

Mutator Dynamics on a Smooth Evolutionary Landscape

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We investigate a model of evolutionary dynamics on a smooth landscape which features a “mutator” allele which increases the mutation rate. We show that when the fitness is far from its equilibrium value the expected proportion of mutators approaches a value governed solely by the transition rates into and out of the mutator state, resulting in a much faster fitness increase than would be the case without the mutator allele. Near the fitness equilibrium, the mutators are severely suppressed, due to the detrimental effects of a large mutation rate near the fitness maximum. We discuss the results of a recent experiment on natural selection of *E. coli* in the light of our model. [S0031-9007(98)05492-1]

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In a recent paper [1], Sniegowski *et al.* presented results concerning the mutation rate of a series of *E. coli* populations undergoing natural selection in a laboratory setting. They found that three out of twelve populations had mutated to states with much higher mutation rates, becoming, in the language of population genetics, “mutators.” These changes were traced to the disabling of some specific DNA repair mechanisms [2] in each of the three mutators. While similar results had been obtained in chemostats utilizing artificially hobbled bacterial strains [3,4], this is the first time that natural populations had shown selection for more rapid mutation. These results have important implications for a variety of topics, including the debate over “directed mutation” [5] and the accumulation of multiple mutations in cancer cells [6].

Models of mutator selection have, in general, taken one of two forms. On one hand, Painter [7] and others [8] have considered the case of a small number of genetic “states” and used mean-field theory to predict mutator population. In the simplest realization, a bacterium can be in one of four states, mutator-nonmutator and high-low fitness. While this approach may be suitable for the aforementioned chemostat experiments, it is inadequate to describe the slow overall improvement in fitness seen in long-term natural evolution [9]. At the opposite extreme, Taddei *et al.* [10] have produced a complex model by combining measured data on *E. coli* with other more arbitrary assumptions. This model, while in principle useful, does not easily lend itself to analysis and the identification of which details are essential and which are not.

In this paper, we propose a simple approach to mutator selection based on the fitness landscape being smooth. In previous work [11,12], we and our collaborators have studied a simple model of evolution in a smooth landscape. By extending the model to include the possibility of a mutator state [13], we will show that the basic features of the experimental data can be understood, provided that the transition rate from the mutator state to the normal,

nonmutator state is much slower than the time scale of the experiment. The model then predicts that the system at the time of measurement is in fact near a crossover between a far-from-equilibrium state where the system is “climbing” the fitness hill and the equilibrium state; this is consistent with the measured fitness data [9]. The model allows us to make a number of other predictions which can hopefully be tested by future results of the ongoing experiment.

Our basic model assigns a “fitness,” i.e., reproduction rate, to each individual in a population. This fitness is determined by its genome, which consists of L binary genes, with values 0 and 1, and is simply the number of 1’s in the genome. Reproduction for each individual is modeled as a Poisson process whereby a new individual with the same fitness (modulo mutation) as the parent is added to the population. At the same time as this asexual reproduction event occurs, one of the existing members of the population is chosen at random and “killed,” so as to maintain a fixed population size N [14]. Mutation may accompany birth so that, with probability μ , one of the genes of the baby is chosen at random and flipped. The usual assumption in the population genetics literature that most mutations are deleterious arises here as a consequence of a population lying close to the fitness peak, so that most genes have the value 1. This creates an imbalance in the overall probability of moving up or down the landscape via mutation. The analysis of this model and its application to RNA virus experiments [15] has been given elsewhere [11,12].

To apply this framework to the *E. coli* experiments, we add one special two-allele gene which controls the mutation rate [16]. With the mutator allele, the mutation rate is increased from μ to $\lambda\mu$ without any direct effect on fitness. We take σ_f , (σ_b) to be the forward (backward) mutation rate to (from) the mutator state, which we consider as new independent parameters.

We first analyze the equilibrium state of the population. Assuming $N \gg L$, we can use mean-field theory and ignore any fluctuations in the population. This leads

immediately to the equations

$$\begin{aligned}
0 = \dot{P}_x &= (x - \bar{x})P_x \\
&+ \mu x [p_{x-1}P_{x-1} + (1 - p_{x+1})P_{x+1} - P_x] \\
&- \sigma_f x P_x + \sigma_b x Q_x, \\
0 = \dot{Q}_x &= (x - \bar{x})Q_x \\
&+ \lambda \mu x [p_{x-1}Q_{x-1} + (1 - p_{x+1})Q_{x+1} - Q_x] \\
&+ \sigma_f x P_x - \sigma_b x Q_x.
\end{aligned} \tag{1}$$

Here, p_x is the probability that a mutation results in moving up in fitness, which equals $1 - x/L$. P_x and Q_x are, respectively, the normal and mutator population fractions at fitness x , and \bar{x} is the mean fitness of the population, considering both normal and mutator types on an equal footing. To solve this equation, we assume that L is large and define $y \equiv L - x$. To leading order in L ,

$$\begin{aligned}
0 = (\bar{y} - y)P_y &+ \mu L(-P_y + P_{y-1}) \\
&- \sigma_f L P_y + \sigma_b L Q_y,
\end{aligned} \tag{2a}$$

$$\begin{aligned}
0 = (\bar{y} - y)Q_y &+ \lambda \mu L(-Q_y + Q_{y-1}) \\
&+ \sigma_f L P_y - \sigma_b L Q_y.
\end{aligned} \tag{2b}$$

This equation also applies for $y = 0$ if we set $P_{-1} = Q_{-1} = 0$. At $y = 0$, we obtain

$$Q_0 = P_0 \frac{\sigma_f L}{\sigma_b L + \lambda \mu L - \bar{y}}, \tag{3}$$

as well as a quadratic equation for \bar{y} . It is easy to see from this equation that if $\lambda = 1$, then $\bar{y} = \mu L$, giving $\sigma_b Q_0 = \sigma_f P_0$ as expected by naive balance between the forward and backward transitions. On the other hand, if λ is large, $\bar{y} = (\mu + \sigma_f)L$; this is easily seen since $Q_0 \approx (\sigma_f/\lambda\mu)P_0$ is then small and can be dropped from the P_0 equation.

To make further progress, we let λ be large. Then, to leading order, the P subpopulation decouples and

$$P_y = P_0 \frac{(\mu L)^y}{\Gamma(y + 1)}, \tag{4}$$

where P_0 is fixed by normalization to $P_0 = e^{-\mu L}$. This is precisely the result in the absence of the mutator state. The Q distribution follows from the inhomogeneous recursion relation, Eq. (2b), with the sources fixed by the known P_y . Solving this equation, we see that the relative narrowness of the P distribution essentially ‘‘collapses’’ all the source terms to $y = 0$, giving the simple result for $1 \ll y \ll \lambda$,

$$Q_y \sim \frac{\sigma_f}{\lambda \mu} \left[\frac{(\lambda \mu L)^y \Gamma(\lambda \mu L + 1)}{\Gamma(\lambda \mu L + y + 1)} \right] \sim \frac{\sigma_f}{\lambda \mu} e^{-y^2/(2\lambda \mu L)}. \tag{5}$$

Thus, even though each individual Q_y is of order $\sigma_f/\lambda\mu$, the width of the q distribution is large, of order $\sqrt{\lambda\mu L}$, so the total number of fast individuals is much larger, $\sigma_f \sqrt{\frac{2L}{\pi\lambda\mu}}$. One can further check this calculation by

computing the value of \bar{y} from the P and Q distributions. The mean y of the normal type is just μL , but the small number of fast type have anomalously high y and contribute a total of $\sigma_f L$ to the total fitness without changing the total number of individuals significantly, reproducing the result obtained above.

The reason for the suppression of the fast type is clear, and has been appreciated for a long time [17]. The ‘‘natural’’ equilibrium of the fast type, if there were no slow type around, would place them λ times farther from the fitness peak than the slow type. Thus, the faster mutation rate of the fast species places a ‘‘mutational load’’ on them, so they lose out in competition with the normal species and are suppressed. The noteworthy part of the calculation is the prediction of the size of the suppression, which would be difficult to guess *a priori*.

We now turn to the far-from-equilibrium case where the typical fitness of an individual is close to $L/2$ on the scale of L . Here, mutations will produce movement up or down the landscape with equal probability. In this case, with just the normal type present, we found [12] that the population increases its mean fitness at a constant rate on average. In this regime, mean-field theory is an utter failure, leading [11,12] to finite-time singularities caused by the inability to properly account for the essential variance limiting property of birth-death processes [18]. We turn instead to an approach [12] which involves truncating the state space of the exact Markov process, utilizing the assumption that the mutation probabilities μ , σ_f , and σ_b are much smaller than unity. To see the structure of the problem, we focus first on the case where the population consists of only two individuals, i.e., $N = 2$. In this case, the states we need to consider are those with the two individuals having the same fitness x , either both normal, $(f11)_x$, both mutator, $(f22)_x$, or one normal and one mutator, $(f12)_x$. In addition, we need to consider the states where the two individuals have adjacent fitnesses at x and $x + 1$, with both being either normal, $(g11)_x$, or mutator, $(g22)_x$. The states $(g12)_x$ and $(g21)_x$ where the two individuals having different fitness and type are of order $\mu\sigma_f$ and are therefore dropped along with the states where the two individuals differ in fitness by more than one, which are higher order in μ . Truncating the master equation to these states yields

$$\begin{aligned}
\dot{(f11)}_x &= -2\mu x (f11)_x + \frac{1}{2} x (g11)_x \\
&+ \frac{1}{2} x (g11)_{x-1} - 4\sigma_f x (f11)_x \\
&+ \frac{1}{2} x (f12)_x
\end{aligned} \tag{6}$$

and similar equations for the other four densities. In the case with just normal individuals, we found [12] that the long-time solution had the scaling form $f_x = \frac{1}{x} F(x/t)$, which indicates directly the linear growth of fitness with time. Examining our system of equations, we see that

such a scaling form is not possible unless

$$\begin{aligned}\sigma_b f(22) &= \sigma_f f(11) + (\Delta 22)(x/t)/(xt^2), \\ f(12) &= 8\sigma_f f(11) + (\Delta 12)(x/t)/(xt^2).\end{aligned}\quad (7)$$

The physical meaning of these relationships is that the system must quickly evolve to a state of “local equilibrium” between the normal and fast types before it can achieve the linear-velocity climbing state. In this local equilibrium, the ratio of fast to normal types is given by $2(f22) + f12)/2[(f11) + f12 + f22] = \sigma_f/\sigma_b$, just as it would if there were no fitness degrees of freedom. Substituting this scaling form into the truncated master equations and dropping all time derivatives of the g 's and of $f12$ (they are second-order quantities), we get, after eliminating the Δ terms,

$$\begin{aligned}\left(1 + \frac{\sigma_f}{\sigma_b}\right) f \dot{11} &= \left(1 + \frac{\lambda \sigma_f}{\sigma_b}\right) \\ &\times \left\{ \frac{\mu}{2} [(f11)' + x(f11)'] \right\}.\end{aligned}\quad (8)$$

This equation shows that the velocity has been renormalized by the factor $(\sigma_f \lambda + \sigma_b)/(\sigma_f + \sigma_b)$, which is very reasonable given the ratio of mutator to normal types and the fact that the velocity is exactly linear in the mutation rate and the number of individuals.

The above methodology can be extended to arbitrarily large N with the basic results concerning the percentage of mutators and the renormalization of the velocity unchanged. In Fig. 1, we show the prediction of this analysis along with direct simulations of our Markov process. The agreement of the theory with the asymptotic state is quite satisfactory. There is, however, a transient period in which a larger number of mutators are selected. This latter behavior is due to the fact that evolutionary advance of the *initial* population (consisting entirely of wild-type cells) occurs most readily by creating mutators; eventually, these mutators start making back transitions and es-

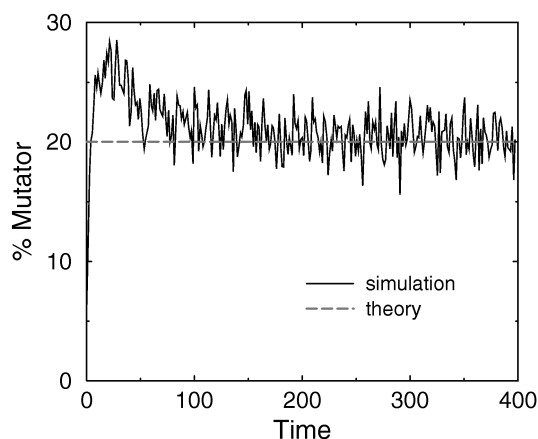


FIG. 1. Percentage of mutators in the far-from-equilibrium case, with $\sigma_f = 0.001$, $\sigma_b = 0.004$, together with the asymptotic prediction. $\mu = 0.01$, $\lambda = 10$, $N = 100$, averaged over 400 realizations.

tablish the steady-state ratio. This transient response is analogous to what has been termed “hitch hiking” in the genetics literature. We see that this naive picture of the selection of mutators in the climbing state breaks down rather quickly and the true situation is one of balance based solely on the forward and backward rates.

In a given experiment, the population is placed in a new environment and allowed to evolve towards the fitness peak. Initially, the rate of fitness improvement will be correlated with the mutator percentage in any given realization, with the average effect as given above. Eventually, the system will begin to approach equilibrium and the mutators will start to be at a disadvantage. Roughly, the crossover should take place when the average fitness equals the equilibrium mean fitness of the mutator type considered alone: namely, a distance $\lambda\mu L$ from the peak. After this point, it is advantageous for the population to shed its mutators and continue to climb to its final resting point, a distance $(\mu + \sigma_f)L$ from the top. In essence, then, the system gets a “free ride” from the presence of the mutators. They help the system to get close to the fitness peak, but then politely bow out of the picture so as not to significantly impair the final mean fitness [19].

We now turn to a discussion of the results of the experiment detailed in Ref. [1]. This work reported that three out of twelve populations fixed completely the mutator genotype; yet there was no clear correlation between fitness and mutator status at the current epoch. While it is possible that fluctuations are dominating the average behavior, we will assume the experimental results reflect the typical behavior of the system and ask how they relate to our model. It is clear that the only way to make our model correspond to the experimental findings is to take the backward mutation rate σ_b to be so small as to play no role on the time scale of the experiment. Otherwise, one would have expected to see reversions from the mutator state to the normal state, which were not observed. Biologically, this vanishingly small σ_b corresponds to the mutation of the DNA repair mechanism being due to something other than a (reversible) point mutation. This assumption of no back mutations implies that it is possible to irreversibly fix the mutator gene, with all nonmutators eliminated from the population. The percentage of systems so fixed will increase monotonically with time, with the rate of fixation becoming vanishingly small as the mean fitness in the non-fixed systems approaches the equilibrium mutator fitness. After this crossover point, the mutators become suppressed and fixation becomes extremely unlikely. This behavior is indicated in Fig. 2, in which a set of 40 populations experienced nine instances of mutator fixation. The fact that no additional fixations were seen in the last third of the experiment indicates that the system was near this crossover point at the end of the run. This fact is consistent with the leveling off of the rate of fitness improvement in the experiment, as reported in Ref. [9]. Near the crossover point, there is no clear correlation between mutator status and fitness, as can be verified from our simulations (see Fig. 3).

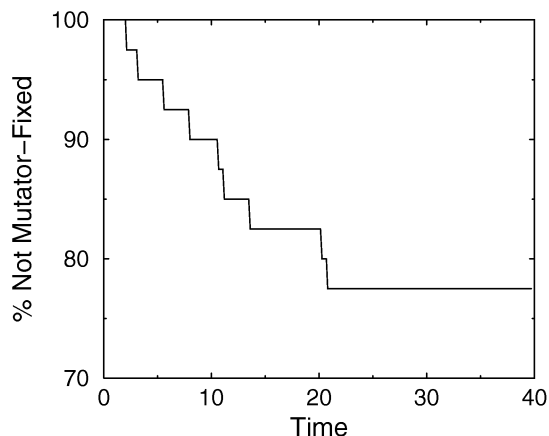


FIG. 2. Fraction of populations which have not completely fixed the mutator gene, for a simulation with 40 independent realizations of our stochastic evolution model. $\mu = 0.005$, $\sigma_f = 0.0005$, $\sigma_b = 0$, $\lambda = 15$, $L = 100$, $N = 1000$. After the times shown, no more populations became mutator fixed.

This lack of correlation is also consistent with the experimental findings.

If our understanding proves correct, we can make the following predictions for what should be seen as the experiment is continued past the times reported: Since σ_b is small, no reversions should be seen. Since we are near the crossover, we expect no additional mutator fixations. More significantly, the correlation between fitness and mutator status should have been positive in the past and should become negative in the future. This can be tested by studying isolates from fixed times in the past and by repeating the measurements as the evolution continues. Also, we predict that the percentage of mutation fixations should depend on the initial distance from the fitness peak; that is, how much the experimental growth conditions depart from the usual wild-type habitat.

To summarize, we have presented a simple model which describes how the dynamics of mutation rate changes

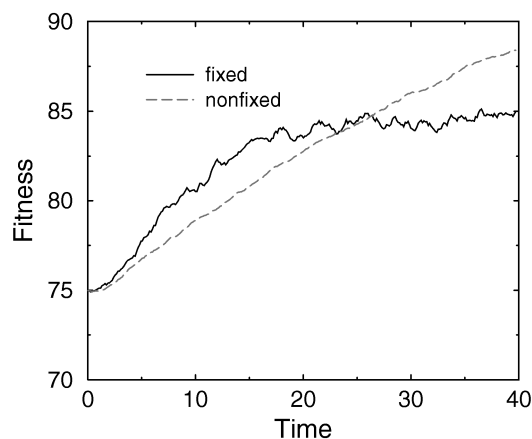


FIG. 3. Fitness vs time, for the simulations described in Fig. 2, plotted separately the average fitness over the subset of our populations which fix (9 out of 40) or do not fix (31 out of 40) the mutator gene sometime during the run.

affects and is affected by natural selection. The analytic tractability of our evolutionary dynamics allows us to focus directly on the issues which determine selection for or against mutator states. Our various predictions for the experiment should test whether this type of generic analysis is powerful enough to make reliable statements regarding these complex biological processes.

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