The Rate of Adaptation in Asexuals

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ABSTRACT

I study the population genetics of adaptation in asexuals. I show that the rate of adaptive substitution in an asexual species or nonrecombining chromosome region is a bell-shaped function of the mutation rate: at some point, increasing the mutation rate *decreases* the rate of substitution. Curiously, the mutation rate that maximizes the rate of adaptation depends solely on the strength of selection against *deleterious* mutations. In particular, adaptation is fastest when the genomic rate of mutation, U, equals the harmonic mean of selection coefficients against deleterious mutations, where we assume that selection for favorable alleles is milder than that against deleterious ones. This simple result is independent of the shape of the distribution of effects among favorable and deleterious mutations, population size, and the action of clonal interference. In the course of this work, I derive an approximation to the probability of fixation of a favorable mutation in an asexual genome or nonrecombining chromosome region in which both favorable and deleterious mutations occur.

CONSIDER an asexual species that encounters a novel or changing environment. Under what conditions will it adapt fastest? In particular, what rate of mutation allows the fastest adaptation?

The problem of how adaptation rate depends on mutation rate in asexuals (or in chromosome regions that do not recombine) is subtle. Adaptive evolution obviously requires the production of beneficial mutants. Thus all else being equal, that clonal lineage having the highest mutation rate might seem best poised for long-term evolution. Such a clone enjoys what Leigh (1970, 1973) has called high "adaptability," as opposed to present "adaptedness." But all else is not equal, as there are at least two complications. The first is that as favorable mutations grow too common they begin to get in each other's way. The fixation of a first favorable mutation can, for instance, be blocked by the appearance of a more strongly favored one that arises during the first's transit to fixation. Gerrish and Lenski (1998) recently studied this phenomenon—which they call "clonal interference," a variant of the Hill-Robertson effect (Hill and Robertson 1966). [In the Drosophila literature, clonal interference is often referred to as a "traffic problem" (Kirby and Stephan 1996; Stephan 1995).] Gerrish and Lenski showed that clonal interference increases the mean time between fixation events and so slows the rate of adaptive substitution. In particular, they showed that the rate of substitution does *not* increase without bound as the mutation rate increases. Instead it plateaus. They thus suggested that clonal interference may impose a "speed limit" on the rate of adaptation in asexuals. Miralles *et al.* (1999) recently attempted to detect this speed limit experimentally in asexual populations of vesicular stomatitis virus.

Second, an increase in the mutation rate increases the number of deleterious mutations. These deleterious alleles have several effects. For one, they cause asexuals to suffer an increased mutational load. The resulting trade-off between long-term adaptability and short-term adaptedness forms the foundation of a large body of work on the evolution of mutation rates in asexuals (Kimura 1967; Leigh 1970, 1973; Gillespie 1981; Dawson 1998, 1999; Johnson 1999a). But as we will see, deleterious mutation also plays an important role in determining the maximal *adaptability*, *i.e.*, the rate of mutation that yields the fastest adaptation.

Here, following Fisher (1930), Peck (1994), and Barton (1995), I consider the fate of asexual lineages experiencing mutation to both favorable and deleterious alleles. In particular, I derive the rate of adaptive substitution when favorable mutations encounter traffic problems due to both other favorable mutations and to deleterious mutations. I find that the rate of adaptation does not plateau with increasing mutation rate, as claimed by Gerrish and Lenski (1998). Instead it peaks. Contrary to intuition, the rate of mutation that yields the fastest adaptation depends solely on the strength of selection against *deleterious* mutations.

THE MODEL AND RESULTS

A simple model: Consider an asexual haploid with large population size N (extensions to asexual diploids are straightforward but not pursued here). The total rate of mutation per genome (or nonrecombining chromosome region) is U. In the present environment, a

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fixed proportion p_b of all mutations are beneficial. Because our species is nonrecombining, adaptive evolution gets complicated by the presence of linked deleterious alleles: favorable mutations often arise in genomes bearing one or more deleterious mutations, as emphasized by Fisher (1930), Manning and Thompson (1984), and Peck (1994). I assume that selection coefficients for new beneficial mutations, s_b, are typically smaller than those for new deleterious mutations, s_d. Although surely not universally true, this is likely to be biologically realistic in many cases. [Indeed, analysis of Fisher's geometric model of adaptation (Hartl and Taubes 1996; Orr 1998) shows that the mean effect of new deleterious mutations must be greater than that for new favorable ones.] In any case, this assumption is relaxed somewhat in the simulations described below.

When $s_b < s_d$, adaptive evolution is essentially constrained to those favorable mutations that appear in deleterious-mutation-free genomes (Fisher 1930; Peck 1994; Barton 1995). Such mutations enjoy normal probabilities of fixation of about $2s_b$. In all other cases, genomes carrying a new favorable mutation suffer a negative net selection coefficient and cannot get fixed. Peck (1994) has called this the "ruby in the rubbish" effect.

If adaptation reflects the substitution of new alleles and favorable mutations have independent fates, the rate of adaptive substitution approximately equals the number of favorable mutations appearing per generation multiplied by each mutation's probability of fixation, or

$$k = (NUp_b)(2s_bP_0), \tag{1}$$

where P_0 is the size of the zero class, *i.e.*, the proportion of genomes free of deleterious mutations. Equation 1 is equivalent to Equation 2 of Orr and Kim (1998), who studied adaptive evolution on nonrecombining *Y* chromosomes. It should hold whenever the rate of adaptation is limited by the rate of mutation to favorable alleles and not by the rate of environmental change. At mutation-selection balance, the number of deleterious alleles per chromosome is Poisson distributed with mean U_d/s_d, where U_d is the per genome rate of deleterious mutation, and we assume constant s_d with no epistasis, *i.e.*, fitness is multiplicative across loci. The size of the zero class is therefore $P_0 = e^{-U_d/s_d}$. Because almost all mutations are deleterious ($U \approx U_d$), we can rewrite Equation 1 as

$$k = 2NUp_bs_be^{-U/s_d}. \tag{2}$$

Equation 2 shows that the rate of adaptive substitution is a bell-shaped function of the rate of mutation (see Figure 1). *k vs. U peaks*, not plateaus.

We now ask: What rate of mutation maximizes the rate of adaptation? Differentiating,

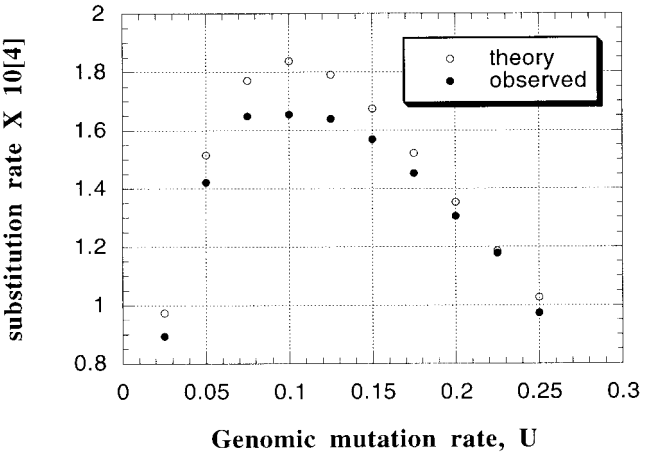

Figure 1.—The rate of adaptive substitution *vs.* the genomic mutation rate, *U*. Theory points are from Equation 2, while the observed points are from exact computer simulations (see text for details). In all cases, selection coefficients for deleterious and favorable mutations were constant: $s_d = 0.1$ and $s_b = 0.01$. $N = 10{,}000$ and $p_b = 2.5 \times 10^{-5}$ of mutations were beneficial. At least 220 favorable substitutions were sampled for each *U*.

$$\frac{\partial k}{\partial U} = 2Np_bs_be^{-U/s_d}\left(1 - \frac{U}{s_d}\right), \tag{3}$$

and adaptation is maximized when the term in parentheses is zero, *i.e.*, when

$$U = s_d. \tag{4}$$

($\partial^2 k/\partial U^2 < 0$ at $U = s_d$.)

Three interesting results emerge from Equation 4. The first is that the rate of mutation yielding the fastest adaptation takes an *intermediate* (nonzero) value even though we have focused solely on long-term adaptability and ignored short-term genetic load. The intuitive reason is straightforward. The optimal mutation rate walks a line at which the product of the number of favorable mutations and the size of the zero class—a quantity that might be viewed as the effective number of favorable mutations—is maximized. When $U > U_{opt}$, there are too many deleterious mutations, mutation-free genomes are too rare, and too many favorable mutations are thrown away. When $U < U_{opt}$, the zero class is larger, but the population produces too few favorable mutations to take advantage of the number of mutation-free genomes, and adaptation slows. Note that, to the order of our approximations, the optimal mutation rate in asexuals is independent of population size, the proportion of mutations that are favorable, and the selective advantage enjoyed by favorable alleles—all poorly known quantities.

The second point emerging from (4) is that those lineages that adapt fastest have their mutation rate set equal to a quantity that might be roughly constant across

lineages, the selection coefficient against deleterious mutations. We pursue this point in the discussion. Third, because an average of U/s_d deleterious mutations exist per genome at mutation-selection balance, an asexual population that enjoys a maximal rate of adaptation carries a mean of $U_{opt}/s_d = 1$ deleterious alleles per genome.

The fact that adaptation proceeds fastest when $U = s_d$ is not intuitive. It also depends on a number of assumptions and approximations. One is that we assume the population always resides at mutation-selection balance, which is unlikely to be true, especially following the fixation of a favorable mutation (Johnson 1999a). (Another assumption is discussed below.) Although it seems unlikely that our approximations would qualitatively affect our conclusions, it seemed worth checking Equation 4 against exact computer simulations.

These simulations were brute force, following a population composed of N haploid asexual genomes, each of which may experience mutation to deleterious and/or favorable alleles. In particular, the number of deleterious mutations per genome per generation was Poisson distributed with mean $U(1 - p_b)$, while the number of favorable mutations per genome per generation was Poisson distributed with (much smaller) mean Up_b (see Figure 1 legend for parameter values). The order of events was mutation followed by selection, and fitness was multiplicative. Generations were discrete and the program recorded the number of generations between successive adaptive substitutions. Preliminary simulations showed that, when favorable mutations were introduced singly (*i.e.*, no other beneficial mutations were segregating) into a population at mutation-selection balance, probabilities of fixation were nearly perfectly predicted by $2s_bP_0$ (not shown). More important, Figure 1 shows that Equation 4 remains quite accurate over long stretches of time in which the simultaneous segregation of several favorable mutations as well as departures from mutation-selection balance are allowed.

Distribution of fitness effects: We have restricted our attention to the case in which all deleterious mutations have the same fitness effect. This is not necessary. The above theory remains reasonably accurate if we replace s_d with the mean effect of deleterious mutations that segregate at mutation-selection balance, a quantity that equals the harmonic mean, $\bar{s}_H$, of effects among new mutations (Charlesworth 1996; Orr and Kim 1998, Appendix 1). To see this, consider the discrete case in which there are n classes of deleterious mutation; in the ith class, the mutation rate is $\sim\alpha_i U$ and the deleterious effect is s_i. With no epistasis, Johnson (1999a) shows that the numbers of mutations in each class at equilibrium are independently Poisson distributed with mean $\alpha_i U/s_i$. Thus the probability that no deleterious mutations from the ith class are present is $\exp(-\alpha_i U/s_i)$ and the probability that no deleterious mutations from *any* of the n classes are present is $\Pi_{i=1}^{n}\exp(-\alpha_i U/s_i) = \exp(-U\Sigma_{i=1}^{n}\alpha_i/s_i)$. But the sum is just the mean of reciprocals and thus the frequency of the zero class is $\exp(-U/\bar{s}_H)$; *i.e.*, we can replace s_d with the harmonic mean $\bar{s}_H$, as claimed. This result holds regardless of the distribution of s_d, so long as fitness effects do not become infinitesimally small.

Similarly, because Equations 1 and 2 are linear in s_b, the relevant selection coefficient is the arithmetic mean of effects among beneficial mutations, $\bar{s}_b$. Thus, with distributions of both deleterious and favorable effects, the expected substitution rate becomes

$$E[k] \approx 2NUp_b\bar{s}_b e^{-U/\bar{s}_H}, \tag{5}$$

and the rate of substitution is maximized when

$$U_{opt} = \bar{s}_H, \tag{6}$$

i.e., when the genomic mutation rate equals the harmonic mean of deleterious effects among new mutations.

This result was again tested against exact computer simulations. The simulations were identical to those above except that exponential distributions of both deleterious and favorable effects were allowed (see Figure 2 legend for details and note that in a small fraction of cases $s_b > s_d$). Once again, the simulations showed that our analytic solution is reasonably accurate. Although the predicted k tends to overestimate the rate of adaptation, the error is fairly small.

A more exact model: The above theory depends on an important simplification: we assume that favorable mutations enjoy independent fates. That is, we ignore clonal interference (Gerrish and Lenski 1998). Although favorable mutations may be sufficiently rare that clonal interference is unimportant, we cannot be sure of this, particularly in taxa having large populations. Fortunately we can incorporate clonal interference into the above model, at least approximately. The required calculations, a straightforward combination of the above and those of Gerrish and Lenski (1998), are presented in the appendix.

It is shown there that, when both ruby in the rubbish and clonal interference effects are allowed, the probability of fixation of a beneficial mutation is $\sim 2s_b e^{-U/\bar{s}_H} e^{-I}$, where I is the number of interfering favorable mutations that appear and escape stochastic loss during a first mutation's transit to fixation. In other words, because favorable mutations confront two varieties of traffic problems in asexuals, the normal probability of fixation $2s_b$ must be discounted by the probability that no deleterious mutations reside on the relevant chromosome *and* by the probability that no interfering mutations block the first mutant's spread. I, which takes into account the fact that any interfering mutation must itself arise in a deleterious-mutation-free genome, is roughly

$$I = 2Up_bN \ln Ne^{-U/\bar{s}_H}(1/s_b)\int_{s_b}^{\infty} vf(v)dv, \tag{7}$$

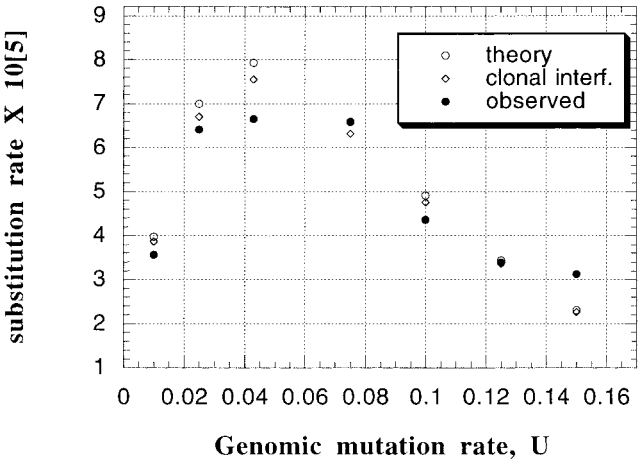

Figure 2.—The rate of adaptive substitution given distributions of deleterious and beneficial effects. Deleterious mutations were drawn from a truncated exponential distribution with mean effect of $\bar{s}_d = 0.1$ and $\bar{s}_H = 0.0431$. Favorable mutations were also drawn from a truncated exponential distribution with a mean of $\bar{s}_b = 0.01$. For both types of mutation, $s > 7.5 \times 10^{-3}$, ensuring that mutations were not effectively neutral and thus slowing Muller's ratchet. $s_b < s_d$ 97.5% of the time. All other parameter values are as in Figure 1. The theory points are from Equation 5, while the clonal interference points are from (8). At least 150 favorable substitutions were sampled at each U.

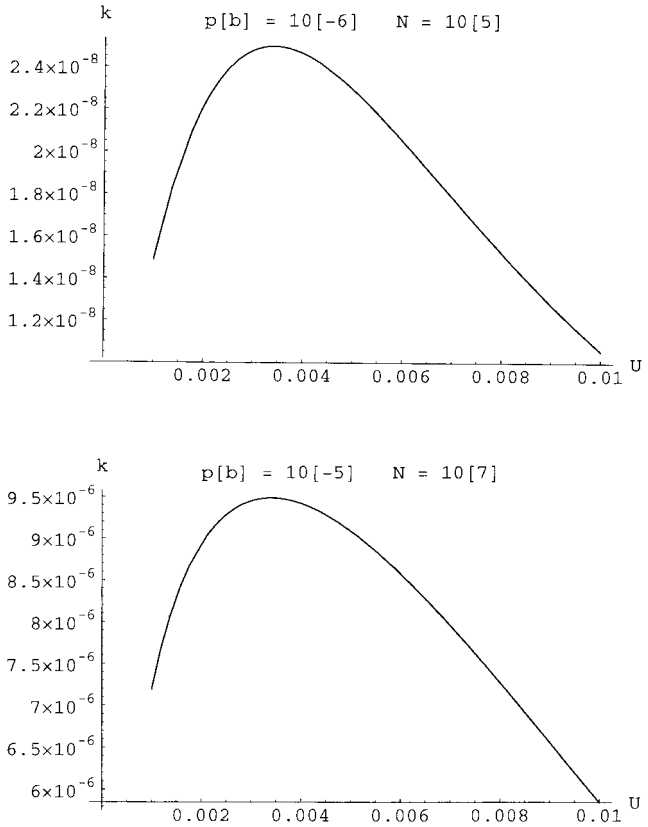

Figure 3.—The rate of substitution *vs.* U, allowing clonal interference. Curves show Equation 8, with $\bar{s}_H = 0.0034$ and $\bar{s}_b = 10^{-4}$. N and p_b were varied as shown. In the top, 0.1 favorable mutations appear per generation, while in the bottom, 100 appear per generation. In both cases (and in others not shown), the rate of adaptation is maximized at $U = \bar{s}_H = 0.0034$.

where f is the density of beneficial selection coefficients among new mutations.

The expected rate of substitution is therefore

$$E[k] \approx \int_0^\infty 2NUp_b s_b e^{-U/\bar{s}_H} e^{-I} f(s_b) ds_b. \quad (8)$$

When clonal interference is absent ($I = 0$), (8) reduces to (5), as expected. Numerical analysis confirms that, when favorable mutations are rare (5) provides a good approximation to (8). But as the number of favorable mutations produced per generation grows, (8) is influenced by clonal interference (sometimes substantially), and the effect is as expected intuitively: adaptation is slowed. Simulation results (*e.g.*, Figure 2) agree reasonably well with (8).

Equation 8 again shows that the plot of adaptive substitution rate *vs.* mutation rate peaks (Figure 2). To find the U that maximizes the rate of adaptation, we must solve $\partial E[k]/\partial U = 0$. The appendix shows that this occurs when

$$U = \bar{s}_H, \quad (9)$$

just as before. This is our most important result. Even with clonal interference, adaptation is fastest when the genomic mutation rate equals the harmonic mean of deleterious effects. This can be seen in Figure 3, which plots (8) as a function of U while varying the number of favorable mutations that appear per generation 1000-fold. Although we have assumed in Figure 3 that s_b is exponentially distributed, this is not necessary. As the Appendix shows, adaptation is fastest when $U = \bar{s}_H$ regardless of the distribution of s_b.

DISCUSSION

Our calculations, although mathematically trivial, lead to a counterintuitive result. The rate of mutation in asexuals that maximizes the rate of *adaptation* depends solely on the strength of selection against *deleterious* mutations. In particular, asexuals adapt fastest when the genomic mutation rate equals the harmonic mean of deleterious effects among new mutations. We assume only that selection for new favorable alleles is typically milder than that against new deleterious ones. (We do not assume that the favorable mutations that actually get *fixed* have such small effects.)

The reason for this dependence on deleterious mutation is clear. As U grows too large, too many genomes carry deleterious alleles and, consequently, too many favorable mutations arise in deleterious "loaded" genomes, thus suffering zero probabilities of fixation. But as U gets too small, there are too few favorable mutations

to take advantage of the existing deleterious-mutation-free genomes and adaptation slows. At $U = \bar{s}_H$, these tendencies optimally trade off. The effective rate of mutation to favorable alleles—the product of the favorable mutation rate and the frequency of deleterious-mutation-free chromosomes—gets maximized.

Consequently, adaptation is fastest when U assumes an *intermediate* value. This contradicts traditional intuition, which held that long-term adaptability increases as the production of favorable mutations grows. Leigh (1973, pp. 15–17), for instance, asked "What mutation rate is best for evolutionary progress?" and concluded "[t]he larger u, the larger the eventual fitness." But real mutation rates are obviously not infinite and thus short-term costs were invoked to rein in such absurdly high mutation rates (Kimura 1967; Leigh 1970, 1973; Dawson 1998, 1999; Johnson 1999b; and see below). The present work shows that intermediate mutation rates are favored in asexuals even when ignoring short-term costs.

Our finding was (as usual) anticipated by Fisher (1930, pp. 120–122). After noting that asexuals can use all of the favorable mutations that escape accidental loss only if the mutation rate is so low that the species adapts at a glacial pace, he points out that:

> [I]f on the contrary the mutation rates, both of beneficial and of deleterious mutations, are high enough to maintain any considerable genetic diversity, it will be only the best adapted genotypes which can become the ancestors of future generations, and the beneficial mutations which occur will have only the minutest chance of not appearing in types of organisms so inferior to some of their competitors, that their offspring will certainly be supplanted by those of the latter. Between these two extremes there will doubtless be an optimum degree of mutability. . . .
>
> Fisher (1930, pp. 120–122)

Fisher did not, however, find this optimum. [Indeed, the required distribution of number of deleterious mutations at multilocus mutation-selection balance was determined fairly late in the history of population genetics, by Kimura and Maruyama (1966) and Haigh (1978).] Our results are likely also related to those of Woodcock and Higgs (1996), who found in computer simulations that when both deleterious and favorable mutations occur, fitness in asexuals increases fastest when U assumes small, but intermediate, values. (Woodcock and Higgs assumed, however, that $s_b = s_d$; their results are not, therefore, directly comparable to the present ones.)

Given the robustness of our findings—our main conclusion is independent of $\bar{s}_b$, the shape of the distributions of s_d and s_b, population size, and the proportion of mutations that are favorable (as long as it is small)—it might not be too farfetched to suggest that one could invert traditional attempts to measure the deleterious effects of new mutations. In other words, in lieu of traditional direct approaches, one might estimate $\bar{s}_H$ by finding the value of U that yields the fastest adaptation in a novel environment, *e.g.*, under radically changed chemostat conditions.

The finding that adaptation is fastest when $U = \bar{s}_H$ is significant for another reason. Gerrish and Lenski (1998), who ignored deleterious mutation, argued that clonal interference may impose a speed limit on adaptive evolution. At some point, favorable mutations block each other's fixation often enough that further increases in U fail to boost the rate of adaptive substitution and the plot of k *vs.* U plateaus (see their Figure 5). But the present analysis suggests that this conclusion is misleading. When deleterious mutations are allowed, the rate of adaptive substitution does not plateau. Instead it peaks. Moreover, this peak occurs early on and its position is independent of the action of clonal interference. Thus while clonal interference might lower the absolute rate of adaptation, it does not by itself set a speed limit on adaptation. Instead, the curve of substitution rate *vs.* mutation rate is largely shaped by deleterious, not favorable, mutations. This reflects the fact that deleterious mutations are more common than beneficial ones: given realistic parameter values, any given beneficial mutation is more likely to interact with a deleterious allele than with a beneficial allele.

The present calculations also show that Gerrish and Lenski's (1998) and Miralles *et al.*'s (1999) attempts to use experimental evolution data from *Escherichia coli* and vesicular stomatitis virus (VSV) to estimate (i) the proportion of mutations that are favorable, and (ii) the mean selection coefficient among new favorable mutations, were compromised, at least quantitatively. (Gerrish and Lenski estimated that 1 in 10^6 mutations are favorable in *E. coli*, while Miralles *et al.* arrived at 1 in 10^8 in VSV. Similar analysis suggested that $\bar{s}_b \approx 0.03$ in *E. coli* and $\bar{s}_b \approx 0.31$ in VSV, where the latter value is per day, not per generation.) Unfortunately, these quantities were back-calculated from observed substitution rates and selection coefficients among fixed favorable mutations. But both of *these* quantities depend on I, the expected number of interfering favorable mutations. [For instance, the expected s_b among fixed favorable mutations is $E[s_{b,\text{fixed}}] = C\int_0^\infty s_b \Pi f(s_b) ds_b$, where C is a normalizing constant and $\Pi = 2s_b \exp(-U/s_d)\exp(-I)$.] Unfortunately, I is affected by deleterious mutation, a fact that Gerrish and Lenski (1998) and Miralles *et al.* (1999) did not take into account. Although the magnitude of the resulting bias is unclear (it depends on the values of U and $\bar{s}_H$), Gerrish and Lenski's estimates of p_b and $\bar{s}_b$ cannot be taken at face value.

Given our results, it may be tempting to conclude that asexuals will, over vast stretches of evolutionary time, evolve to the optimal mutation rate of $U = \bar{s}_H$. But the problem of the evolved mutation rate in asexuals is difficult. To see this, first consider the argument that asexuals *will* evolve to such an optimal mutation rate. Imagine a single clone that resides in a perpetually changing environment. Its fitness at time t is $w(t) = w_d w_b$, where w_d gives the effects of deleterious mutation

and w_b those of beneficial mutations. Because at equilibrium $w_d = \exp[-U]$, we have

$$w(t) \approx e^{-U}(1 + s_b)^{kt} \approx e^{kts_b - U}. \quad (10)$$

That clone that maximizes $kts_b - U$ will have the highest fitness. Looking into the distant future (letting $t \to \infty$), the fittest clone is that which sets $U_{opt} = \bar{s}_H$, as expected from our previous arguments. Over long stretches of evolutionary time, then, we might expect such a clone to predominate.

The difficulty is that we have assumed that—when our optimal clone competes with others having lower U—the optimal clone survives the intervals *between* adaptive fixation events (Leigh 1973, p. 16). But we have no such guarantee. During these intervals, any mutant clones having smaller U enjoy a short-term advantage and so invade, causing the frequency of the "optimal" clone to fall.

Thus we can give no simple answer to the question of whether asexuals will converge on genomic mutation rates in the neighborhood of $U \approx \bar{s}_H$. If selection is very strong and favorable substitutions occur at a high rate, adaptive dynamics may prevail, keeping U near $\bar{s}_H$ among successful clones. If so, it is worth noting that our findings might well explain Drake's well-known rule that genomic mutation rates are roughly constant across DNA-based microbes *regardless* of genome size (Drake 1991; Drake *et al.* 1998): U might be roughly constant across largely asexual microbes because $\bar{s}_H$ might be roughly constant across microbes. (We assume here that the deleterious mutation rate scales with total genome size as measured in base pairs; this should be roughly true in microbes, which possess far less noncoding DNA than do higher eukaryotes.) But if adaptive substitutions are rarer, asexuals may not spend most of their time near $U \approx \bar{s}_H$. [See Johnson (1999a,b) and Woodcock and Higgs (1996) for more complete discussions.]

It is, however, worth noting that if and when clones move to the optimal rate identified here, they will not suffer absurdly high mutation loads. Indeed, the resulting mutation load will be much closer to the *smaller* than to the larger values of s_d, a well-known property of harmonic means. Assuming that selection coefficients on the order of 10^{-3} are realistic, a load of $1 - e^{-U} \approx U = \bar{s}_H \approx 10^{-3}$ would appear tolerably minute. [For rough estimates of s_d in *E. coli*, see Kibota and Lynch (1996). But also see Keightley and Eyre-Walker (1999) for how such estimates may be affected by variation in s_d.] Organisms need not, therefore, suffer enormous loads to enjoy the advantages of rapid adaptation.

In closing, it should be noted that this analysis required us to address a problem of perhaps wider interest. We have found a simple approximation to the probability of fixation of a favorable mutation in a nonrecombining genome or chromosome region. Such a mutation faces two kinds of traffic problems. First, it must escape stochastic loss due to linked deleterious mutations and, second, it must avoid being displaced by a later favorable mutation of greater advantage. When both forces act, the probability of fixation is $\sim 2s_b \exp(-U/\bar{s}_H)\exp(-I)$. (Note that I is itself a function of U and $\bar{s}_H$ as subsequent favorable mutations can interfere only if they arise in a deleterious-mutation-free background.) Roughly speaking, then, the joint action of background selection and clonal interference reduces the fixation effective population size by a factor of $\exp(-U/\bar{s}_H)\exp(-I)$, a result that makes good intuitive sense.

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APPENDIX

Combined effects of deleterious mutation and clonal interference: I derive the rate of adaptive substitution when both deleterious mutation and clonal interference are allowed. The derivation proceeds in two main steps. First, I find the number of interfering mutations that arise during a first favorable mutation's transit to fixation; second, I derive a rate of adaptation given this number of interfering mutations. These calculations are a straightforward combination of those of Gerrish and Lenski (1998) and those from the first half of the text. Unlike Gerrish and Lenski, however, I allow for deleterious mutation as well as for any arbitrary distribution of favorable selection coefficients.

Deleterious mutations have a harmonic mean effect of $\bar{s}_H$ and favorable mutations have an arbitrary distribution of effects with an arithmetic mean $\bar{s}_b$. A favorable mutation having an advantage of s_b is going to fixation and we wish to calculate the expected number of subsequent "lucky" favorable mutations of larger effect that might interfere with its fixation. By lucky mutations, we mean those that escape stochastic loss when rare; only these are capable of interfering. The number of interfering mutations, I, will approximately equal the product of the number of favorable mutations that appear on the ancestral (wild) background while the first mutation is going to fixation and the probability that such mutations both have an effect greater than s_b and are not lost.

A total of NUp_bt favorable mutations appear during time t, where t is the transit time to fixation of our favorable mutation. Because allele frequency under selection is logistic, $t = (2/s_b)\ln N$, where the mutation starts at $p = 1/N$ and goes to pseudofixation at $p = 1 - 1/N$. But by symmetry over the logistic curve, only half of these mutations appear on ancestral (wild) chromosomes. Of these $NUp_bt/2$ relevant mutations, some fraction both has an effect greater than s_b and escapes stochastic loss (where we include loss due to mutations arising in deleterious loaded genomes). This fraction is

$$F = \int_{s_b}^{\infty} 2v\, e^{-U/\bar{s}_H} f(v)\, dv, \tag{A1}$$

where f is the probability density of favorable selection coefficients among new mutations.

The expected number of interfering favorable mutations is thus $\sim I = NUp_btF/2$, yielding Equation 7 of the text. Our approach to calculating the number of interfering mutations is clearly approximate: we ignore the effect on N_e of subsequent mutations whose effects are less than s_b, as well as the fact that favorable mutations that are destined to fixation increase in frequency in the first few generations somewhat faster than expected under our logistic argument (see Otto and Barton 1997, Appendix C). Similarly, P. Gerrish (personal communication) has shown that estimates of I can be improved by taking into account favorable mutations that appear *before* the one whose fate we follow. (This quantitative improvement does not, however, affect our results, *i.e.*, the value of the optimal U.) Despite these approximations, simulations show that our analytic estimate of I is fairly accurate.

We can now calculate the probability that our first favorable mutation is neither lost (*e.g.*, by appearing on a chromosome bearing a deleterious mutation) nor displaced by an interfering mutation. This probability is $2s_be^{-U/\bar{s}_H}e^{-I}$, where e^{-I} is the probability that no events occur in a Poisson process having rate I/t. Thus the rate of substitution involving mutations of size s_b is

$$k \approx 2NUp_bs_be^{-U/\bar{s}_H}e^{-I}. \tag{A2}$$

Given a distribution of s_b, we have $E[k] \approx \int_0^\infty 2NUp_bs_be^{-U/\bar{s}_H}e^{-I} f(s_b)\, ds_b$, as in (8) of the text. If $I = 0$, $E[k]$ reduces to our simple $E[k] \approx 2NUp_b\bar{s}_be^{-U/\bar{s}_H}$, as expected. Similarly, if no deleterious alleles are present ($U/\bar{s}_H = 0$), $E[k]$ reduces to that of Gerrish and Lenski (1998), also as expected.

The maximum rate of adaptive substitution: We find the value of U that maximizes $E[k]$. This requires solving $\partial E[k]/\partial U = (\partial/\partial U)\int_0^\infty 2NUp_bs_be^{-U/\bar{s}_H}e^{-I}f(s_b)ds_b = 0$. Switching the order of differentiation and integration, we have

$$\frac{\partial E(k)}{\partial U} = \int_0^\infty \frac{\partial k}{\partial U} f(s_b)ds_b = 0, \tag{A3}$$

where k is given in (A2). The product rule shows that

$$\begin{aligned}\frac{\partial k}{\partial U} &= 2Np_bs_be^{-U/\bar{s}_H}e^{-I}\left(1 - \frac{U}{\bar{s}_H} - U\frac{\partial I}{\partial U}\right)\\ &= 2Np_bs_be^{-U/\bar{s}_H}e^{-I}(1 - I)\left(1 - \frac{U}{\bar{s}_H}\right).\end{aligned} \tag{A4}$$

Substituting into (A3), we have

$$\frac{\partial E[k]}{\partial U} = \left(1 - \frac{U}{\bar{s}_H}\right) \int_0^\infty 2Np_b s_b e^{-U/\bar{s}_H} e^{-I}(1 - I) f(s_b) ds_b = 0. \quad \text{(A5)}$$

(A5) is satisfied when the term in front of the integral equals zero, *i.e.*, when $U = \bar{s}_H$. Further analysis shows that this solution is a maximum, not a minimum or inflection point. Extensive numerical analysis failed to uncover any other solutions to (A5), although we cannot formally rule them out. Note that we made no assumption about the form of $f(s_b)$. Adaptation is fastest when $U = \bar{s}_H$ *regardless* of the distribution of s_b. Thus while clonal interference changes the absolute rate of adaptation as a function of U, it does not change the value of U that yields the fastest adaptation.