

Role of mutator alleles in adaptive evolution

F. Taddei^{*#}, M. Radman^{*}, J. Maynard-Smith[†], B. Toupance[‡], P. H. Gouyon[‡] & B. Godelle^{‡§}

^{*} Laboratoire de Mutagenèse, Institut J. Monod, CNRS Université Paris 7, 2 Place Jussieu, 75251 Paris, France

[†] University of Sussex, Microbial Genetics Group, School of Biological Sciences, Falmer, Brighton BN1 9QG, UK

[‡] Université de Paris-Sud CNRS, Laboratoire Évolution et Systématique, Bat. 362 F91405 Orsay cedex, France

[§] Institut National Agronomique Paris-Grignon, 16 rue Claude Bernard, 75005 Paris and # Ecole Nationale du Génie Rural, des Eaux et des Forêts, 19 avenue du Maine, 75732 Paris, France

Because most newly arising mutations are neutral or deleterious, it has been argued¹⁻³ that the mutation rate has evolved to be as low as possible, limited only by the cost of error-avoidance and error-correction mechanisms. But up to one per cent of natural bacterial isolates are 'mutator' clones that have high mutation rates⁴⁻⁶. We consider here whether high mutation rates might play an important role in adaptive evolution. Models of large, asexual, clonal populations adapting to a new environment show that strong mutator genes (such as those that increase mutation rates by 1,000-fold) can accelerate adaptation, even if the mutator gene remains at a very low frequency (for example, 10^{-3}). Less potent mutators (10 to 100-fold increase) can become fixed in a fraction of finite populations. The parameters of the model have been set to values typical for *Escherichia coli* cultures, which behave in a manner similar to the model in long-term adaptation experiments⁷.

Early models of the evolution of the mutation rate were based on group selection for an optimal compromise between adaptability and adaptedness^{2,3}. However, later models, incorporating mutators and antimutators (modifiers of the mutation rate) showed that a mutator can reduce individual fitness while increasing the probability for an adaptive mutation to appear in the population. The prediction of these models was that a minimal mutation rate would be selected in a stable environment (reduction principle⁸), whereas in an oscillating environment, infinite populations at equilibrium could have a non-minimal mutation rate^{3,9,10}.

However, most of evolution may take place with the population being far from equilibrium, with organisms facing an ever-changing

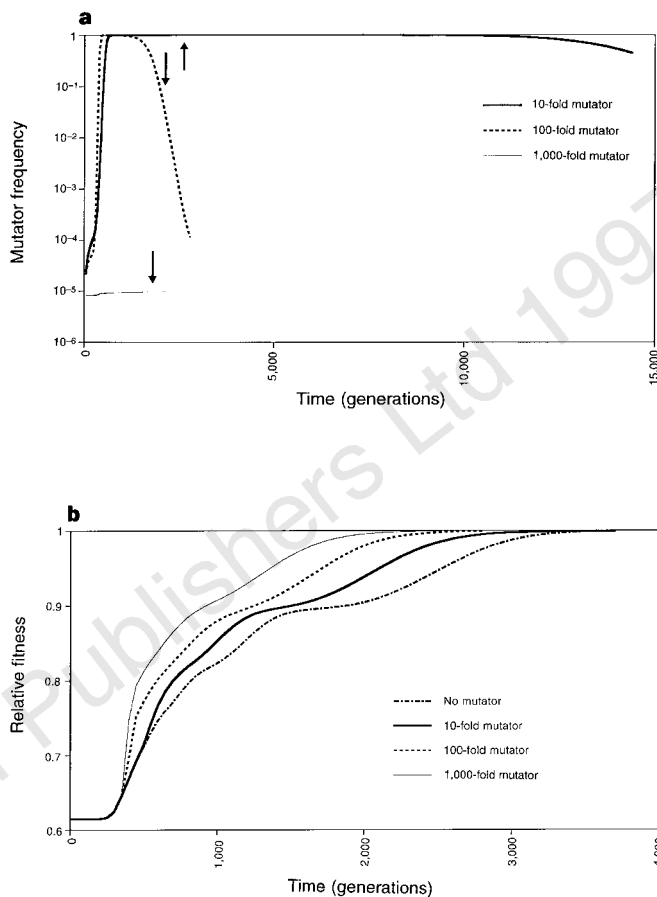


Figure 2 Mutators speed up evolution even when they are not fixed in infinite populations. Major effect mutators remain at very low frequency (**a**) but allow rapid fitness increase of the whole population (**b**) thanks to reversion to non-mutator genotypes associated with favourable mutations. **a**, Evolution of the frequency of mutator genotypes. Intermediate strength mutators become fixed, and then disappear from the population when all favourable mutations are fixed (an arrow symbolizes the time when relative fitness has reached 0.99, generation 3,100, 2,650, 2,200 and 1,850 for populations with no mutator, a 10-, a 100- and a 1,000-fold mutator, respectively.) **b**, Evolution of the mean fitness of asexual populations subjected to mutation and selection.

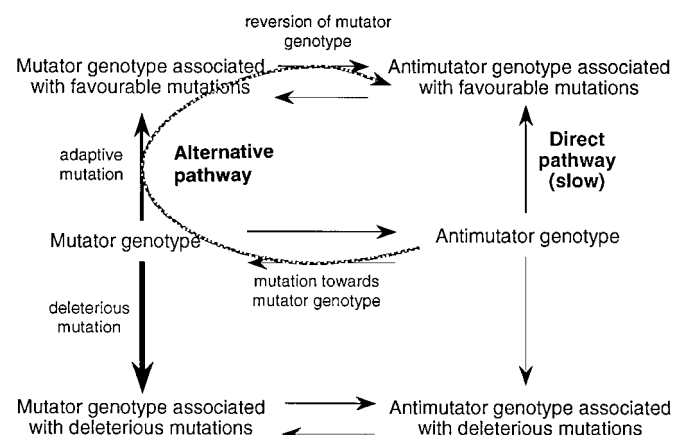


Figure 1 Mutators as a fast track to generate adaptive mutations. Fixation of adaptive mutations can proceed in two ways: favourable mutants appear in a non-mutator genetic background, and then spread by selection; mutator genotypes, obtained by mutating an antimutator gene (such as a mismatch repair gene) can also be transiently involved by generating favourable mutations and then reverting to the wild-type allele. (See Methods for values of parameters.)

environment¹¹, a situation that favours a non-minimal mutation rate^{12–14}. Previous studies did not consider the effects of random drift. In fact, finite population size with moderate mutation rates maintains favourable mutants at such low frequencies that they are absent in many natural populations. Experiments with *Escherichia coli* held for many generations in a chemostat lead to a paradoxical unexpected outcome: a mutator allele (monitored by the use of a linked selectable marker) increased in frequency when abundant but decreased in frequency when rare^{15–19}. The present work targets the difference between finite and infinite populations under directional selection. Our model uses mutation rates typical for *E. coli* (see Fig. 1 for a general overview and Methods for details), using the large amount of mutagenesis data available for this organism (see refs 1, 20).

In the absence of selection for adaptive mutations, a mutation/selection equilibrium is reached where the spontaneous generation of mutator alleles by inactivation of an ‘antimutator’ gene at a frequency of 5×10^{-7} is balanced by increased production of deleterious and lethal mutations by the mutator (the cost of

deleterious mutations was set at 0.05). The equilibrium value observed in the simulations was, respectively, 6×10^{-4} , 6×10^{-5} and 10^{-5} for 10-, 100- and 1,000-fold mutator alleles.

The evolution of a population can be very different when adapting to a new environment if adaptation is limited by mutation availability. Mutator genotypes generate adaptive mutations efficiently. Therefore we suggest that a transient increase in mutator frequencies should be a common event in natural asexual populations subjected to sporadic adaptive evolution (Fig. 1).

We modelled this by assuming that favourable alleles were possible in 15 to 39 loci, with selective advantages ranging from 0.005 to 0.03, values that are consistent with those observed in long-term experiments with *E. coli*^{21,22}. In an infinite population, 10- and 100-fold mutator alleles can be fixed by ‘hitch-hiking’ with favourable mutations in about 500 generations (Fig. 2a), whereas a 1,000-fold mutator will not be fixed during the course of evolution.

However, provided there are enough adaptive mutations, there is a positive correlation between the speed of increase in fitness and the strength of the mutator allele. A population containing a 1,000-fold

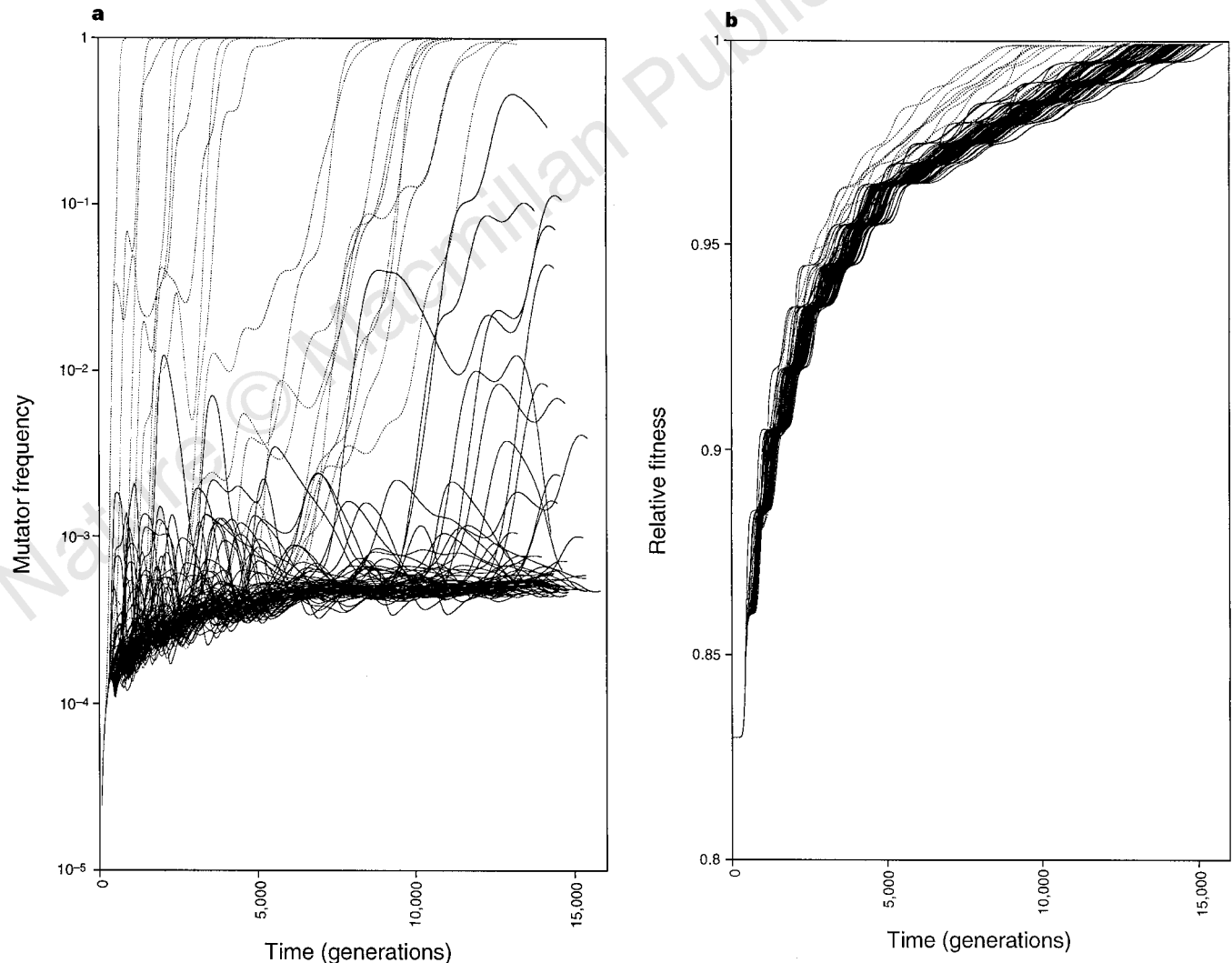


Figure 3 Intermediate mutators can be fixed during adaptation of finite size populations (10-fold mutators are shown). The model is similar to the one described in Fig. 2. Here, however, finite populations were allowed to grow exponentially from 10^3 to 10^{10} individuals and then were diluted back to 10^8 , with random sampling occurring every 7 generations for frequency classes lower than 13×10^{-8} (see Methods for more details about the sampling procedure). Each of

100 independent simulations is represented on these plots. Dotted lines symbolize the populations where the mutator allele has reached over 50%. **a**, Change in mutator frequency. Mutators can be favoured by hitch-hiking with adaptive mutations and thus become fixed in the population. **b**, Evolution of the mean fitness of populations subjected to mutation, selection and drift. Fixation of mutator genotypes can accelerate fitness increase.

mutator evolves much faster than a population without a mutator (Fig. 2b). The fact that an allele can have such a dramatic effect, and yet remain rare, can be explained by its high reversion rate (we assumed a point mutation that can easily be reverted by such a strong mutator), which eliminates linkage disequilibrium with favourable mutations. When its reversion rate was set to zero (modelling a deletion of the antimutator gene), the presence of a strong mutator at low frequency did not improve the rate of increase of the fitness of the population, because the favourable mutants produced were handicapped by continued linkage to this mutator allele and thus by its deleterious effects on the whole genome. Once the adaptive peak has been reached, the frequency of the mutator will decline (Fig. 2a), albeit very slowly for a 10-fold mutator, which requires about 20,000 generations to reach its equilibrium value, thus showing a strong hysteresis effect.

After modelling infinite populations, we have simulated more realistic finite populations. In the colon of mammals, population sizes of *E. coli* vary between 10^6 and 10^8 cells per g of intestinal content²³, whereas in a liquid culture density typically reaches 10^9 ml⁻¹. Finite size populations were simulated by periodical probabilistic samplings (see details below). Repeated simulations of a finite population, oscillating between 10^8 and 10^{10} cells, showed stochastic behaviour (Fig. 3a). Mutators with 10- and 100-fold effects reached a frequency of above 50% in a fraction of the trials (19 and 7% respectively). On average the fitness of populations with a high frequency of mutators increased faster during the process of adaptation (Fig. 3b). However, once all adaptive mutations were fixed, the load of deleterious mutations generated by the mutator, that had not yet reverted, lowered the fitness of the populations (Fig. 3a).

The stochastic pattern observed in Fig. 3a is due to the low probability that a mutator present in a small population will produce a favourable mutation. Once this happens, the mutator allele increases in frequency by hitch-hiking, thus facilitating the appearance of a second adaptive mutation. Mutators can then become fixed by this reiterated process, which is hampered by reversion to the non-mutator genotype. These patterns, obtained as a result of drift in finite populations, can explain why mutators have a high probability of disappearing when rare, but increase in frequency when abundant.

One of the main assumptions that we have made in this analysis is the absence of recombination, which would disrupt the hitch-hiking effect of the mutator and the linkage of favourable with deleterious mutations. Some bacterial populations are largely asexual, and these results should apply to them, but for bacteria with high levels of genetic exchange²⁴ further modelling is needed; such a model should take into account that some mutator alleles increase the rate of these genetic exchanges (see ref. 25 for a review) and that sex might allow the recovery of favourable mutations from a deleterious background²⁶. The high frequency of mutators associated with pathogenic bacteria⁶ suggests that the evolution of increased mutation rates is relevant to the evolution of parasites¹³. Our conclusions might also apply to clonal eukaryotic lineages such as large populations of autogamous plants (similarly, the outcrossing rate of autogamous plants can increase under directional selection²⁷) or tumours where mutators are associated with malignancy²⁸, but key parameters are not as well known as in the case of bacteria, and accurate modelling will have to be delayed.

Furthermore, these results show that during the course of evolution, where phases of adaptation and stasis alternate²⁹, there is no pure strategy of mutation rate. Rather, selection seems to result in an alternation of high and low mutation rate through forward and reverse mutations at the mutator locus. Alternatively, transient mutators²⁰ might allow clonal populations to enhance their adaptability by increasing their mutation rate: for example, inducible mechanisms (see ref. 30 for a review) might be particularly useful in response to stress. □

Methods

Mutation rates and selection. Mutation occurs at fixed rates (deleterious mutations, 10^{-4} ; lethal mutations, 10^{-5} ; favourable mutations, 10^{-8}). All mutation rates are increased by a given factor m in the mutator genotype. Exchange between the mutator and the wild type occurs by mutation at fixed rates (5×10^{-7} forward and $5 \times 10^{-10} \times m$ reverse). Each deleterious mutation causes an additive loss of fitness of 0.05. Different adaptive mutations are possible, allowing an additive increase in fitness of 0.005, 0.01, 0.015, 0.02, 0.025, 0.03, respectively. In infinite populations there were 21, 8, 4, 3, 2 and 1, respectively, of each class whereas in finite populations these numbers were limited to 7, 3, 2, 1, 1 and 1.

Sampling procedure used to model drift. After each 7 generations, we used a Poisson sampling procedure except for classes larger than 13 individuals, for which the size of the sample was set to the expected value (for these classes, the probability that a genotype is lost by drift is lower than 10^{-6}).

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Correspondence should be addressed to F.T. (e-mail: taddei@ijm.jussieu.fr). Request for the C code used to model mutators should be sent to B.G. (e-mail: godelle@psisun.u-psud.fr).