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The effects of genetic drift in experimental evolution

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Abstract

Experimental evolution is characterized by exponential or logistic growth and periodic population bottlenecks. The fate of a rare beneficial mutation in these systems is influenced both by the bottleneck effect and by genetic drift. This paper explores the effects of incorporating genetic drift into models of fixation probability in populations with periodic bottlenecks. To model the inherent stochasticity during the growth phase in these populations, we assume a Poisson distribution of offspring. An analytical solution is developed to calculate the fixation probability and a computer simulation is used to verify the results. We find that the fixation rate of a favourable mutant is significantly lower when genetic drift is considered; fixation probability is reduced by over 25% for realistic experimental protocols. Our method is valid for both weak and strong selection; since very large selection coefficients have been reported in the experimental literature, this is an important improvement over previous results.

1. Introduction

The fixation of a favourable new mutant is a classical question in population genetics. Past research has been conducted on this problem using a constant population size in which the favourable mutant appears (Fisher, 1922; Haldane, 1927; Wright, 1931; Kimura, 1957, 1962). Other studies have examined this problem using population sizes that change over time, e.g., populations that grow or decline (Otto and Whitlock, 1997) or populations which experience cycles of growth and decline (Ewens, 1967; Otto and Whitlock, 1997; Pollack, 2000). In each of these models the selective advantage of the mutant is constant through all stages of population growth or decline.

In experimental evolution, rapidly evolving organisms such as bacteria, viruses and protozoa will adapt to laboratory conditions on short, experimentally feasible timescales. In a single controlled experiment, major evolutionary change may occur in these populations, while both genotypic and phenotypic differences can be monitored (Lenski et al., 1991; Lenski and Travisano, 1994; Rosenweig et al., 1994; Bell and Reboud, 1997; Bull et al., 1997; Sniegowski et al., 1997; Treves et al., 1998; Rainey and Travisano, 1998; Papadopoulos et al., 1999; Wichman et al., 1999). An inherent feature of experimental evolution is population bottlenecks—at the end of a growth phase, the population is reduced by a fixed "dilution" ratio, i.e., when fresh media are inoculated during serial transfer (Lenski et al., 1991), or when chemostat tubes are changed (Bull et al., 1997). It is clear that any selective advantage realized during population growth need not translate into an "advantage" in surviving these bottlenecks. In fact, the bottlenecks are designed to select individuals at random from the population, as far as that is possible.

The probability that a beneficial mutation will reach fixation in an environment where the population is allowed to grow and then experiences a population bottleneck has recently been approximated (Wahl and Gerrish, 2001) using a discrete solution based on a branching process (Haldane, 1927; Fisher, 1930) and a continuous solution based on the Kolmogorov backwards equation (Kimura, 1957, 1962). In both cases weak selection is assumed and a deterministic exponential model is used to approximate bacterial growth. Thus, the probability that a rare mutation is eliminated by population bottlenecks alone is determined; other factors which may influence survival are not considered.

In particular, fluctuations in the bacterial population that occur between generations cannot be modelled

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using deterministic growth. In contrast, a bacterial growth model based on a stochastic distribution of offspring in each generation allows for random fluctuations in population size. Like population bottlenecks, these fluctuations may also eliminate a rare beneficial mutation—a process known as genetic drift. Although the wildtype population is large, the mutant population is small for the first few generations, and therefore subject to this effect.

In the sections that follow, we derive the probability that a rare, beneficial mutation will ultimately survive genetic drift *and* population bottlenecks. Following the derivation we confirm our results using stochastic simulation techniques. We also derive an approximation to the analytical result and discuss the similarity between this approximation and the classic result for a rare mutation surviving drift. An important feature of our analysis is that we do not assume that selection is weak; the fixation probability we derive is valid for mutations with large selective advantage as well.

2. Fixation probability in experimental evolution using stochastic growth

To model the effects of genetic drift, a stochastic distribution of offspring in each generation must be used. Stochastic growth can also be used to model factors such as micro-environmental or nutrient fluctuations, which are too complex to incorporate into a deterministic model. Since stochastic models take more of these factors into consideration, it is expected that the fixation rate for the model using stochastic growth will be lower than that calculated using deterministic growth. However, for large populations such as those used in experimental evolution, it was unclear at the outset whether the magnitude of this difference would be significant.

We consider an initial population of size N_0, which grows to a final size N_f during time interval $[0,\tau]$. At time τ the population experiences a population bottleneck D, such that $DN_f = N_0$. At the bottleneck, the population is randomly sampled and N_0 individuals form the new founding population. This cycle of growth and sampling is repeated many times. We are interested in the fixation rate of a rare beneficial mutation with selective advantage S, which appears at time t during the growth phase ($0 \leqslant t \leqslant \tau$).

2.1. Analytical solution

The probability that a beneficial mutation with selective advantage S will become fixed in the population that experiences cyclic growth was first studied by Ewens (1967). For a population which cycles through $k = \tau + 1$ population sizes, $N_1, N_2, \ldots, N_k, N_1, N_2, \ldots$ and assuming a Poisson distribution of offspring, Ewens derived the following system of equations:

$$-\ln(1-\pi_i) = (1+S)\frac{N_{i+1}}{N_i}\pi_{i+1} \quad (i = 1, \ldots, k), \tag{1}$$

where π_i is the survival probability of the mutant first appearing when the population is size N_i and k is the number of generations in the cycle such that $\pi_{k+1} = \pi_1$.

To illustrate, consider the cyclic sequence of populations $N, 2N, 4N, 8N, 16N, 32N, 64N, 128N, N, \ldots$. This sequence models the growth of a population for 7 doublings (generations) followed by a bottleneck to the original population size. Using the above equation and setting $S = 0.01$ we obtain a system of equations:

$$2.02\pi_{i+1} = -\ln(1-\pi_i) \quad (i = 1, \ldots 7),$$

$$1.01/128\pi_9 = -\ln(1-\pi_8), \tag{2}$$

where $\pi_9 = \pi_1$.

In Ewens' derivation however, it is assumed that the mutant has a selective advantage in every generation. System (2) therefore models a situation in which the mutant has the same selective advantage in surviving the bottleneck as it has during growth. This system has also been recently studied by Otto and Whitlock (1997). In experimental evolution, however, the more likely scenario is that an advantageous mutant may have a selective advantage during growth, but the "bottleneck" is designed to select individuals at random from a population. To model the case when each individual has the same probability of being chosen to survive the bottleneck from $128N$ to N, it follows from Ewens' original derivation that Eq. (1) should be modified to be

$$-\ln(1-\pi_i) = (1+S)\frac{N_{i+1}}{N_i}\pi_{i+1} \quad (i = 1, \ldots, k-1),$$

$$-\ln(1-\pi_i) = \frac{N_{i+1}}{N_i}\pi_{i+1} \quad (i = k). \tag{3}$$

As an example, using values of $\tau = 7$ and $S = 0.01$ and substituting them into the above system we obtain

$$2.02\pi_{i+1} = -\ln(1-\pi_i) \quad (i = 1, \ldots, 7)$$

$$1/128\pi_9 = -\ln(1-\pi_8), \tag{4}$$

where $\pi_9 = \pi_1$.

Solving this system of equations numerically we find that $\pi_1 = 0.0677$ which is the probability that a single mutant occurring in the first population of size N_0 will ultimately become fixed (survive both genetic drift and bottlenecks). For this numerical solution, an iterative technique was used to calculate the π_i's by first choosing an initial value of π_1 and then modifying the values of π_i until π_1 converged to a value with a tolerance of 10^{-7} (Ewens, 1967).

Fig. 1a illustrates this analytical solution as a function of S for a fixed value of t. Fig. 1b plots the analytical solution as a function of t for fixed S. We see that the

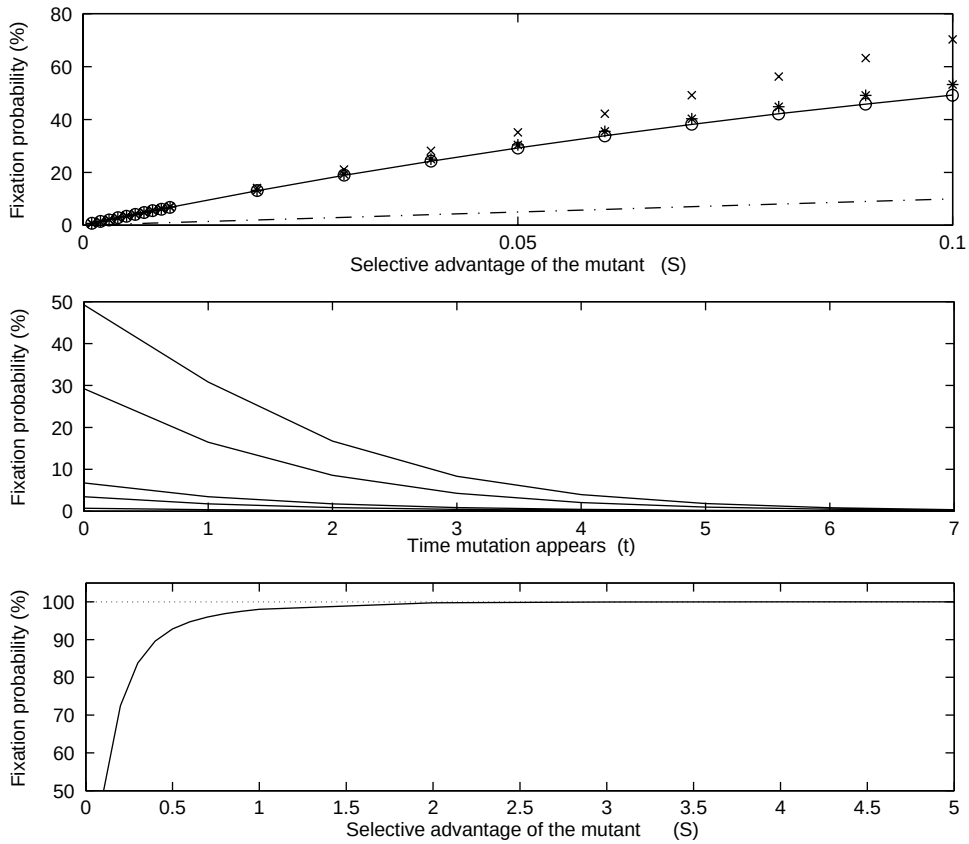

Fig. 1. Fixation probabilities including the effects of genetic drift and population bottlenecks. In the top panel the fixation probability of a beneficial mutant as a function of selective advantage S that originally occurs at time $t = 0$ is plotted for the analytical solution (solid line), approximation (Eq. (5), crosses; Eq. (6), asterisks) and computer simulation (circles) for stochastic growth. Parameters for growth are $\tau = 7$, $N_0 = 10^3$, $R = 1$. For comparison, the classic fixation probability, $2S$, is also plotted (dot–dashed line). The centre panel shows the fixation probabilities for a mutant that first appears at time t in the growth phase. The values of S shown from bottom to top are 0.001, 0.005, 0.01, 0.05 and 0.1. In the bottom panel the fixation probability for large values of S is shown. The fixation probability approaches 1 as S increases.

fixation probability increases as S increases and that it decreases as t, the time at which the mutant first appears, increases. Note that Eq. (3) does not assume that selection is weak; in Fig. 1c we plot the fixation probability for very large values of S. The fixation probability rapidly approaches 1 as S increases.

Clearly, the assumption of a Poisson distribution of offspring is not the most appropriate distribution to model, for example, bacterial fission. For an investigation of the effects of relaxing this assumption, see Pollack (2000). For an alternate derivation of the fixation probability in bacterial fission when the mutant has two offspring in a shorter generation time, see Wahl (2002).

2.2. Approximation of closed form solution for small values of S

The system of equations above can only be solved numerically. Following Ewens (1967) we now demonstrate that when S is small and k, the number of populations, is moderate, a closed-form approximation to the solution exists. Here, we derive the probability of fixation for a beneficial mutant with selective advantage S that originally occurs when $t = 0$ (i.e., $k = 1$) .

Let $R_i = \frac{N_i}{N_{i+1}(1+S)}$ when $i = 1 \ldots k-1$ and $R_k = \frac{N_k}{N_1}$. Using Taylor series and ignoring terms of order π_i^3 or higher for Eq. (3) we find that

$$\pi_2 \approx R_1\left(\pi_1 + \tfrac{1}{2}\pi_1^2\right),$$

$$\pi_3 \approx R_2\left(\pi_2 + \tfrac{1}{2}\pi_2^2\right) = R_2R_1\pi_1 + \tfrac{1}{2}(R_1R_2 + R_1^2R_2)\pi_1^2.$$

Continuing this process we see that

$$\pi_k \approx R_{k-1}\ldots R_1\pi_1 + 1/2(R_1\ldots R_{k-1} + R_1^2R_2\ldots R_{k-1} + \cdots + (R_1\ldots R_{k-2})^2R_{k-1})\pi_1^2$$

and

$$\pi_{k+1} \approx \pi_1 = R_k(\pi_k + \tfrac{1}{2}\pi_k^2),$$

therefore

$$\pi_1 \approx \frac{2(1 - R_k \ldots R_1)}{R_1 \ldots R_k + R_1^2 R_2 \ldots R_k + \cdots + (R_1 \ldots R_{k-1})^2 R_k}.$$

Now $R_1 \ldots R_k = (1+S)^{-(k-1)}$ so

$$\pi_1 \approx \frac{2((1+S)^{k-1} - 1)}{N_1[N_1^{-1} + N_2^{-1}(1+S)^{-1} + \cdots + N_k^{-1}(1+S)^{-k+1}]}.$$

Since S is small, powers of $(1+S)$ in the denominator can be ignored, yielding:

$$\pi_1 \approx \frac{2((1+S)^{k-1} - 1)}{N_1[N_1^{-1} + N_2^{-1} + \cdots + N_k^{-1}]}.$$

But for small k and small S we can use a Taylor series approximation of $(1+s)^{k-1} = 1 + (k-1)S$ therefore

$$\pi_1 \approx 2(S)(k-1)N_1^{-1}[N_1^{-1} + N_2^{-1} + \cdots + N_k^{-1}]^{-1}.$$

In the case of population doublings where $N_i = 2^{i-1}N_1$, we can simplify further to obtain

$$\pi_1 \approx \frac{2^k S(k-1)}{2^k - 1}. \tag{5}$$

In our example $k = 8$, thus using the above equation we can approximate the solution to equation system (3). This approximation gives a fixation probability of 0.0702 which is close to the analytical solution of 0.0677. Fig. 1a illustrates that the approximation is a good indicator of the fixation probability only when S is small.

Note that Pollack (2000) also derives an approximation to the fixation probability in a population experiencing cyclic growth. Pollack uses a Poisson distribution of offspring and expansion of functions into Bernoulli polynomials. From Eq. (3), using Pollack's method, it can be shown that

$$\pi_1 < \frac{2^k[(1+S)^{k-1} - 1](1+2S)}{[2(1+S)]^k - 1} \tag{6}$$

assuming population doublings. This equation gives a fixation probability of 0.0682 for $k = 8$ and $S = 0.01$. This is a closer approximation to the analytical solution of 0.0677 but it is still only valid for small values of S (see Fig. 1a).

2.3. Computer simulation

To simulate a Poisson distribution of offspring the number of daughter cells, x, for each parent bacterium in each generation is a random number distributed as

$$\text{prob}(x) = \frac{e^{-\lambda}\lambda^x}{x!}, \tag{7}$$

where λ is the expected number of offspring for a single individual. It is easily shown that for n_i identical individuals, the total number of offspring is distributed as

$$\text{prob}(x_i) = \frac{e^{-n_i\lambda_i}(n_i\lambda_i)^{x_i}}{x_i!}, \tag{8}$$

where $i = 1, 2$ represents the wildtype and mutant genotypes, respectively. λ_i is the expected number of offspring for a single individual in the ith genotype, n_i is the number of individuals in the ith genotype and x_i is the total number of offspring that the ith genotype had in that generation.

If we assume that the parameter $\lambda_1 = 2$, this means that each wildtype expects two offspring on average (and that the parent does not exist in the next generation). For an individual carrying a rare beneficial mutation with selective advantage S, the number of offspring at the end of a growth phase will be based on a Poisson distribution with $\lambda_2 = 2(1+S)$. In order to determine the number of offspring of the ith genotype, a Poisson random variable is generated using the algorithm "poidev" based on the rejection method (Press et al., 1992). Note that this number is an integer since part of an offspring cannot exist in a generation.

When the expected number of offspring, $n_i\lambda_i$, increases, the Poisson algorithm runs into numerical difficulties. For large numbers, the Normal distribution with mean $\mu_i = n_i\lambda_i$ and standard deviation $\sigma_i = \sqrt{\mu_i}$ is a good approximation to the Poisson distribution (Lewis and Traill, 1999). Using this approximation, the probability of x_i offspring is distributed as

$$\text{prob}(x_i) = \frac{1}{\sqrt{2\pi n_i\lambda_i}} e^{\frac{-(x_i - n_i\lambda_i)^2}{2n_i\lambda_i}}. \tag{9}$$

As the mean $n_i\lambda_i$ increases, the Normal distribution and the Poisson distribution converge (Lewis and Traill, 1999). We introduce a cutoff value such that when the expected number of offspring is less than this value the Poisson algorithm is used, otherwise the Normal algorithm is used. The Normal algorithm that we used, "gasdev", is based on the Box–Muller transformation (Press et al., 1992). We judged that the Normal distribution is a sufficiently close approximation to the Poisson distribution when the mean $\mu_i \geqslant 100$, and use this value throughout the paper.

In each generation the number of wildtype and mutant individuals are calculated using the respective Poisson or Normal distributions. At the end of a generation the frequency of the wildtype and mutant are recalculated. This is repeated until the end of the growth phase, the τth generation.

At this point the wildtype and mutant experience a population bottleneck. We use a Binomial deviate, "bnldev" (Press et al., 1992), to model the population bottleneck. The Binomial deviate calculates the number of individuals of the ith genotype that survive the bottleneck. This allows chance to play a role in the survival of the mutant and the wildtype as well. For gene frequency p_i and sample size N_0, the probability that x_i copies of the ith genotype survive the bottleneck is given

by

$$\text{prob}(x_i) = \frac{N_0!}{x_i!(N_0 - x_i)!} p_i^{x_i}(1 - p_i)^{N_0 - x_i}. \quad (10)$$

At the end of the bottleneck the frequencies of the wildtype and mutant populations are recalculated. This initiates a new growth phase and the cycle repeats until the mutant population is eliminated or it is fixed in the population.

When the mutant population is eliminated or reaches fixation, this marks the end of an iteration of the computer simulation. The mutant is eliminated when the frequency of the mutant population is 0 and fixed when it reaches a frequency of 1. Practically, for population sizes used in experimental evolution, the probability of the mutant being lost becomes negligible once it has reached a frequency of 0.20. Therefore the mutant population is recorded as fixed if it reaches a frequency of 0.20 and the iteration is ended. This allows us to decrease the runtime of the computer simulation.

The fixation probability of the mutant in the population is estimated by repeating the method for 10 million iterations.

Using the values $\tau = 7$, $S = 0.01$, $N_0 = 10^4$ and $t = 0$ we find that the probability that an individual carrying a rare mutation with selective advantage S that first occurs at time t ultimately survives bottlenecks is 0.0677, which is identical to the analytical result to three significant digits. The simulation results are illustrated in Fig. 1a for different values of S.

2.4. Computer simulation for deterministic growth

To investigate the magnitude of genetic drift, we also simulated deterministic growth, when individuals can only be eliminated by population bottlenecks. To simulate deterministic growth of the wildtype and mutant populations, we use the following equations:

$$N_1(t) = e^{rt} N_1(0), \quad (11)$$

$$N_2(t) = e^{r(1+s)t} N_2(0), \quad (12)$$

where $N_i(t)$ is the size of the ith population at time t, $N_i(0)$ is the initial size of type i at the beginning of the growth phase, r is the growth rate, t is the number of generations, and s is the selective advantage of the mutant.

Note that this type of exponential growth is related to growth used above by the following equations:

$$r = \ln(1 + R), \quad (13)$$

$$s = \frac{\ln(1 + S)}{\ln(1 + R)}. \quad (14)$$

The lowercase growth rate and selective advantage are used in this section to be consistent with the analytical work of Wahl and Gerrish (2001). The uppercase variables are consistent with Ewens (1967).

At the end of a growth phase, the size of the wildtype population is $N_1(\tau)$, while the mutant population is given by $N_2(\tau)$. At this point the population experiences a bottleneck and then it starts another growth phase. The algorithm for the bottleneck is as described for the stochastic growth case. This is repeated until the mutant is eliminated or it reaches fixation in the population. The mutant population is recorded as fixed when it reaches a frequency of 0.20 in the population as in the stochastic case.

The fixation probability of the mutant in the population is estimated by repeating the method for 10 million iterations.

Using the values $\tau = 7$, $s = 0.014355$, $N_0 = 10^4$, $r = \ln(2)$ and $t = 0$ we find that the probability that an individual carrying a rare mutation with selective advantage s that first occurs at time t ultimately survives bottlenecks is 0.1312.

The open triangles in Fig. 2a show the fixation probability of the mutant as a function of s. It is clear that the fixation probability due to bottlenecks rises as s increases and that it is greater than the fixation probability that includes genetic drift. The fixation probabilities determined by the computer simulations for stochastic and deterministic growth were used to calculate the percent change due to genetic drift. This is illustrated in Fig. 2b for selected values of s. For these values of s the percent change is approximately 36–50%.

For comparison, Fig. 2a also plots the analytical approximation derived by Wahl and Gerrish (2001), for deterministic growth and weak selection (dot–dashed line). We can see that the analytical solution compares well with the simulation described above, although when s is large the simulation and the analytical results diverge. We can also see in Fig. 2a that the stochastic and deterministic results diverge as s increases. This means that incorporating genetic drift makes a large difference in the fixation probability of the mutant.

2.5. Effect of population size

In the analytical solutions for the stochastic and the deterministic cases, the size of the initial population, N_0, in the sequence does not affect the fixation rate. We verified that this is also true for the computer simulations for stochastic and deterministic growth. This is illustrated in Fig. 3 for population sizes from 5×10^2 to 4×10^6.

3. Discussion

In experimental evolution a beneficial mutant must survive genetic drift and population bottlenecks to

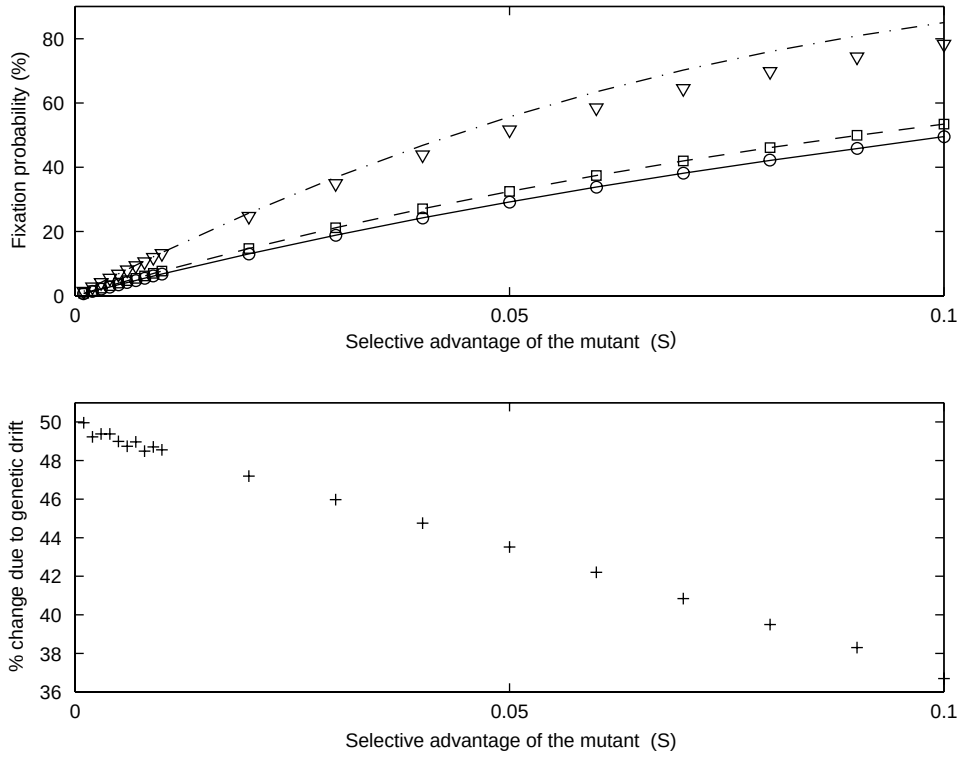

Fig. 2. Relative magnitude of genetic drift. The fixation probability of a beneficial mutant that originally occurs at time $t = 0$ is plotted as a function of the selective advantage S. The first panel plots the fixation probability determined analytically (lines) and by simulation (symbols) for deterministic (dot–dashed, triangles), cyclic (dashed, squares) and stochastic (solid line, circles) growth. Deterministic growth includes the effect of bottlenecks alone, while stochastic includes both bottlenecks and genetic drift. In 'cyclic' growth (Ewens, 1967), the mutant also has a $(1 + S)$ advantage in surviving the bottleneck. The second panel illustrates the percent change between stochastic and deterministic growth, i.e., the percent change in fixation probability due to the inclusion of genetic drift in this model. To calculate these values, simulation results were used because the deterministic analytical solution is a small s approximation. For both panels the parameters for growth are $\tau = 7$, $N_0 = 10^3$, $R = 1$.

eventually become fixed in a population. We have demonstrated analytically and through computer simulation that the fixation probability of a beneficial mutant that ultimately survives genetic drift and population bottlenecks is significantly lower than previous results where only population bottlenecks were considered. The fixation probability including the effect of genetic drift is approximately 36–50% lower for the values of S illustrated in Fig. 2b.

Our analytical solution does not assume that selection is weak. Recent evidence suggests that the selective advantage of adaptive traits can be quite large (Golding and Dean, 1998; Orr, 1998), particularly in experimental evolution (Wichman et al., 1999; Bull et al., 2000) where selective advantages as large as 13.8 have been reported (Bull et al., 2000). When this occurs the analytical solution must be used.

When S is very large (greater than 3) the effect of including genetic drift in the analysis decreases and eventually becomes negligible. This is because fixation probability can only obtain a value as high as 1. When S is greater than 3 the fixation probability is approximately 1 regardless of whether genetic drift is included in the analysis.

Classically, in a population of constant size, the probability that a beneficial mutation survives drift is approximately $2S$ (Haldane, 1927). We have derived a simple approximate expression for the probability that a beneficial mutation ultimately survives genetic drift *and* periodic bottlenecks. From Eq. (5), for a mutation occurring at the start of a growth phase this probability is given by

$$\pi_i = 2S(k-1)\frac{2^{k-1}}{2^k-1} \approx 2S\frac{k-1}{2}. \tag{15}$$

Thus, for a population which grows exponentially for k generations between bottlenecks, the fixation also varies as $2S$, but is increased by roughly a factor of $\frac{k-1}{2}$. This implies that even when genetic drift is included in the analysis, exponential growth between bottlenecks is a more important factor than elimination during bottlenecks; fixation probability is *higher* in these populations than in a population of constant size (see Fig. 1a).

Our derivation only takes into account the loss of beneficial mutations due to genetic drift and bottlenecks. In asexual populations rare beneficial mutations may also be lost during the growth phase due to competition (Gerrish and Lenski, 1998). The results presented here

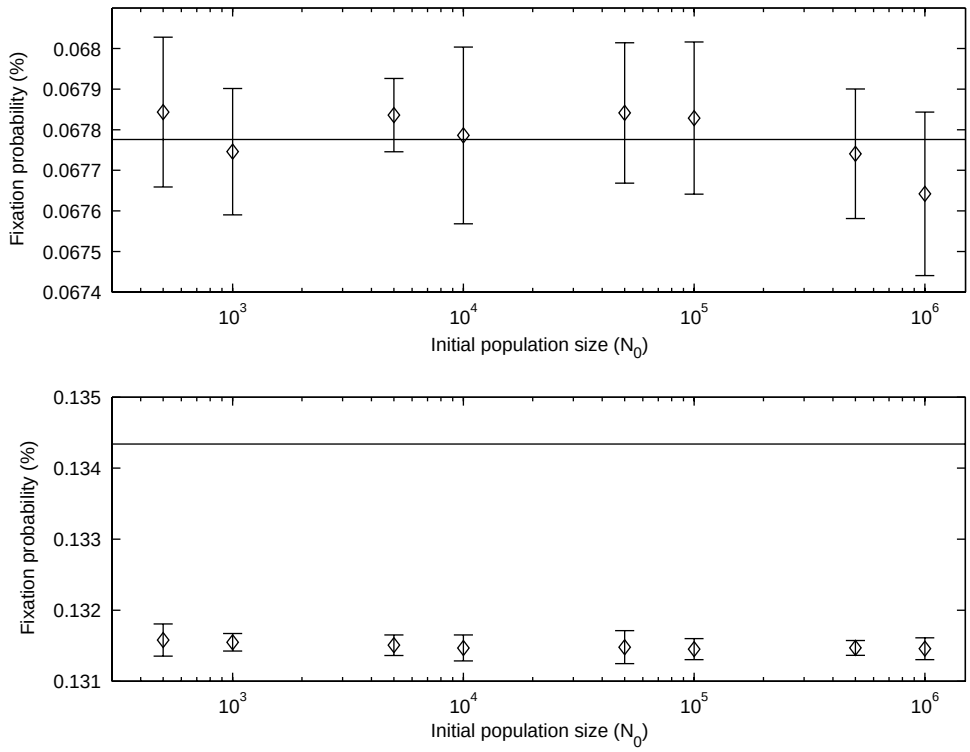

Fig. 3. Fixation probabilities with variable N_0. The fixation probability of a beneficial mutant with selective advantage S that originally occurs at time $t = 0$ is plotted for stochastic (top panel) and deterministic (lower panel) growth in populations of various sizes. Parameters for growth are $\tau = 7$, $S = 0.01$, $R = 1$. The diamonds show the computer simulation results, error bars show the standard deviation of the results, and the solid lines plot the analytical result in both panels. The analytical result in panel a is the solution to Eq. (3); in panel b, the approximation provided by Wahl and Gerrish (2001) is shown.

are an essential prerequisite to answering this more complex question in future research.

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