



Fixation probability of a nonmutator in a large population of asexual mutators



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ABSTRACT

In an adapted population of mutators in which most mutations are deleterious, a nonmutator that lowers the mutation rate is under indirect selection and can sweep to fixation. Using a multitype branching process, we calculate the fixation probability of a rare nonmutator in a large population of asexual mutators. We show that when beneficial mutations are absent, the fixation probability is a nonmonotonic function of the mutation rate of the mutator: it first increases sublinearly and then decreases exponentially. We also find that beneficial mutations can enhance the fixation probability of a nonmutator. Our analysis is relevant to an understanding of recent experiments in which a reduction in the mutation rates has been observed.

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1. Introduction

Following the conclusion that mutation rates are subject to the action of evolutionary forces (Sturtevant, 1937), there have been various experimental (Chao and Cox, 1983; Giraud et al., 2001; Lynch, 2010; McDonald et al., 2012; Notley-McRobb et al., 2002; Singh et al., 2017; Sniegowski et al., 1997; Sung et al., 2012; Tröbner and Piechocki, 1984; Wielgoss et al., 2013) and theoretical (Desai and Fisher, 2011; Good and Desai, 2016; Jain and Nagar, 2013; James, 2016; James and Jain, 2016; Johnson, 1999; Kimura, 1967; Leigh, 1973; Lynch, 2011; Palmer and Lipsitch, 2006; Sniegowski and Gerrish, 2010; Taddei et al., 1997; Tenaillon et al., 1999b; Wylie et al., 2009) works on the evolution of mutation rates. Many theoretical and empirical studies on adapting populations (Raynes and Sniegowski, 2014) have shown that the mutator alleles that elevate the mutation rates can reach a high frequency by generating beneficial mutations and hitchhiking with them (Smith and Haigh, 1974).

However, once the population has adapted to an environment, due to high rate of production of deleterious mutations, the mutators experience a selective disadvantage and the nonmutator allele that lowers the mutation rate is favored due to indirect selection. Indeed, in a long term evolution experiment on *E. coli*, the frequency of mutators increased in three out of twelve replicate lines while the population was rapidly adapting (Sniegowski et al., 1997). But when the rate of fitness increase slowed down consid-

erably, one of the mutator lines experienced a decrease in its mutation rate (Wielgoss et al., 2013). Several other experiments have also provided evidence for the rise in frequency of nonmutator allele in an adapted population (McDonald et al., 2012; Notley-McRobb et al., 2002; Singh et al., 2017; Tröbner and Piechocki, 1984).

In this article, we are interested in a theoretical understanding of the evolution of mutation rates in adapted populations. In particular, using a multitype branching process (Harris, 1963; Patwa and Wahl, 2008), we study the fixation probability of a nonmutator allele in a large asexual population of mutators that is moderately well adapted. In a recent work by us (James and Jain, 2016), this question was addressed when the nonmutator arises in the background of strong mutators whose mutation rate is ten to hundred fold higher than the nonmutator (Oliver et al., 2000; Sniegowski et al., 1997). However, as experiments show that the mutation rate decreases merely by a factor two to three in an adapted population (McDonald et al., 2012; Wielgoss et al., 2013), here we undertake a more general investigation by allowing the nonmutator's mutation rate to be comparable to that of the mutator. We also address how beneficial mutations in the mutator that increase its fitness affect the nonmutator fixation. Unlike in James and Jain (2016) where this question was studied in a limited parameter regime, here aided by an exact solution for the population frequency distribution that was obtained recently (Jain and John, 2016), we explore the parameter space completely.

The article is organized as follows: we define the model, and describe the simulation details and a multitype branching process in Section 2. The results for the fixation probability of a nonmutator are obtained in Section 3 followed by a discussion in Section 4.

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2. Models and methods

2.1. Individual-based computer simulations

We consider an asexual population of mutators in which a mutation, irrespective of its location on the genome, changes fitness by a constant factor. Thus the fitness of an individual carrying $k \geq 0$ deleterious mutations (or, in the k th fitness class) is given by

$$W(k) = (1 - s)^k, \quad (1)$$

where $0 < s < 1$ is the selection coefficient. The population is of finite size N and evolves via the standard Wright–Fisher dynamics (Ewens, 1979) in which a parent in the fitness class k is selected with a probability equal to $W(k)/\bar{W}(t)$, where $\bar{W}(t)$ is the average fitness of the population at generation t . The selection step is followed by mutations; we employ a single-step mutation model in which mutations are allowed to occur in the neighboring fitness classes only. In an individual carrying $k > 0$ unfavorable mutations, a deleterious mutation occurs at rate U_d to fitness class $k + 1$ and a beneficial one at rate $U_b < U_d$ to fitness class $k - 1$. In the fittest individual, only deleterious mutations are allowed.

Motivated by a long-term evolution experiment on *E. coli* in which the nonmutator allele emerged in a mutator population when its fitness had almost saturated (Sniegowski et al., 1997; Wielgoss et al., 2013), we allow the nonmutator to appear after the mutator population has attained a steady state (James, 2016; James and Jain, 2016). The invading nonmutator with deleterious and beneficial mutation rates u_d and u_b , respectively, carrying k unfavorable mutations arises in the mutator subpopulation in the k th fitness class with a probability equal to the stationary fraction of that subpopulation.

We measured the fixation probability of a single copy of nonmutator in a large population of mutators of strength $\lambda > 1$ which is given by the ratio $U_d/u_d = U_b/u_b$. As we are interested in adapted populations in which beneficial mutations are rare, we first ignore the beneficial mutations completely (as discussed in Section 3.1) and then include beneficial mutations (see Section 3.2). In the former case, as the population size N is finite, Muller's ratchet (Haigh, 1978) operates in the mutator population and there is no true steady state. For this reason, we simulated large enough populations in which the Muller's ratchet clicks very slowly (Jain, 2008) and the mutator population is close to the stationary state of an infinitely large population. The fixation probability of a nonmutator was obtained using 10^5 independent stochastic realizations of the mutator population; the results are shown in Figs. 1 and 2 when beneficial mutations are ignored and in Fig. 5 when they are taken into account.

2.2. Multitype branching process

In a finite population of mutators, a rare nonmutator allele - although beneficial due to indirect selection - can get lost because of stochastic fluctuations. But if it manages to survive random genetic drift, the nonmutator population can reach a frequency comparable to that of the mutators or even substitute them. Then it is interesting to ask: what is the probability that a rare beneficial allele arising in a large resident population does not go extinct? The branching process (Harris, 1963; Patwa and Wahl, 2008) is tailor-made to answer precisely such questions and here we employ it to obtain an analytical understanding of our simulation results.

Let $1 - \pi(k, t)$ denote the extinction probability that a nonmutator arising at generation t in a mutator background with k deleterious mutations is eventually lost. If such a nonmutator gives rise to n offspring in the next generation with probability $\psi_n(k)$, then all the n lineages must go extinct in order to contribute to the probability $1 - \pi(k, t)$. Furthermore, if mutations are also al-

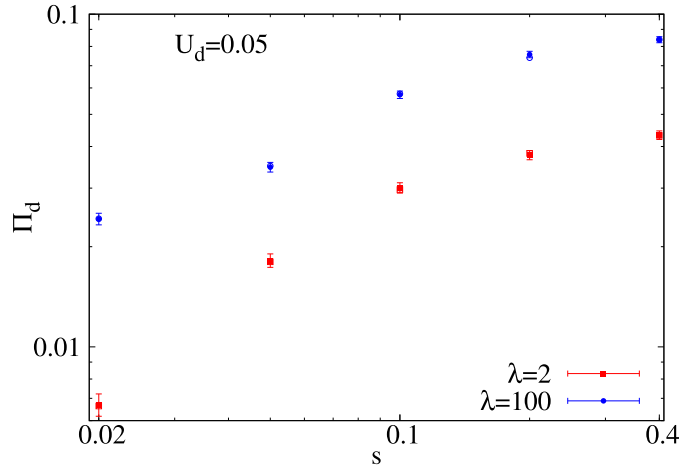


Fig. 1. Variation of the total fixation probability Π_d with the selection coefficient s when beneficial mutations are absent for weak ($\lambda = 2$) and strong mutators ($\lambda = 100$). The filled symbols show the simulation results for population size $N = 5000$ (with error bars representing ± 2 standard error) and the open symbols show the data obtained by numerically solving the recurrence relation (4). The overlapping points signify that the agreement between the two methods is very good.

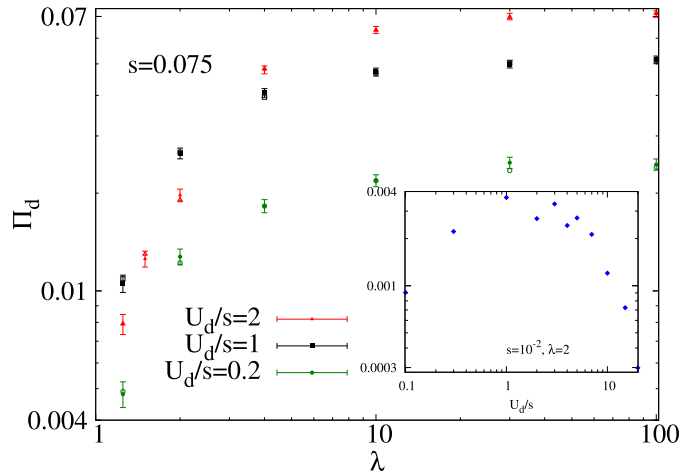


Fig. 2. Main: Variation of the total fixation probability with the mutator strength λ when beneficial mutations are absent. The simulation data (filled symbols) for $N = 5000$ and the numerical solution of (4) (open symbols) are shown. Inset: Non-monotonic behavior of the fixation probability Π_d as a function of the scaled mutation rate U_d/s for $0 \leq k_{\max} \leq 10$.

lowed to occur in the nonmutator from fitness class k to j with a probability $M(k \rightarrow j)$, then summing over the number of offspring produced, we can write (Johnson and Barton, 2002)

$$1 - \pi(k, t) = \sum_{n=0}^{\infty} \psi_n(k) \left[\sum_j M(k \rightarrow j) (1 - \pi(j, t+1)) \right]^n. \quad (2)$$

For the Wright–Fisher process described in the last section, the offspring number distribution can be approximated by a Poisson distribution ($\psi_n(k) = e^{-\mu_k} \mu_k^n / n!$) with mean μ_k equal to the relative fitness $W(k)/\bar{W}(t)$. We then arrive at

$$1 - \pi(k, t) = \exp \left[-\frac{W(k)}{\bar{W}(t)} \sum_j M(k \rightarrow j) \pi(j, t+1) \right], \quad (3)$$

where we have used that $\sum_j M(k \rightarrow j) = 1$. As discussed in Section 2.1, we assume that the nonmutator appears only after the mutator population has attained a steady state ($t \rightarrow \infty$). In this limit, the fixation probability becomes independent of time and in

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