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The Evolution of Mutation Rate in Finite Asexual Populations

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ABSTRACT

In this article, we model analytically the evolution of mutation rate in asexual organisms. Three selective forces are present. First, everything else being equal, individuals with higher mutation rate have a larger fitness, thanks to the energy and time saved by not replicating DNA accurately. Second, as a flip side, the genome of these individuals is replicated with errors that may negatively affect fitness. Third, and conversely, replication errors have a potential benefit if beneficial mutations are to be generated. Our model describes the fate of modifiers of mutation rate under the three forces and allows us to predict the long-term evolutionary trajectory of mutation rate. We obtain three major results. First, in asexuals, the needs for both adaptation and genome preservation are not evolutionary forces that can stabilize mutation rate at an intermediate optimum. When adaptation has a significant role, it primarily destabilizes mutation rate and yields the emergence of strong-effect mutators. Second, in contrast to what is usually believed, the appearance of modifiers with large mutation rate is more likely when the fitness cost of each deleterious mutation is weak, because the cost of replication errors is then paid after a delay. Third, in small populations, and even if adaptations are needed, mutation rate is always blocked at the minimum attainable level, because the rate of adaptation is too slow to play a significant role. Only populations whose size is above a critical mass see their mutation rate affected by the need for adaptation.

WHAT is the optimum fidelity when living organisms are replicating their own information? This basic question is the keystone of self-replicating systems and the basis of evolutionary process. An organism somewhat fit to its environment either can be prudent and replicate unchanged or, improvements being certainly possible, can take a risk and innovate, most often through random modifications. The first step toward this general question is the study of the evolution of error rate at replication (mutation rate) in the case of asexuals. Heritable variation of mutation rate has indeed been documented in numerous asexual microbes (Sturtevant 1937; LeClerc *et al.* 1996; Sniegowski *et al.* 1997, 2000; Mansky and Cunningham 2000; Oliver *et al.* 2000; Denamur *et al.* 2002; Richardson *et al.* 2002; Shaver *et al.* 2002). Therefore, mutation rate is subject to alteration through the action of natural selection. In the following, we introduce the current theory on mutation rate evolution in asexual organisms. We then point out important features requiring enlightenments.

The general framework undertaken in numerous preceding works, as well as in the present one, is game theory. Let us consider a population fixed for a given mutation rate (the resident) and introduce a rare variant bearing a modifier gene affecting replication accuracy. The aim of analytical models is to predict the fate of the variant and ultimately to find a resident mutation rate in which no variant can invade (*i.e.*, an evolutionarily stable mutation rate; Maynard-Smith 1982). In this purpose, the fitness of modifier-bearing individuals must be calculated. This fitness may be affected directly by the mutation rate modifier. For instance, owing to the thermodynamic cost of replication fidelity, a modifier increasing mutation rate may have a positive effect on fitness (Dawson 1998, 1999). In addition, fitness is also affected indirectly by the carriage of the modifier, through linkage disequilibrium with other loci. This indirect effect, the most peculiar effect of mutation rate, is double sided. Consider the case of a modifier increasing mutation rate. On one side, when they replicate their DNA, modifier-bearing individuals generate more unfavorable errors than wild-type individuals. Therefore, the modifier allele is positively linked with deleterious mutations, which generates an indirect fitness cost. However, on the other side, modifier-bearing individuals are also more likely to generate favorable errors at replication, which generates an indirect fitness benefit for the modifier. The aim of theoretical models is to measure the respective strength of these three effects.

At first, one could get the impression that mutation rate evolution depends simply on the average effect of

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DNA alterations. If, in expectation, random mutations increase fitness, then mutation is good; if they decrease fitness then it is bad. Mutation rate evolution would then be a trivial issue. Indeed, even when a population is in the course of adaptation, the vast majority of mutations are still deleterious. Therefore, in expectation, altering an individual's DNA by mutation always leads to a reduction of its fitness. An individual who must choose between producing mutated or nonmutated offspring should always prefer nonmutated ones, and mutation rate should be fixed at the minimum one possible.

Theoretical models have shown that this simple answer is not accurate because the indirect cost of deleterious mutations and the indirect benefit of advantageous ones are not symmetric effects. Consider again a modifier increasing mutation rate. In a large asexual population, any individual carrying more than the minimum number of deleterious mutations ultimately leaves no descendants; *i.e.*, it is evolutionarily dead (Fisher 1930, p. 136). Therefore, the indirect cost of the modifier is characterized by a slight increase in the number of "dead" offspring generated by modifier-bearing individuals (Leigh 1970; Dawson 1998, 1999; Johnson 1999a). The indirect effect of beneficial mutations is different. When a new favorable mutation appears, it rises in frequency until complete fixation and, in the absence of recombination, yields the simultaneous fixation, by hitchhiking, of the genetic background in which it appeared (Maynard-Smith and Haigh 1974). In the following we call this phenomenon a *selective sweep*. This is important in the evolution of mutation rate, because a modifier increasing mutation rate is more likely than at random to generate beneficial mutations and reach fixation with them. Therefore, selective sweeps generate a very strong indirect benefit for the modifier, and this benefit is much stronger than the cost of deleterious mutations (see, for instance, Leigh 1970).

To describe the long-term fate of a modifier, Leigh (1970) and Johnson (1999a) consider a population for a large number of generations and assume that a selective sweep occurs with a constant probability K per generation (*e.g.*, after the environment has changed). The expected frequency of a modifier gene after T generations is then the product of selection due to deleterious mutations along the T generations times the selection owing to the KT selective sweeps that have occurred. From this analysis, Leigh (1970) and Johnson (1999a) find a resident's mutation rate in which no modifier's expected frequency can increase. They show that, in the absence of recombination, the evolutionarily stable strategy is to generate errors at the exact same rate that the environment is changing.

However, this approach involves several assumptions that should be relaxed for a more profound analysis. First, to be able to measure the selection upon the modifier in each generation, Leigh (1970) and Johnson (1999a) had to assume that the modifier stays rare in all the considered generations. This is reasonable for a weak-effect modifier in an infinite population (Leigh 1970) or in a finite sexual population because the strong recombination rate between modifier and advantageous mutations prevents important modifiers' increases during selective sweeps (Johnson 1999a). In a finite asexual population, however, each selective sweep is a bottleneck, reducing polymorphism everywhere in the genome, including at the modifier locus. Particularly, if the sweep is the fixation of a single advantageous mutation, then the final modifier's frequency is either one or zero, which represents a strong variation relative to an initial low frequency (see discussion on this point by Johnson 1999a). Therefore, in a finite asexual population, the modifier cannot be assumed rare along all the generations considered, which implies important modifications of the model.

Second, Leigh (1970) assumes that the rate of selective sweeps is controlled solely by the environment. However, in a finite population the generation of genetic polymorphism also affects the frequency of adaptation events. In other words, the frequency of selective sweeps relies both on external factors, *i.e.*, the pace of environmental changes, and on internal factors, *i.e.*, the population size and mutation rate. As a first consequence, the evolution of mutation rate might depend on population size. This has been observed in simulations of the dynamics of strong-effect modifiers (Taddei *et al.* 1997; Tenaillon *et al.* 1999); a convincing model of mutation rate evolution should therefore account for this effect. As a second consequence, the fate of modifiers may rely on the resident mutation rate itself, which should change importantly the long-term evolutionary trajectories of mutation rate.

In this article, we describe the evolutionary trajectory of mutation rate owing to the recurrent appearance and fixation of weak-effect modifiers. In this aim, we first develop analytical tools to measure the effect of each selection component on the modifier's frequency (cost of accuracy, deleterious mutations, and adaptive mutations). For clarity, the cost of accuracy is described only in appendix b. Second, we develop three complete models of mutation rate evolution corresponding to different ecological scenarios; each of these models is described in the main text of this article (models A, B, and C). All models are analyzed under two distinct hypotheses regarding the interference between adaptive and deleterious mutations (hypotheses 1 and 2). Hypothesis 1 is described in the main text, and hypothesis 2 is developed in appendix a.

MEASURES OF SELECTION COMPONENTS

Here the two indirect evolutionary forces acting on mutation rate are described separately. The direct effect of mutation rate, owing to the cost of replication accuracy, is described in appendix b.

Deleterious mutations: Let us first describe the indirect cost of a high mutation rate, owing to the generation of deleterious mutations. Modifiers are assumed to stay rare in all the generations where deleterious mutations affect their frequency. Note that this is not equivalent to assuming that they stay rare in all generations (Leigh 1970; Johnson 1999a), as is made clear later on.

An asexual and haploid population of constant size N and discrete generations is considered. The population is first fixed for wild-type individuals, generating errors in DNA replication at a rate μ per base pair. Mutations are deleterious to fitness when they affect one among L base pairs, hence $U = \mu L$ is the genomewide deleterious mutation rate. A rare modifier gene, appearing by random mutation from wild-type individuals, is in frequency $p(0) \ll 1$ at time $t = 0$ and yields a base pair mutation rate $\mu' = \mu + \delta$ and a deleterious mutation rate $U' = U + \delta L$.

Before the appearance of the modifier, the wild-type population is at a stationary distribution regarding the number of deleterious mutations per individual. Assuming that no deleterious mutation ever reaches fixation, the average relative fitness at this equilibrium is $\bar{w} = \exp(-U)$ (Kimura and Maruyama 1966). This equilibrium is not affected by the appearance of a rare modifier. Let us consider the modifier lineage. At mutation–selection balance, it will ultimately have an average fitness $\bar{w}' = \exp(-U')$. The modifier's frequency will hence be multiplied in expectation by $\bar{w}'/\bar{\bar{w}}$ in each generation (where $\bar{\bar{w}}$ is the average relative fitness in the population). If the modifier is rare and of relatively weak effect, then $\bar{\bar{w}}$ is controlled only by wild types and is given by $\bar{\bar{w}} = \bar{w} = \exp(-U)$; hence the modifier's frequency will follow

$$E[p(t+1)] = p(t) \cdot \exp(-\delta L), \tag{1}$$

where $E[X]$ stands for the expectation of the random variable X and $p(t)$ is the realized frequency of the modifier in generation t.

However, Equation 1 is valid only after the modifier has reached its own stationary distribution, which is not the case immediately after appearance (see Johnson 1999b). Indeed, the modifier initially appears within the wild-type background with an expected fitness $\bar{w} = \exp(-U)$. To circumvent this problem we adopt a slightly different approach.

Let us first follow the number of modifier individuals that carry none but the minimum number of deleterious mutations (called nondeleterious modifiers in the following). This number in generation t is written $n_0(t)$, while the number of modifiers carrying k deleterious mutations is $n_k(t)$, and the total number of modifiers is $n(t)$. At appearance, modifiers are drawn randomly from the resident population. Assuming that the resident population is at stationary distribution and that every deleterious mutation has the same multiplicative effect on fitness $(1 - s_d)$, the proportion of individuals from the resident population who carry none but the minimum number of deleterious mutations is $\exp(-U/s_d)$ (Haigh 1978). Therefore, at appearance, the number of nondeleterious modifiers has the expectation

$$E[n_0(0)] = \exp(-U/s_d) \cdot n(0). \tag{2}$$

Let us now derive the expectation of the number of nondeleterious modifiers in any generation $t + 1$, conditional on the realized number of nondeleterious modifiers being $n_0(t)$ in the previous generation. This gives $E[n_0(t+1)|n_0(t)] = n_0(t) \cdot \exp(-U')/\bar{\bar{w}}$. Assuming that modifiers stay rare in all generations, the average relative fitness in the population is determined solely by the resident and is a constant $\bar{\bar{w}} = \bar{w} = \exp(-U)$. In consequence, the effect of selection is linear, and the conditional expectation of $n_0(t+1)$ can be averaged over all realized values of $n_0(t)$, giving the unconditional expression $E[n_0(t+1)] = E[n_0(t)] \cdot \exp(-\delta L)$. Solving this recurrence equation, and using Equation 2 for $E[n_0(0)]$, we derive the expected number of nondeleterious modifiers as a function of time,

$$E[n_0(t)] = \exp(-U/s_d) \cdot \exp(-\delta L \cdot t) \cdot n(0). \tag{3}$$

Dividing by the constant total population size, N, this finally gives the expected frequency of nondeleterious modifiers,

$$E[p_0(t)] = \exp(-U/s_d) \cdot \exp(-\delta L \cdot t) \cdot p(0). \tag{4}$$

However, we might need also to follow the total frequency of modifier individuals ($p(t)$). From Equation 3, this quantity can be deduced when the modifier subpopulation reaches its own mutation–selection stationary distribution. By definition, at stationary distribution, the ratio of the expected number of modifiers of each deleterious class relative to the expected number of modifiers of the zero class is constant. This gives the condition

$$\forall k, \quad \frac{E[n_k(t+1)]}{E[n_0(t+1)]} = \frac{E[n_k(t)]}{E[n_0(t)]}, \tag{5}$$

where n_k is the number of modifiers carrying k deleterious mutations (modifiers of the k-class). From Equation 3, we have $E[n_0(t+1)] = E[n_0(t)] \cdot \exp(-\delta L)$, and Equation 5 then becomes

$$\forall k, \quad E[n_k(t+1)] = E[n_k(t)] \cdot \exp(-\delta L). \tag{6}$$

In other words, at stationary distribution, the number of modifier individuals of each deleterious class varies according to the same rate [*i.e.*, it is multiplied by $\exp(-\delta L)$ in each generation]. Following Haigh (1978), let us then assume that the number of new deleterious mutations per individual per generation

follows a Poisson distribution of expectation U' and express the expected number of modifiers of the k-class in generation $t+1$, conditionally on the realized number of modifiers of each class in the previous generation [given by the vector $\mathbf{n}(\mathbf{t})$]. This gives

$$E[n_k(t+1)|\mathbf{n}(\mathbf{t})] = \frac{1}{\bar{w}} \sum_{j=0}^{k} (1-s_d)^{k-j} \exp(-U') \frac{U'^j}{j!} n_{k-j}(t). \quad (7)$$

Assuming again that the modifier stays rare in all generations, the average fitness in the population is controlled solely by the resident and is the constant $\bar{w} = \exp(-U)$. Therefore, here again, the effect of selection is linear, and Equation 7 can be expressed unconditionally as

$$E[n_k(t+1)] = \exp(-\delta L) \cdot \sum_{j=0}^{k} (1-s_d)^{k-j} \frac{U'^j}{j!} E[n_{k-j}(t)]. \quad (8)$$

Introducing Equation 8 into condition (6) yields the following condition for the stationary distribution to be reached:

$$\forall k, \quad E[n_k] = E[n_0] \cdot \frac{(U'/s_d)^k}{k!}. \quad (9)$$

To obtain the expected total number of modifiers at stationary distribution, $E[n]$, Equation 9 is summed over all k, giving $E[n] = E[n_0] \cdot \sum_{k=0}^{+\infty} \left[(U'/s_d)^k / k! \right]$, which simplifies to

$$E[n] = E[n_0] \cdot \exp(U'/s). \quad (10)$$

Therefore, the expected total number of modifier individuals in any generation at stationary distribution can be found as a function of the expected number of nondeleterious modifiers at the same generation. Finally, from Equations 3 and 10 the expected total number of modifiers in the population can be written as a function of time,

$$E[n(t)] = \exp(-\delta L \cdot t) \cdot \exp(\delta L/s_d) \cdot n(0). \quad (11)$$

Dividing by the total population size, N, this finally gives the expected total frequency of modifiers as a function of time, once the modifier subpopulation has reached stationary distribution:

$$E[p(t)] = \exp(-\delta L \cdot t) \cdot \exp(\delta L/s_d) \cdot p(0). \quad (12)$$

Note that this derivation is valid even if the number of modifiers is very low at appearance (*e.g.*, even if a single modifier is initially present). Modifiers may be affected by drift and often be lost, but the expectation of their frequency is always given by Equation 12. The only assumption needed for this result to hold is that the average relative fitness in the population is the constant $\exp(-U)$, which implies (i) that the total population size is large and (ii) that the modifier stays rare in all generations.

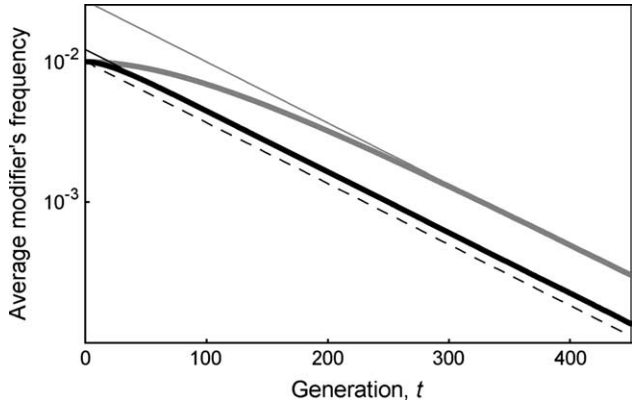

FIGURE 1.—The average modifier's frequency, plotted as a function of the number of generations after appearance, according to analytical models (thin lines) and to stochastic individual-based simulations (thick lines). The generation of deleterious mutations affects the modifier's frequency; the cost of accuracy and the existence of adaptive mutations are not considered. Simulations are performed with a population size $N = 10^6$ and are averaged over 10^4 runs. They are performed in two cases with different costs of deleterious mutations: $s_d = 0.05$ (thick solid line) and $s_d = 0.01$ (thick shaded line). The result of the analytical model neglecting the cost delay (Equation 14) is given by the dashed line. The results of the analytical model with delay (Equation 13) are given by the two thin lines, for each cost of deleterious mutation ($s_d = 0.05$ and 0.01, respectively, thin solid and thin shaded lines). Initial modifier's frequency is $p(0) = 10^{-2}$; wild-type mutation rate is $\mu = 10^{-6}$; modifier's effect is $\delta = 10^{-6}$; and the deleterious genome has size $L = 10^4$.

For comparison, let us now take the logarithm of Equation 12,

$$\ln E[p(t)] = \ln p(0) - \delta L(t - 1/s_d), \quad (13)$$

and contrast it with the logarithm of the modifier's frequency obtained from Equation 1 (*i.e.*, supposing that modifiers reach stationary distribution immediately after appearance):

$$\ln E[p(t)] = \ln p(0) - \delta L \cdot t. \quad (14)$$

The log-slope of the modifier's frequency with time is the same in both cases [(13) and (14)] except that Equation 13 is shifted $1/s_d$ generations back. Owing to the delay before reaching mutation–selection balance, it is merely as if the cost of deleterious mutations was paid only $1/s_d$ generations after appearance (see also JOHNSON 1999b). For instance, if deleterious mutations are lethal ($s_d = 1$), then the shift is only of one generation because the mutation–selection balance is attained in a single generation. Both expressions are compared with stochastic individual-based simulations (Figure 1). Equation 14 assumes that modifiers have an average fitness

$\bar{w}' = \exp(-U')$ immediately after introduction whereas they have the average fitness of wild types. As a consequence it yields an underestimation of the expected frequency of modifiers when they increase mutation rate ($\delta > 0$) and an overestimation when they reduce it ($\delta < 0$; not shown). Equation 13 provides a correct approximation, but only when the modifier has reached stationary distribution, which occurs a certain number of generations after introduction, this number being inversely proportional to the effect of deleterious mutations.

Adaptation: We then examine the effect of adaptation on the expected frequency of a modifier. Let us assume that a selective pressure is present in the population, requiring the fixation of one adaptive mutation arising at one among l base pairs ($u = \mu l$ is the advantageous mutation rate). In this article, a selective sweep is assumed to be the total fixation of a single mutant (see also Johnson 1999a); *i.e.*, the population size is small with regard to the average advantageous mutation rate ($\overline{u\pi}ND \ll 1$, where $\bar{\pi}$ is the average fixation probability of an advantageous mutant, $\bar{u}$ is the average advantageous mutation rate, and D is the number of generations needed for the fixation of the advantageous mutation to occur). Hence the simultaneous or successive generation of several advantageous mutants during one selective sweep is not considered.

At this point, two alternative hypotheses need to be envisaged. The first hypothesis (hyp. 1) assumes that the beneficial mutations are much stronger than the deleterious ones and hence that selective sweeps involve random individuals, irrespective of the number of deleterious mutations they carry. According to this hypothesis, the expected total frequency of modifier individuals $\{E[p(t)]\}$ needs to be considered as they may all participate in selective sweeps; this frequency is evaluated from Equation 12. The second hypothesis (hyp. 2), known as the "ruby in the rubbish" hypothesis (Peck 1994; Orr 2000; see also Bachtrog and Gordo 2004), assumes that beneficial mutations can fix only in nondeleterious backgrounds. This is true provided that deleterious mutations are stronger than advantageous ones. According to this hypothesis, the expected frequency of nondeleterious modifiers $\{E[p_0(t)]\}$ is the only relevant quantity; it is evaluated from Equation 4. These two hypotheses should be seen as two extremes of a continuum; in the general case indeed, the average fixation probability of an advantageous mutation is quantitatively reduced by the presence of deleterious mutation(s) in the same genome (Johnson and Barton 2002), which yields an interference between the background (modifier or not) and the probability to generate a selective sweep. However, this general case being extremely difficult to model, the two extremes are considered instead (hyps. 1 and 2). In the following the methods employed are detailed only for the first hypothesis; the analysis of the ruby in the rubbish case is detailed in appendix a.

Under hypothesis 1, conditional on the presence of a selective pressure, the expected probabilities that in generation t the modifier {in expected frequency $E[p(t)]$} and wild-type subpopulations generate an adaptive mutation destined to fix are, respectively,

$$M_t = N\pi \cdot u' \cdot E[p(t)] \tag{15}$$

and

$$R_t = N\pi \cdot u \cdot (1 - E[p(t)]), \tag{16}$$

where π is the average fixation probability of an advantageous mutation occurring in the modifier or wild-type background.

MODELS AND ANALYSES

Let us now describe the evolution of mutation rate under the three selective forces. For clarity, however, the models presented in the text do not include the cost of fidelity. They are "neutral" models of mutation rate evolution (Johnson 1999a), which provide the best comprehension of indirect selection. The complete models including the cost of fidelity are described in appendix b (but their principal results are presented in the text). We also recall that hypothesis 1 is considered only in the text, hypothesis 2 being considered in appendix a.

Here we present models valid for weak selection ($\delta \approx 0$). Recall that the effect of deleterious mutations on the frequency of modifiers (Equation 12) is valid only at mutation–selection balance. Selective sweeps must therefore not occur before this equilibrium is reached by the modifier subpopulation. Our model is then valid if selective sweeps are rare and if the cost of deleterious mutations is relatively high (rapid convergence to mutation–selection equilibrium). Remember finally that, in this article, a selective sweep is assumed to be the total fixation of a single mutant (see also Johnson 1999a), which is valid only if population size is small with regard to the average advantageous mutation rate ($\overline{u\pi}ND \ll 1$).

Leigh's model: Leigh (1970) assumes that, each generation, a selective sweep can occur with a fixed probability K. The overall probability that a selective sweep begins in generation t is $M_t + R_t$ (Equations 15 and 16). Let us take a modifier gene in total frequency p in any focal generation, and let us assume that a selective sweep begins in this focal generation; the expected frequency of the modifier at the end of the selective sweep (conditional on the occurrence of the sweep) is $M/(M + R)$. From Equations 15 and 16, this yields

$$\frac{u'}{\bar{u}} \cdot p = \frac{\mu'}{\bar{\mu}} \cdot p, \tag{17}$$

where $\overline{\mu} = \mu + \delta p$ is the average mutation rate per base pair in the population. This is the classic result of Leigh (1970, 1973), derived also in Johnson (1999a), giving the expected variation of the frequency of a modifier owing to one selective sweep. If the modifier is rare ($p \ll 1$), then the average mutation rate is controlled only by wild types ($\overline{\mu} \approx \mu$) and Equation 17 is simplified to $(\mu'/\mu) \cdot p$.

Leigh (1970) aims at predicting the expected variation in a modifier's frequency during a very large number of generations T, where exactly KT sweeps occur (see also Johnson 1999a). The expected frequency of the modifier should be given simply by the product of selection due to deleterious mutations along the T generations times the selection owing to the KT selective sweeps. The difficulty of this approach comes from the fact that selection on the modifier depends upon its own frequency, which varies in a stochastic manner along the T generations. To circumvent this problem, Leigh (1970) considers only infinite populations. Therefore, weak-effect modifiers can be assumed to stay rare in the entire period of study. Note that in Johnson (1999a), population size is finite, but recombination is assumed to be frequent between modifiers and beneficial mutations; therefore, the modifier remains rare during the T generations as well. In Leigh (1970), the expected frequency of the modifier in generation T is given by

$$E[p(T)] = p(0) \cdot \left(\frac{\mu + \delta}{\mu}\right)^{KT} \cdot e^{-\delta L \cdot T}. \qquad (18)$$

In this model, the delay in the cost of deleterious mutations does not need to be considered but only the long-term, per-generation, variation in the modifier's frequency owing to deleterious mutations does. Indeed, replacing the effect of deleterious mutations $e^{-\delta L \cdot T}$ (Equation 18) by $e^{-\delta L(t-1/s_d)}$ (from Equation 12) would be equivalent merely to a variation of the initial frequency of modifiers. As stated in the Introduction, from Equation 18, Leigh (1970) finds the evolutionarily stable mutation rate, as given by $L\mu_{ES} = K$ (see also Johnson 1999a).

However, in an asexual finite population, if each sweep is the fixation of a single advantageous mutation, then the modifier's frequency after each selective sweep is either one or zero. As a result, after the first selective sweep, mutation-rate polymorphism is lost and selection is absent. Therefore, the effect of indirect selection on the modifier's frequency cannot be measured as $\exp(-\delta L)$ and μ'/μ in all generations, even for a weak (or even neutral) modifier. In other words, selection must not be measured through its long-term effect on the modifier's frequency (Equation 18; Leigh 1970; Johnson 1999a) but through its effect on the probability that the modifier is fixed or lost during the first selective sweep. Our approach is therefore very different from that of Leigh (1970) and Johnson (1999a), as described in the following section.

Model A—constant rate of selective sweeps: In a first model, let us follow Leigh (1970) and Johnson (1999a) and assume that, each generation, a selective sweep can occur with a fixed probability K.

After its introduction in generation 0, the modifier is rare and its expected frequency varies according to Equation 12. After an infinite number of generations, a selective sweep has necessarily occurred; hence the modifier is either fixed or lost. The modifier's expected frequency, $E[p_\infty]$, is then given by the probability that it is fixed, F_∞. Let us first derive F_t (and G_t), the probability that the modifier is fixed (and lost), in generation t and then find F_∞ as $\lim_{t\to\infty} F_t$.

The modifier is assumed rare in generation 0 (and of relatively weak effect); therefore, at any generation t, preceding the first selective sweep, we have $p(t) \ll 1$ and $u'p(t) \ll u(1 - p(t))$. The average mutation rate in the population is controlled only by wild types, and the probability that the modifier fixes during the first selective sweep is μ'/μ, as described above (Equation 17). The probabilities of fixation (F_t) and loss (G_t) of the modifier are given by the following recurrence equations:

$$\begin{aligned} F_{t+1} &= F_t + (1 - F_t - G_t)K\frac{\mu'}{\mu}E[p(t)], \\ G_{t+1} &= G_t + (1 - F_t - G_t)K\left(1 - \frac{\mu'}{\mu}E[p(t)]\right). \end{aligned} \qquad (19)$$

Finally, from the hypothesis of the modifier's rarity and relatively weak effect, the probability that the modifier is fixed in any generation is negligible relative to the probability that it is lost ($F_t \ll G_t$). In other words, the model describes a situation where the modifier is lost most of the time but occasionally goes to fixation from its original low frequency. The recurrence equation for G_t therefore simplifies to $G_{t+1} = G_t + (1 - G_t)K$ and G_t is given by $G_t = 1 - (1 - K)^t$, the probability that at least one selective sweep has occurred in t generations. As a result, the recurrence equation for F_t becomes $F_{t+1} = F_t + (1 - K)^t K(\mu'/\mu)\exp(-\delta L \cdot t) \cdot \exp(\delta L/s_d) \cdot p(0)$. The limit F_∞ can therefore be expressed as a sum from 0 to ∞. If the modifier is of weak effect, then $(1 - K) \cdot e^{-\delta L} < 1$, and this sum converges, giving

$$\begin{aligned} F_\infty &= \frac{K}{1 - (1 - K) \cdot e^{-\delta L}} \cdot \frac{\mu + \delta}{\mu} \cdot \exp(\delta L/s_d)p(0) \\ &= w_\infty(\mu, \delta) \cdot p(0), \end{aligned} \qquad (20)$$

where $w_\infty(\mu, \delta)$ is the expected number of descendants, after an infinite number of generations, of an individual modifier with per base pair mutation rate $\mu + \delta$ in a resident population with per base pair mutation rate μ. One can verify that $w_\infty(\mu, 0) = 1$; *e.g.*, the expected number of descendants of a neutral variant is one. A modifier of mutation rate is considered favored by natural

selection if its ultimate fixation probability is higher than the fixation probability of a neutral allele, *e.g.*, $F_\infty > p(0) \Leftrightarrow w_\infty(\mu, \delta) > 1$, and disfavored if $w_\infty(\mu, \delta) < 1$.

Developing $w_\infty(\mu, \delta)$ into a Taylor series around $\delta = 0$ gives

$$w_\infty(\mu, \delta) = 1 + \delta \cdot \frac{\partial w_\infty(\mu, \delta)}{\partial \delta}\Big|_{\delta=0} + o(\delta).$$

Therefore the direction of selection on weak modifiers is given by the sign of

$$\mathrm{Sel}(\mu) = \frac{\partial w_\infty(\mu, \delta)}{\partial \delta}\Big|_{\delta=0},$$

giving after simplifications

$$\mathrm{Sel}(\mu) = \frac{1}{\mu} - L\left(\frac{1-K}{K} - \frac{1}{s_\mathrm{d}}\right). \qquad (21)$$

If $\mathrm{Sel}(\mu) > 0$ any rare mutant with small $\delta > 0$ increases in frequency in expectation (*e.g.*, selection favors a higher mutation rate), while if $\mathrm{Sel}(\mu) < 0$ mutants increase in frequency if $\delta < 0$ (*e.g.*, selection favors a lower mutation rate).

If $\mathrm{Sel}(\mu) = 0$ then the resident mutation rate μ is a singular strategy (Geritz *et al.* 1998); the second-order derivative of $w_\infty(\mu, \delta)$ must be taken into account in the Taylor development, giving

$$w_\infty(\mu, \delta) = 1 + \delta^2 \cdot \frac{\partial^2 w_\infty(\mu, \delta)}{\partial \delta^2}\Big|_{\delta=0} + o(\delta^2).$$

If

$$\frac{\partial^2 w_\infty(\mu, \delta)}{\partial \delta^2}\Big|_{\delta=0} > 0,$$

then any weak modifier ($\delta \neq 0$) is favored by natural selection; *i.e.*, the singular strategy is not evolutionarily stable. In contrast, if $\partial^2 w_\infty(\mu, \delta)/\partial \delta^2|_{\delta=0} < 0$, then any nonneutral modifier is counterselected; *e.g.*, the singular strategy is an evolutionarily stable strategy (ESS) (Maynard-Smith 1982).

From Equation 21, $\mathrm{Sel}(\mu) > 0 \Leftrightarrow \mu < \mu_\mathrm{conv}$; if the resident's mutation rate is lower than a threshold, then the direction of selection on mutation rate is positive. In contrast, $\mathrm{Sel}(\mu) \leq 0 \Leftrightarrow \mu \geq \mu_\mathrm{conv}$; when the resident's mutation rate is higher than the threshold, selection favors a reduction of mutation rate. Evolution will therefore tend to bring the resident's mutation rate toward a convergence stable strategy (Geritz *et al.* 1998) μ_conv, which is found as the unique solution of $\mathrm{Sel}(\mu) = 0$ from (21), giving

$$L\mu_\mathrm{conv} = \frac{K}{1 - K(1 + 1/s_\mathrm{d})}. \qquad (22)$$

First, note that, owing to the delay, the convergence stable mutation rate decreases with the cost of deleterious mutations, s_d (Figure 2). Second, let us consider the effect of K, the rate of selective sweeps. For low K relative to the cost of deleterious mutations ($K(1 + 1/s_\mathrm{d}) \ll 1$), the genomic mutation rate toward which evolution is converging is approximately equal to the rate of sweep ($L\mu_\mathrm{conv} \approx K$), which resembles the classic result of Leigh (1970). However, if selective sweeps are not extremely rare relative to the effect of deleterious mutations, then (i) the expected amount of time open for selection in favor of the reduction of the mutation rate is short, and (ii) a newly introduced modifier with large mutation rate is likely to experience a sweep before having paid entirely the cost of generating deleterious mutations. For these two reasons, as selective sweeps become more and more frequent, the weight of deleterious mutations in the fate of modifiers becomes increasingly negligible, especially if deleterious mutations are of weak effect. As a consequence, for relatively large K, the mutation rate toward which evolution is converging is higher than that predicted by Leigh (1970).

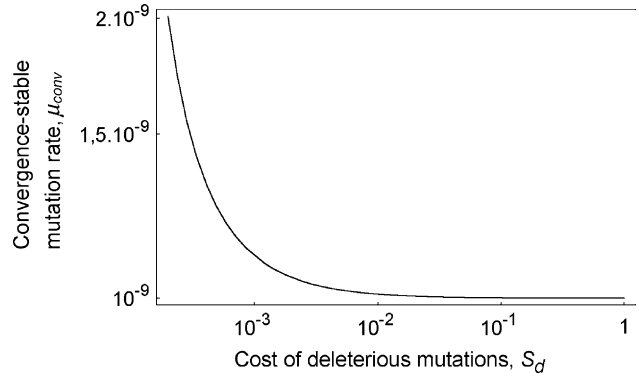

Figure 2.—Convergence stable mutation rate as a function of the fitness cost of each deleterious mutation in model A, under hypothesis 1 (advantageous mutations stronger than deleterious mutations, Equation 22). The size of the deleterious genome is $L = 10^5$, the frequency of selective sweeps is $K = 10^{-4}$, and the cost of replication accuracy is absent ($f = 0$).

The results are illustrated in Figure 3 by plotting the convergence stable mutation rate as a function of the rate of selective sweeps. Qualitatively, the results are equivalent when the cost of replication accuracy is taken into account. This cost is quantified through a parameter f representing the mutation rate where half of the maximum fecundity is attained. Quantitatively, the more important is the cost of accuracy (*i.e.*, the larger is f), the larger is the convergence stable mutation rate and the less influential is adaptation in the evolution of mutation rate (see Figure 3).

Interestingly, and this also contrasts with Johnson (1999a) and Leigh (1970), μ_conv is not an evolutionarily stable mutation rate (Maynard-Smith 1982; Dieckmann 1997; Geritz *et al.* 1998). The second-order derivative of $w_\infty(\mu, \delta)$ in μ_conv is

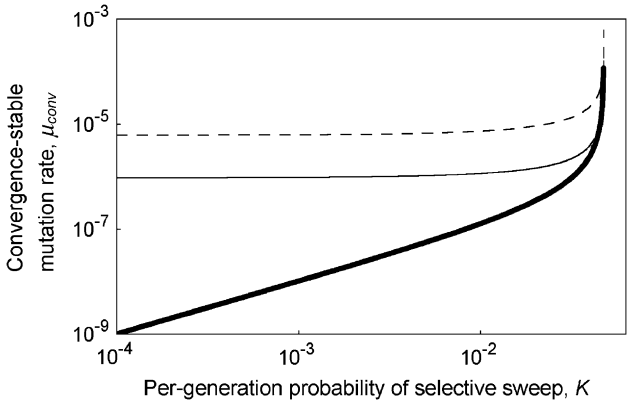

FIGURE 3.—Convergence stable mutation rate as a function of the rate of selective sweep in model A, under hypothesis 1 (advantageous mutations stronger than deleterious mutations, Equation 22). The size of the deleterious genome is $L = 10^5$; the cost of deleterious mutations is $s_d = 0.05$. The cost of replication accuracy is characterized by $f = 0$ (no cost of accuracy, thick line), $f = 10^{-7}$ (thin line), or $f = 10^{-5}$ (dashed line).

$$\frac{\partial^2 w_\infty(\mu_{conv}, \delta)}{\partial \delta^2}\Big|_{\delta=0} = \frac{L^2}{K}\left[\frac{1+2}{s_d - K(1+1/s_d)^2}\right],$$

which is indeed strictly positive provided that K is small. Therefore, when $\mu = \mu_{conv}$, selection favors any nonneutral modifier. Hence evolution converges to the singular strategy $\mu = \mu_{conv}$, but then any modifier can invade. We will discuss more generally the instable nature of mutation rate in a subsequent part of this analysis.

Under hypothesis 2 (ruby in the rubbish) we obtain very similar results (see APPENDIX A): the singular strategy is given by $L\mu_{conv} = K/(1-K)$ and the second-order derivative of $w_\infty(\mu, \delta)$ in μ_{conv} is positive (not shown). The singular strategy is convergence stable but not ESS stable. Surprisingly, here the cost of deleterious mutations has no effect on the fate of modifiers. This is because (i) the first cost of deleterious mutations—a reduction of the efficient initial frequency of modifiers by a factor e^{-U/s_d}—is the same as that paid by wild types, and (ii) the second cost of deleterious mutations—a factor $e^{-\delta L}$ each generation—is then paid by the modifier immediately after introduction, whatever is the effect of deleterious mutations.

Models B and C—internal control of the rate of selective sweeps: The preceding model assumes, as in LEIGH (1970), that the average probability of selective sweep per generation is a constant, which is valid if the rate of environmental changes is the only limiting factor. However, in a finite population, the frequency of selective sweeps should also be limited by the generation of adaptive mutations. Therefore, the rate of selective sweep K should depend itself on the mutation rate established in the population.

To take this mechanism into account, a new model is built. A population is fixed for a resident mutation rate μ and a modifier with mutation rate $\mu + \delta$ is introduced. Let us assume that the population is undergoing a selective pressure (*i.e.*, some mutations are adaptive) with a probability S in each generation (the value of S will be calculated later on, in two submodels). Conditional on the existence of this pressure, and making the same assumptions as in model A (modifier initially rare and of relatively weak effect), the population has a probability $R = N\pi l \cdot \mu$ to generate a selective sweep in each generation, where we recall that N is the population size, π is the fixation probability of favorable mutations, and l is the number of base pairs where mutations are favorable. Therefore, the overall per generation probability of occurrence of a selective sweep is the product $S \cdot R$.

Following the approach of model A, we then derive the probability that the modifier is ultimately fixed in the population, F_∞, by writing recurrence equations. These equations are shown to be identical to Equation 19 with the constant rate of selective sweep, K, replaced simply by the product $S \cdot R$ (not shown). Therefore, if only weak-effect modifiers are present, the direction of selection on mutation rate is given by

$$\mathrm{Sel}(\mu) = \frac{1}{\mu} - L\left(\frac{1 - S \cdot R}{S \cdot R} - \frac{1}{s_d}\right), \qquad (23)$$

where we recall that the product $S \cdot R$ is not a constant but actually depends on the mutation rate itself.

Model B—ecological scenario: This model describes a population undergoing occasional environmental changes, with a probability ε per generation ($\varepsilon \ll 1$). The population may then adapt by the fixation of one adaptive mutation. Successive environmental changes do not add up: if adaptation to a first change has not occurred before the next change takes place, the second change effaces the first and only one selective sweep is required for adaptation. Before the modifier is introduced in the population, the adaptive mutation rate is $u = \mu l$, and the probability that the population adapts in any generation is $R(\mu) = N\pi l \cdot \mu$ (conditional on the presence of a maladaptation). At balance between environmental changes and adaptation, the probability per generation that the population is maladapted is found as

$$S(\mu) = \frac{\varepsilon}{R(\mu) + \varepsilon(1 - R(\mu))}. \qquad (24)$$

Equation 24 remains true if a rare modifier of relatively weak effect is present in the population; it can therefore be introduced as an expression for S in Equation 23, and the direction of selection on mutation rate can be derived after simplification as

$$\mathrm{Sel}(\mu) = \frac{1}{\mu}\left(1 - \frac{L}{N\pi l}\right) - L\left(\frac{1}{\varepsilon} - \frac{1}{s_d} - 2\right). \qquad (25)$$

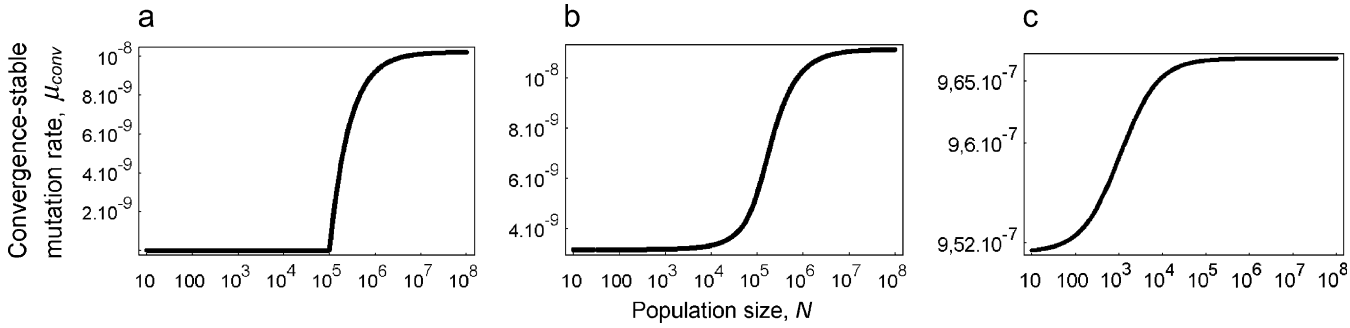

FIGURE 4.—Convergence stable mutation rate as a function of population size, in model B (Equation 26). The size of the deleterious genome is $L = 10^5$; the size of the adaptive genome is $l = 10$; the probability of fixation of adaptive mutations is $\pi = 0.1$; the rate of environmental changes is $\epsilon = 10^{-3}$; and the cost of deleterious mutations is $s_d = 0.05$. (a) The cost of accuracy is neglected ($f = 0$); the population size has a threshold effect on convergence stable (CS) mutation rate. (b and c) The cost of accuracy is taken into account with $f = 10^{-12}$ and 10^{-7}, respectively; the population size has a continuous and weak relative effect on CS mutation rate. Note that a, b, and c have different scales.

Slow environmental changes: First, we consider the case where the environment is changing rarely ($(1/\epsilon) - (1/s_d) > 2$):

1. If population size is large in relation to the size of the deleterious genome (precisely if $N\pi l > L$), then $\mathrm{Sel}(\mu) > 0$ for $\mu < \mu_{conv}$ and $\mathrm{Sel}(\mu) < 0$ for $\mu > \mu_{conv}$, μ_{conv} being the only solution of $\mathrm{Sel}(\mu) = 0$, giving

$$\mu_{conv} = \frac{1}{(1/\epsilon) - (1/s_d) - 2}\left(\frac{1}{L} - \frac{1}{N\pi l}\right). \qquad (26)$$

   The second-order derivative of $w_\infty(\mu, \delta)$ in μ_{conv}, $\partial^2 w_\infty(\mu_{ES}, \delta)/\partial\delta^2|_{\delta=0}$, is strictly positive as long as $(1/\epsilon) - (1/s_d) > 2$ (not shown); hence μ_{conv} is convergence stable but not ESS stable. The model is valid only when each sweep is the fixation of one advantageous mutant and never more; this should be true around μ_{conv} also for the model to be correct, This implies that $N\pi l \cdot \mu_{conv} \ll 1$, which gives $1 + N\pi l/L \ll 1/\epsilon - 1/s_d$. This condition will be fulfilled, even for large populations, provided that the rate of environmental changes is low and the effect of deleterious mutations is not too weak. The results here are qualitatively similar to the results found with a constant rate of selective sweeps (model A). Evolution converges to a mutation rate μ_{conv}, but then any weak modifier is favored.
2. If population size is small in relation to the size of the deleterious genome ($N\pi l \le L$), then $\mathrm{Sel}(\mu) < 0$ for all $\mu \ge 0$; selection always favors weak-effect modifiers with lower mutation rate. Small-step evolution converges to $\mu = 0$, which is a locally stable strategy as shown by the analysis of $w_\infty(0, \delta)$ (not shown).

In conclusion, let us sum up the effect of population size in the case of slow environmental changes. Supposing that only weak-effect modifiers are present, evolution should tend to move the mutation rate close to a value μ_{conv}, which is nil if $N\pi l \le L$ and strictly positive if $N\pi l > L$. The threshold effect of population size is illustrated in Figure 4a. As population size increases, the convergence stable mutation rate fits more and more the rate of environmental changes (if $\epsilon \ll 1$, then $\lim_{N\to+\infty}\mu_{conv} \approx \epsilon/L$, as in LEIGH 1970).

When the cost of replication accuracy is taken into account, the mutation rate cannot reach zero because this implies an infinite cost (see APPENDIX B). Therefore, when population size is small, instead of blocking at a nil mutation rate, the population reaches the minimal error rate attainable without impairing too much the replication process. Further, the more important is the accuracy cost (*i.e.*, the larger is the parameter f), the less influential are adaptive events and hence population size in the evolution of the mutation rate. This is illustrated in Figure 4. When the cost of accuracy is present (Figure 4, b and c), the effect of population size on μ_{conv} becomes continuous and moderate.

Rapid environmental changes: Second, we consider the case where the environment is changing frequently $[(1/\epsilon) - (1/s_d) < 2]$.

1. If population size is large in relation to the deleterious genome ($N\pi l \ge L$) then $\mathrm{Sel}(\mu) > 0$ for all $\mu \ge 0$; in this case selection always favors a higher mutation rate, until infinity. This result is obtained also when the cost of accuracy is taken into account. The reason is that the higher is the resident mutation rate, the higher is the probability of selective sweep, and thus the lower is the importance of selection against deleterious mutations. This positive feedback yields the infinite escalation of mutation rate. However, the model will then depart from its own limits of validity, as the number of mutants implied in a selective sweep will become higher than one. In other words, the generation of polymorphism will become less limiting in the rate of selective sweeps. For that reason, the frequency of sweeps will stop increasing linearly with mutation rate and will begin to saturate. This

effect has been called "clonal interference" in asexuals by Gerrish and Lenski (1998), even though it is strictly equivalent to what was previously known as the Hill–Robertson effect (Hill and Robertson 1966). Such saturation should reduce the positive feedback of the rate of sweeps on the evolution of mutation rate and probably yield a stabilization of mutation rate. The evolutionary outcome of the system in this case is impossible to predict from our model. Note that the attained mutation rate should not maximize any global parameter of the population such as the rate of adaptation or the average relative fitness.

2. In contrast, if population size is small in relation to deleterious genome ($N\pi l < L$), then

$$\mathrm{Sel}(\mu) < 0 \quad \text{for all } \mu < \mu_{\lim} = \frac{1}{2 + (1/s_d) - (1/\epsilon)}\left(\frac{1}{N\pi l} - \frac{1}{L}\right)$$

(including $\mu = 0$), while $\mathrm{Sel}(\mu) > 0$ for all $\mu > \mu_{\lim}$. Furthermore we have $\mathrm{Sel}(\mu_{\lim}) = 0$ and also

$$\frac{\partial^2 w_\infty(\mu_{\lim}, \delta)}{\partial \delta^2}\Big|_{\delta=0} > 0$$

(not shown); $\mu_{\lim}$ is an unstable singular strategy (neither convergence stable nor ESS stable). If the initial mutation rate is lower than $\mu_{\lim}$, then small-step evolution converges to $\mu = 0$, which is the local evolutionary equilibrium of the system. In contrast, if the initial mutation rate is higher than $\mu_{\lim}$, then selection favors an ever-higher mutation rate, because the rate of sweep is accelerating. Here also, the same results are obtained when the cost of accuracy is taken into account. The mere difference, again, is that the mutation rate never goes down to zero but reaches instead the lowest attainable mutation rate (such as in Figure 4, b and c). All results are qualitatively equivalent under hypothesis 2 as well (see appendix a for more details).

Model C—permanent selective pressure: This last model describes a population that is never adapted to its environment, because environmental changes are very frequent and/or imply too many selective sweeps. The probability that a selective pressure is present in any generation is therefore $S = 1$, and the direction of selection on mutation rate can be derived from Equation 23 (not shown).

The outcome of this model is the same as that of Model B in the case of rapid environmental changes [$(1/\epsilon) - (1/s_d) < 2$]. If $N\pi l \geq L$, then selection favors an ever-higher mutation rate. Such as in model B, the model will then depart from its own limit of validity as several independent mutants will sweep together. If $N\pi l < L$, then the system is bistable with a threshold resident mutation rate $\mu_{\lim}$ (not shown). Here also, the results are qualitatively identical when the cost of accuracy is taken into account, except that, again, the mutation rate never reaches zero but only the lowest attainable value. All results are qualitatively equivalent under hypothesis 2 as well (see appendix a)

Cost of accuracy and stability: We introduced the cost of DNA replication, as a function of mutation rate, in all the above models (models A, B, and C, each with hypotheses 1 and 2). Apart from the results already mentioned, the cost of accuracy has another important effect. When the cost of accurate replication is taken into account and is large enough (large f), we showed numerically that the second-order derivative of the fitness function is then always negative around μ_{conv}. In other words, the cost of accuracy stabilizes the evolutionary trajectory of mutation rate at an ESS. The antagonistic interplay of adaptation *vs.* deleterious mutations cannot lead to a stabilization of mutation rate, while the interplay of deleterious mutations *vs.* accuracy costs can. However, the significance of this stability must be tempered, as we see in the following section.

The instability of mutation rate and the emergence of mutators: Our model applies primarily for weak-effect modifiers, but interestingly it can also apply under certain conditions to the case of strong-effect modifiers. Indeed, the basic assumption required for the model to work is that the average mutation rate in a population is controlled merely by resident individuals and is not influenced by modifiers. This hypothesis is always valid for weak-effect modifiers. Further, it may remain valid also in the case of strong-effect modifiers under two conditions. First, the modifiers must be rare when they first appear. Second, they must increase mutation rate, so that they always diminish in frequency after appearance, until the next selective sweep.

Let us then consider a modifier increasing the mutation rate by δ. In model A, under hypothesis 1, the expected number of descendants of such a modifier is given by

$$w_\infty(\mu, \delta) = \frac{K}{1 - (1 - K)\cdot e^{-\delta L}} \cdot \frac{\mu + \delta}{\mu} \cdot \exp(\delta L / s_d)$$

(from Equation 20), and an equivalent expression can be found in all cases, even when the cost of accuracy is considered. Recall that the model is highly stochastic and that the modifiers' fitness is triggered by the probability of fixation of modifier individuals [$F_\infty = w_\infty(\mu, \delta) \cdot p(0)$, where $p(0)$ is the initial frequency of modifiers].

Interestingly, when the modifier has a strong effect (large δ), then its fitness can be approximated by $w_\infty(\mu, \delta) = K \cdot (\mu + \delta)/\mu \cdot \exp(\delta L / s_d)$, which increases monotonously with δ. This result also holds in all models (A, B, and C, with both hypotheses, whatever may be the cost of accuracy). Therefore, in all cases with no exception, as modifiers become stronger and stronger, their probability of fixation increases monotonously. In consequence, a sufficiently strong modifier always exists

whose probability of fixation is significant. More precisely, in evolutionary terms, modifiers whose fitness is greater than one exist. In consequence, even if a locally stable singular strategy exists, there never is a globally stable mutation rate.

Strong-effect modifiers increasing mutation rate are called mutators (Miller 1996). In model A, we can show that the minimal relative strength $[(\mu + \delta)/\mu]$ required for a mutator to be favored is of the order of magnitude of $1/K$, the number of generations needed for a sweep to arise. Therefore, in practice, mutators may arise only when the rate of selective sweeps is large enough. More interestingly, in model B, when population size is very small, mutators may theoretically emerge but they must have an unreasonably strong effect to do so. Therefore, in practice, they may emerge only in large populations. In other words, assuming that the effects of modifiers have any given maximum, then the larger the populations are, the more likely they are to be invaded by mutators, while a small population will remain stabilized at μ_{conv}.

DISCUSSION

In this article, we built an analytical model of mutation rate evolution in an asexual population of finite size. We undertook a game-theoretic approach. A resident mutation rate is considered and a rare variant called a modifier is introduced, with a slightly different mutation rate. Our model predicts the expected frequency of the modifier after a large number of generations. If this frequency is larger than the initial frequency the modifier is considered favored by selection and disfavored in the opposite case. Our model is then used to predict the evolutionary trajectory of mutation rate owing to the recurrent appearance and fixation of variants.

The evolution of mutation rate is affected by the combination of three factors: the cost of exact replication, the cost of deleterious mutations, and the advantage of beneficial mutations. Since beneficial mutations ultimately reach fixation, they cause in the same time the fixation of all other polymorphisms (Maynard-Smith and Haigh 1974); this is a *selective sweep*. In particular, selective sweeps can cause the fixation of the modifier gene itself. This is especially likely if the modifier increases mutation rate and modifier individuals thus generate beneficial mutations at a larger rate than wild types. In this article, we analyzed the outcome of each of these forces (cost of accuracy, deleterious mutations, and adaptive mutations) on the fate of modifiers and on the long-term evolution of mutation rate.

Instability: A previous classical analytic study of mutation rate evolution in asexuals (Leigh 1970) showed that evolution leads to an intermediate evolutionarily stable mutation rate (ESS), such that the overall genomic mutation rate ($U = \mu L$) is exactly equal to the rate of adaptation events (*i.e.*, selective sweeps). In other words, selection leads to a mutation rate perfectly fitting the pace of environmental changes. The results we obtained in this article share similarity with those of Leigh (1970). We showed that the effect of selection on mutation rate leads to a convergence stable mutation rate. In other words, when the resident mutation rate is below (above) a certain level, any modifier with a larger (smaller) mutation rate is favored. However, this convergence stable mutation rate differs from the ESS found by Leigh (1970) in two respects.

First, the overall genomic mutation rate at convergence stability indeed increases with the rate of selective sweep but, in contrast to that in Leigh (1970), it is not equal to but always larger than this rate. In other words, selection does not lead to a perfect fit between genomic mutation rate and the pace of environmental changes. Second, and more importantly, the convergence stable mutation rate is not globally stable. When it is fixed in a population, modifiers with a larger-than-resident mutation rate that are able to invade the population always exist. Further, in the case where the cost of replication accuracy is low, the convergence stable mutation rate is not even locally stable. When it is fixed in a population, any modifier of mutation rate is favored by selection.

How can these two discrepancies between the present model and Leigh's (1970) model be explained? An assumption, differing between both models, is actually the key to these differences: the hypotheses on population size. In Leigh (1970), population size is infinite. In consequence, each selective sweep corresponds to the fixation of an infinite number of independent mutations. At the end of the sweep, the modifier is neither fixed nor lost and its frequency is not even strongly affected by the sweep. In contrast, we consider populations of finite and "reasonable" sizes: each selective sweep is the fixation of a single independent mutation (see also Johnson 1999a). In this case, at the end of a sweep, the modifier and the resident are not segregating anymore: one of them is fixed. This dramatic event constitutes a novel mechanism acting on mutation rate evolution. Consider, for instance, a modifier with a lower-than-resident mutation rate. This modifier benefits from replication accuracy only during the period preceding the selective sweep. Afterward, it is either fixed or lost and thus not affected anymore by selection. In other words, the occurrence of selective sweeps, and hence of strong population bottlenecks, not only favors a larger mutation rate, but also cancels out the advantage of replication accuracy. This relaxation of selection, due to bottlenecks, explains the finding of a larger convergence stable mutation rate than that in Leigh (1970). In addition, modifiers with a larger-than-resident mutation rate pay only the cost of deleterious mutations in the phase preceding the next selective sweep. In consequence, modifiers with

a very strong mutation rate have an opportunity to arise and play a destabilizing role, which is not the case in Leigh (1970) as they are selected against in all generations.

The instability of mutation rate has actually an important consequence. If potential modifiers all have weak effects, then the evolutionary trajectory of mutation rate should not be very different from what is expected in the case of evolutionary stability. Mutation rate should converge toward the convergence-stable value and stay in this region with only minor nondetectable variations. However, if strong-effect modifiers can also be generated, they may strongly affect the evolutionary trajectory of mutation rate, as they can be favored at any time, even if the population reaches local stability. In consequence, the evolutionary trajectory of the mutation rate is strongly dependent on its genetic control. In fact, this is perfectly concordant with empirical data on mutation rate evolution in bacteria. During phases of adaptation, bacterial populations are invaded by strong-effect modifiers called mutators, with a mutation rate 10–10,000 times larger than that of wild types, owing to a deficiency in a DNA reparation enzyme (Miller 1996). Such mutators have been observed repetitively both *in vitro* and *in vivo* (LeClerc *et al.* 1996; Sniegowski *et al.* 1997, 2000; Mansky and Cunningham 2000; Oliver *et al.* 2000; Denamur *et al.* 2002; Richardson *et al.* 2002; Shaver *et al.* 2002). Our theoretical results now suggest that the emergence of these mutators is not an anecdotic phenomenon, but is instead an inevitable and universal outcome of adaptation in asexuals (see also Sniegowski *et al.* 1997; Taddei *et al.* 1997; Kessler and Levine 1998; Tenaillon *et al.* 1999; Travis and Travis 2002; Tanaka *et al.* 2003; Tannenbaum *et al.* 2003).

Further, from results such as Leigh's (1970) it has often been believed that, in asexuals, the conjunction of the need for adaptation and the necessity to preserve the genome could lead to an intermediate "optimal" mutation rate, perfectly fit to the rate of environmental changes. This idea was even sometimes used to explain the finding of a constant genomic mutation rate among DNA microbes (Drake 1991; see also Orr 2000). Our model shows that this is probably not an accurate explanation. In asexuals, the need for both adaptation and genome preservation is not an evolutionary force that can stabilize mutation rate at an intermediate optimum. The cost of accurate DNA replication is a more likely force yielding a stabilization of mutation rate. Further, in the situations where this stabilizing cost is important, then the actual influence of adaptation on mutation rate evolution becomes negligible (see Figures 3 and 4). Therefore, when adaptation has a significant role, it primarily destabilizes mutation rate and yields the emergence of mutators during adaptation phases. In addition, in sexual species, Johnson (1999a) and Sniegowski *et al.* (2000) suggested that the effect of adaptation on mutation rate evolution was unlikely to be important because of recombination. Therefore, it seems that, in both sexuals and asexuals, intermediate stable mutation rates cannot be explained by the effect of adaptation but more probably by the joint effects of replication cost and the need for genome preservation (see, for instance, Dawson 1998, 1999).

Leigh (1970) considers populations of infinite sizes. We consider instead populations with finite and "reasonable" sizes such that each selective sweep is the fixation of a single mutation. What might happen in intermediate cases where a finite number of independent adaptive mutations generate selective sweeps? Note, first, that adaptive mutation rates are usually relatively small. For instance, measuring the rate of evolution in *Escherichia coli* populations, Rozen *et al.* (2002) and Gerrish and Lenski (1998) estimated that the numbers of advantageous mutations per genome per replication were, respectively, $\sim 5.9 \times 10^{-8}$ and 2×10^{-9} (see also Wilke 2004). Therefore, the independent generation of several adaptive mutations occurs only in very large populations. However, this may occur for sure in certain cases and is indeed very difficult to model analytically. After each selective sweep, the modifier reaches an intermediate frequency, very different from the initial one, and highly stochastic. Subsequently, the effect of selection depends on this frequency, until the next sweep, and so on. We cannot make a general prediction on the evolution of mutation rate in this case, apart from the obvious statement that the larger population size gets, the closer to Leigh (1970) the outcome will be. Taddei *et al.* (1997), Tenaillon *et al.* (1999), and Tanaka *et al.* (2003) actually performed simulations in this general case. But simulations allow considering only the dynamics of a given modifier in a given resident population and not the long-term evolution of mutation rate.

Delayed cost: In classical views (*e.g.*, Leigh 1970; Johnson 1999a), the quantitative cost of deleterious mutations does not affect the evolution of mutation rate. Let us briefly explain why. Consider a lineage with a given mutation rate, and thus a given mutational load, and calculate the average fitness of individuals in that lineage. Deleterious mutations with strong cost remain in small frequency in the lineage, while those with moderate cost become frequent. Owing to this compensation, the mutational load in a lineage depends only on mutation rate and is not affected by the quantitative cost of each deleterious mutation (Kimura and Maruyama 1966). However, this simple result holds only if the considered lineage has reached mutation–selection balance. In this article, we are interested in a situation where a lineage changes suddenly its mutation rate by acquiring a modifier allele. In such a case, the modifier lineage is not initially at mutation–selection balance (see Johnson 1999b). We therefore analyzed analytically the consequences of such initial disequilibrium.

Just after the appearance of a mutation rate modifier, its genetic background is that of the resident. For instance, a modifier with a larger-than-resident mutation rate does not initially pay any cost from carrying deleterious mutations, as it carries in expectation the same mutations as the resident. Afterward, it will reach its own mutation–selection balance and end up with its own, larger, mutational load. The quantitative cost of each deleterious mutation does not affect the ultimate load at mutation–selection balance; however, it strongly affects the time required to reach this balance (see also Johnson 1999b). If deleterious mutations are, say, lethal, then the modifier reaches its own mutation–selection balance in a single generation, as it generates right away fewer living offspring than the resident. In contrast, if deleterious mutations have a very weak cost, then it can take a very large number of generations for the modifier to reach its own balance. In this last case, a modifier with a large mutation rate benefits from a delay before having to actually pay the cost of its mutation rate. Interestingly, during this time it can nonetheless generate an adaptive mutation and thus benefit from its large mutation rate. Our model does not allow us to examine the case where deleterious mutations have an extremely weak effect, but it provides us with a good insight into it (see Figure 2). In all cases, one can state that the less costly are the deleterious mutations, the stronger is selection in favor of modifiers with a larger-than-resident mutation rate, because they may generate a selective sweep before having paid the cost of deleterious mutations. This confirms a somehow intuitive idea that no previous model could comprehend (see discussion by Johnson 1999b).

Critical mass: Finally, we pointed out a third important effect. As discussed above, the frequency of selective sweeps in a population is a key determinant of the evolution of mutation rate. Interestingly, in a population of finite size, this frequency does rely not only on the rate of environmental changes, but also on the capacity of the population to generate genetic diversity and henceforth on the average mutation rate in the population. The resident mutation rate itself thus partly determines the selective pressure acting on modifiers of mutation rate. Our theoretical model shows that, owing to this feedback, population size controls the outcome of evolution.

In small populations, selective sweeps stay rare even for fairly high resident mutation rates. As a result, selection favors modifiers with a lower-than-resident mutation rate, and the mutation rate thus decreases through evolution. In turn, this reduction of mutation rate lessens the frequency of selective sweeps, which favors modifiers with even lower mutation rates. Ultimately, this positive feedback yields a blockade of the population at the lowest mutation rate attainable with reasonable accuracy costs. In other words, small populations follow a reduction principle (Liberman and Feldman 1986) and evolve toward a strategy of genomic preservation. Everything happens as if the only two forces acting on mutation rate were the cost of accuracy and the cost of deleterious mutations.

In large populations, selective sweeps are relatively frequent, even for fairly low resident mutation rates. Therefore, individuals cannot afford to preserve their genome, because the risk to be eliminated at the next selective sweep is too important. Individuals thus evolve toward a nonminimal mutation rate, a strategy of adaptation. In other words, in large populations, a critical mass is attained above which adaptation becomes a selective force *per se*, affecting mutation rate and promoting in turn an even larger adaptive potential. In certain cases, if environmental variations are very rapid, this can even lead to an evolutionary runaway in the population. The large mutation rate allows the generation of more genetic diversity. If the environment is changing fast then this diversity causes numerous selective sweeps, favoring modifiers with an even larger mutation rate, and so on. The finding of a larger mutation rate in larger populations confirms results obtained from simulations, showing that mutators invade large populations more easily (Taddei *et al.* 1997; Tenaillon *et al.* 1999).

Individual selection differs from "optimization": The evolution of mutation rate, and more generally of "evolvability," has often been thought of in terms of implicit group selection. One seeks for the mutation rate that maximizes the average fitness in the population or maximizes the rate of adaptation (Kimura 1967; Eshel 1973; Painter 1975; Radman *et al.* 1999, 2000; Orr 2000; Radman 2001; Johnson and Barton 2002). Here we show that selection within populations does not follow this optimization principle.

Consider, for instance, the effect of population size in a parameter range where Muller's ratchet does not operate. Small populations "need" large mutation rates to compensate for their small size and hence to be able to adapt. While large populations do not require so high mutation rates, as they can generate favorable mutations easily even with a low error rate. However, competition within populations does not obey such a rationale. Small populations not only generate little diversity owing to their small size, but also evolve toward a minimal mutation rate, which may totally prevent them from adapting. In contrast, owing to a within-population adaptive race between individuals, large populations evolve toward mutation rates that are much higher than what would be needed simply to follow the pace of environmental changes.

A second example comes from the effect of deleterious mutations. When deleterious mutations have a weak effect, they are particularly dangerous for populations as they accumulate in larger frequency. This type of argument has led, for instance, Orr (2000) to argue that, to maximize their rate of adaptation, populations

should have a lower mutation rate when deleterious mutations are of weak effect. Paradoxically, our model shows the opposite, owing to within-population competition. When deleterious mutations are of weak effect, modifiers with large mutation rates invade very easily, even though they then cause the frequency of deleterious mutations to reach dangerously high levels.

Clearly, selection on the higher level, owing to competition between populations (*e.g.*, between bacterial infections), should also affect the evolution of genetic systems and in particular of mutation rate. Such selection should lead to patterns that are closer to optimization principles. However, the consideration of natural selection acting at the level of entire populations requires building different models and is totally distinct from the problem raised in this article.

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APPENDIX A: HYPOTHESIS 2—RUBY IN THE RUBBISH

Here we describe the same models as in the text, but under the second hypothesis (ruby in the rubbish). This hypothesis assumes that deleterious mutations are stronger than favorable ones. Therefore favorable mutations can fix only if they appear in individuals carrying none but the minimal number of deleterious mutations.

Conditional on the presence of a selective pressure, the probabilities that in generation t, the modifier [in frequency $p(t)$] and wild-type subpopulations generate an adaptive mutation destined to fix are, respectively,

$$M_t = N\pi \cdot u' \cdot p_0(t) \tag{A1}$$

and

$$R_t = N\pi \cdot u \cdot (1 - p(t)) \cdot \exp(-U/s_d), \tag{A2}$$

where π is the average fixation probability of an advantageous mutation occurring in a nondeleterious background. We recall that $\exp(-U/s_d)$ is the fraction of nondeleterious individuals among wild types, at mutation–selection balance, if all deleterious mutations have the same cost s_d.

According to hypothesis 2, and writing p_0 for the frequency of nondeleterious modifiers at the focal generation, the expected frequency of modifiers at the end of the sweep can also be found as $M/(M + R)$ from Equations A1 and A2. If the modifier is rare in the focal generation [$p(t) \ll 1$] this gives

$$\frac{\mu'}{\mu} \cdot \exp(U/s_d) \cdot p_0. \tag{A3}$$

If the modifier is at mutation–selection balance, then we have $p_0 = \exp(-U'/s_d) \cdot p$ and Equation A3 can be written as $p \cdot e^{-\delta L/s_d} \cdot \mu'/\mu$. Comparing this result with Equation 17 (in the case where $\bar{\mu} \approx \mu$) shows that, regarding selective sweeps, the effect of the ruby in the rubbish hypothesis is merely to reduce the efficient number of modifiers by a factor $e^{-\delta L/s_d}$.

Here we write a general model, valid whether sweeps occur at a constant rate K (model A) or at a varying rate $S \cdot R$ (model B). The per-generation probability of sweep is written P in the general case. The recurrence equation giving the probability of fixation of the modifier in generation t (see Equation 19) is written as

$$F_{t+1} = F_t + (1 - P)^t P \frac{\mu'}{\mu} \exp(U/s_d) \cdot E[p_0(t)], \tag{A4}$$

where $E[p_0(t)]$ is the expected frequency of nondeleterious modifiers, given by Equation 4. The equivalent of Equation 20 is then found as

$$F_\infty = \frac{P}{1 - (1 - P)e^{-\delta L}} \cdot \frac{\mu + \delta}{\mu} \cdot p(0) = w_\infty(\mu, \delta) \cdot p(0), \tag{A5}$$

where one can also verify that $w_\infty(\mu, 0) = 1$.

The direction of selection on the modifier is finally found as $\mathrm{Sel}(\mu) = \partial w_\infty(\mu, \delta)/\partial\delta|_{\delta=0}$. After simplification one can show that it is of the same sign as

$$1 - \mu L\left(\frac{1 - P}{P}\right). \tag{A6}$$

In a purpose of comparison, let us recall the general result obtained under the opposite hypothesis (*i.e.*, deleterious mutations do not affect the probability of fixation of advantageous ones). Under hypothesis 1 (see Equation 21), the direction of selection on mutation rate is given by the sign of

$$1 - \mu L\left(\frac{1 - P}{P} - \frac{1}{s_d}\right), \tag{A7}$$

which is also valid whether the rate of selective sweep is a constant $P = K$ (model A) or a variable product $P = S \cdot R$ (model B).

The mere observable difference between Equations A6 and A7 is the absence of the delay in the former. Under the ruby in the rubbish hypothesis (Equation A6), a modifier with larger-than-resident mutation rate pays the cost of deleterious mutations immediately after introduction, because all deleterious-carrying individuals are dead end. On the contrary, a modifier with a lower-than-resident mutation rate receives, without delay, the benefit of fidelity.

The direction of selection under the ruby in the rubbish hypothesis (Equation A6) actually has a somewhat intuitive interpretation. Consider a single selective sweep, as a unitary event favoring larger mutation rates. For this event, any given individual undergoes in expectation $(1 - P)/P$ generations free of sweep, during which it may generate a deleterious mutation with a probability μL. The direction of selection on mutation rate is found by comparing the number of sweeps on one side (equal to 1) and the overall risk to generate a deleterious mutation before the sweep on the other side $\{\mu L[(1 - P)/P]\}$. Note that the same reasoning applies under hypothesis 1. The only difference is that the number of generations before the sweep must be discounted by the delay $1/s_d$ (Equation A7).

Model A—constant rate of selective sweeps: In this model, the per-generation probability of sweep is a constant $P = K$. From Equation A6, there is a single singular strategy μ_{conv} with

$$L\mu_{conv} = \frac{K}{1 - K}, \tag{A8}$$

which is convergence stable but not ESS stable; *i.e.*, evolution is converging to μ_{conv}, but then any modifier is favored. In this model, the only difference with hypothesis 1 is actually the absence of delay.

Models B and C—ecological scenario: In this model, the per-generation probability of sweep writes into the form of a product $P = S \cdot R$, where S is the per-generation probability that a selective pressure is present and R is the probability of sweep conditional on the presence of a selective pressure. This adds a further difference between hypotheses 1 and 2, hidden into the sweep probability, R. Under hypothesis 1, this probability was given by $R(\mu) = N\pi l \cdot \mu$. Whereas, under hypothesis 2, R is affected by the presence of deleterious mutations, writing $R = N\pi l \cdot \mu \cdot \exp(-\mu L/s_d)$. Finally, the probability of selective pressure depends on the ecological scenario. In model B, this probability is given by Equation 24. In model C, the population is always under a selective pressure ($S = 1$). In both models, replacing P by the appropriate value of the product $S \cdot R$ into Equation A6 gives the direction of selection on mutation rate. In this case, however, the singular strategies cannot be found analytically. Numerical analyses show that the results are qualitatively identical to that found under hypothesis 1 (not shown).

APPENDIX B—COST OF FIDELITY

Here we describe the direct effect of mutation rate on fitness. Minimizing the number of errors in replication is costly for biological systems, as for any replicating system. Replicating without error is impossible; hence the fitness of an individual with a nil mutation rate must be zero. However, reproducing is not only a matter of copying DNA; hence various other factors are restricting fitness, even when the error rate is high. We recall that μ is the mutation rate per base pair. The fecundity of a nondeleterious individual with mutation rate μ is written, relative to a maximal attainable fecundity of 1, as $w_c(\mu) = \mu/(f + \mu)$, where f is the mutation rate where half of the maximum fecundity is attained [$w_c(\mu) = 0.5$]. Fecundity increases approximately linearly with low mutation rates and saturates toward 1 for higher rates. If f is very low, then the saturation occurs for low mutation rates; *i.e.*, the fecundity is always maximal [$w_c(\mu) = 1$] for any mutation rate, but suddenly tends linearly toward zero when the mutation rate comes very close to zero. If f is higher, then the saturation occurs for higher mutation rates. The value of f can depend not only upon physiological factors (*e.g.*, the energetic cost of DNA proofreading) but also upon ecological factors (*e.g.*, the strength of selection in favor of rapid replication).

Consider a rare modifier of mutation rate μ in a resident population of mutation rate $\mu' = \mu + \delta$. Owing to fidelity cost, the modifier's frequency is multiplied in each generation by the ratio of its fecundity over the average fecundity in the population, $w_c(\mu')/w_c(\mu)$. This effect is integrated into the equations giving the expected frequency of the modifier after t generations (Equation 4 under hyp. 2 and Equation 12 under hyp. 1).

Under hypothesis 2 (ruby in the rubbish), the direction of selection on the modifier is then found as

$$\mathrm{Sel}(\mu) = 1 - \left(\mu L - \frac{f}{f + \mu}\right)\left(\frac{1 - P}{P}\right), \qquad \text{(B1)}$$

and under hypothesis 1, the direction of selection is given by

$$\mathrm{Sel}(\mu) = 1 - \mu L\left(\frac{1 - P}{P} - \frac{1}{s_d}\right) + \frac{f}{f + \mu}\left(\frac{1 - P}{P}\right). \qquad \text{(B2)}$$

These two equations must be compared with the neutral results (no direct selection) given by Equations A6 and A7. The ruby in the rubbish case is simpler because of the absence of delay. The cost of accuracy appears in Equation B1 as a factor $f/(f + \mu)$, causing selection in favor of larger mutation rate. Quite intuitively, the quantitative effect of this factor is proportional to the ratio $(1 - P)/P$, measuring the expected number of generations lived by a modifier before the selective sweep. The cost of accuracy appears in the exact same way under hypothesis 1 (Equation B2). This cost is paid during the entire $(1 - P)/P$ generations before the sweep, while the cost of deleterious mutations (μL) is paid after a delay $1/s_d$. These equations are then solved to describe the evolutionary trajectory of mutation rate. The results are given in the main text of this article.