med}, as a function of U_b. Again, we compare the simulation results with the theoretical prediction assuming a population at equilibrium. When considering the off-equilibrium regime, the mean selective value s_{med} is considerably smaller than that predicted for the equilibrium regime. From Figure 4 we have learned that Muller's ratchet improves the likelihood of fixation of advantageous mutations, i.e., it means that more advantageous mutations reach fixation in a given time interval. As a consequence, mutations of weaker effect can now reach fixation, and so the average value of those mutations is reduced as compared to the equilibrium situation, in agreement with we observe in the figure. When U_b is very large, clonal interference becomes the major evolutionary force, and now competition amongst beneficial mutations leads to the loss of those mutations of small selective effect. In the region of large U_b, the theoretical prediction underestimates s_{med} because it does not take into account clonal interference.

Although not shown, the results are dependent on the population size N, as we have corroborated from the simulations. Actually, when we consider larger values of N, the speed of the ratchet decreases, since the loss of the least-loaded class of individuals due to finiteness (genetic drift) becomes less probable. On other hand, an increased population size N also leads to a larger supply of favorable mutations, i.e. a larger NU_b, resulting in a larger number of fixation events.

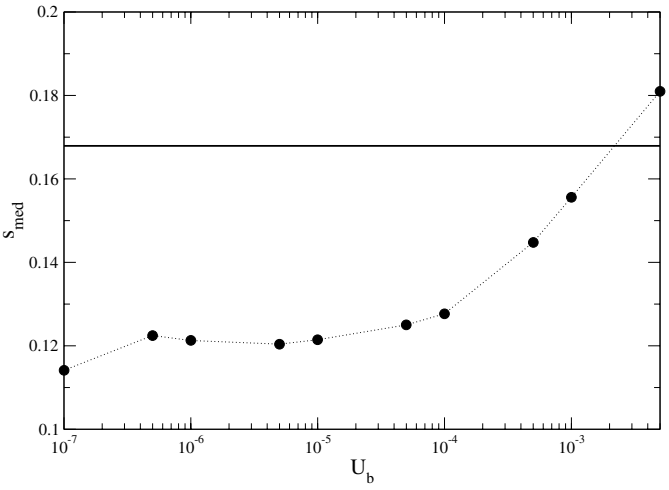

Fig. 5. The mean selective effect of beneficial mutations that have reached fixation, s_{med}, as a function of U_b. The parameters are the same as in Figure 2. The data points correspond to simulation results. The thick line is the theoretical prediction by means of the branching process formulation (see Eq. (12) in Ref. [4]).

4 Conclusions

We have investigated the dynamical properties of finite populations of haploid asexual individuals which are subject to selection and mutations. In our study we examine populations where Muller's ratchet operates and so mutation-selection balance is never attained. We compare our findings with those predicted for equilibrium situations. We have seen that an increased influx of beneficial mutations speeds up the ratchet's speed, especially when the selective effect of the mutations outweight the selective disadvantage of deleterious mutations. Deleterious mutations increase their chance of fixation by linkage with those beneficial mutations that reach fixation. When the benefit of a given mutations is small an increased speed of ratchet is only observed for very high mutation rate U_b.

We have also measured the rate of fixation of advantageous mutations and have observed that its value is higher in the non-equilibrium regime than that supposing an equilibrium situation. Our results show that the difference between the rate of fixation R_b in a non-equilibrium population and an equilibrium population increases as we consider larger rates of deleterious mutations U_d, mainly due to a larger accumulation of deleterious mutations. When competition amongst distinct beneficial mutations takes place we clearly notice that the rate of growth of the rate of adaptation decreases with a further increase of U_b and clonal interference is still relevant in non-equilibrium regimes. Our theoretical prediction does not take into account clonal interference and when $NU_b \approx 1$ it overestimates the rate of fixation events, as we can see from Figure 4. As a consequence of a larger rate of substitution, we obtain smaller values of the mutations that have fixated as compared to an equilibrium regime.

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