Fate of a mutation in a fluctuating environment

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Natural environments are never truly constant, but the evolutionary implications of temporally varying selection pressures remain poorly understood. Here we investigate how the fate of a new mutation in a fluctuating environment depends on the dynamics of environmental variation and on the selective pressures in each condition. We find that even when a mutation experiences many environmental epochs before fixing or going extinct, its fate is not necessarily determined by its time-averaged selective effect. Instead, environmental variability reduces the efficiency of selection across a broad parameter regime, rendering selection unable to distinguish between mutations that are substantially beneficial and substantially deleterious on average. Temporal fluctuations can also dramatically increase fixation probabilities, often making the details of these fluctuations more important than the average selection pressures acting on each new mutation. For example, mutations that result in a trade-off between conditions but are strongly deleterious on average can nevertheless be more likely to fix than mutations that are always neutral or beneficial. These effects can have important implications for patterns of molecular evolution in variable environments, and they suggest that it may often be difficult for populations to maintain specialist traits, even when their loss leads to a decline in time-averaged fitness.

population genetics | fixation probability | fluctuating environment | effective diffusion

Evolutionary trade-offs are widespread: Adaptation to one environment often leads to costs in other conditions. For example, drug resistance mutations often carry a cost when the dosage of the drug decays (1), and seasonal variations in climate can differentially select for certain alleles in the summer or winter (2). Similarly, laboratory adaptation to specific temperatures (3, 4) or particular nutrient sources (5, 6) often leads to declines in fitness in other conditions. Related trade-offs apply to any specialist phenotype or regulatory system that incurs a general cost to confer benefits in specific environmental conditions (7). Despite the ubiquity of these trade-offs, it is not always easy to predict when a specialist phenotype can evolve and persist. How useful must a trait be on average to be maintained? How regularly does it need to be useful? How much easier is it to maintain in a larger population compared with a smaller one?

The answers to these questions depend on two major factors. First, how often do new mutations create or destroy a specialist phenotype, and what are their typical costs and benefits across environmental conditions? This is fundamentally an empirical question, which depends on the costs and benefits of the trait in question, as well as its genetic architecture (e.g., the target size for loss-of-function mutations that disable a regulatory system). In this paper, we focus instead on the second major factor: given that a particular mutation occurs, how does its long-term fate depend on its fitness in each condition and on the details of the environmental fluctuations?

To address this question, we must analyze the fixation probability of a new mutation that experiences a time-varying selection pressure. This is a classic problem in population genetics, and has been studied by a number of previous authors. The effects of temporal fluctuations are simplest to understand when the timescales of environmental and evolutionary change are very different. For example, when the environment changes more slowly than the fixation time of a typical mutation, its fate will be entirely determined by the environment in which it arose (8). On the other hand, if environmental changes are sufficiently rapid, then the fixation probability of a mutation will be determined by its time-averaged fitness effect (9, 10). In these extreme limits, the environment can have a profound impact on the fixation probability of a new mutation, but the fluctuations themselves play a relatively minor role. In both cases, the effects of temporal variation can be captured by defining a constant effective selection pressure, which averages over the environmental conditions that the mutation experiences during its lifetime. This result is the major reason why temporally varying selection pressures are neglected throughout much of population genetics, despite the fact that truly constant environments are rare.

However, this simple result is crucially dependent on the assumption that environmental changes are much slower or much faster than all evolutionary processes. When these timescales start to overlap, environmental fluctuations can have important qualitative implications that cannot be summarized by any effective selection pressure, even when a mutation experiences many environmental epochs over its lifetime. As we will show below, this situation is not an unusual special case, but a broad regime that becomes increasingly relevant in large populations. In this regime, the fate of each mutation depends critically on its fitness in each environment, the dynamics of environmental changes, and the population size.

Certain aspects of this process have been analyzed in earlier studies. Much of this earlier work focuses on the dynamics of a mutation in an infinite population (11–24). However, these infinite-population approaches are fundamentally unsuitable for analyzing the fixation probabilities of mutations that are neutral or deleterious on average (and even for mutations that are beneficial on average, population sizes must often be unrealistically large for

Significance

Evolution in variable environments depends crucially on the fates of new mutations in the face of fluctuating selection pressures. In constant environments, the relationship between the selective effect of a mutation and the probability that it will eventually fix or go extinct is well understood. However, our understanding of fixation probabilities in fluctuating environmental conditions is limited. Here, we show that temporal fluctuations in environmental conditions can have dramatic effects on the fate of each new mutation, reducing the efficiency of natural selection and increasing the fixation probability of all mutations, including those that are strongly deleterious on average. This makes it difficult for a population to maintain specialist adaptations, even if their benefits outweigh their costs.

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this infinite population size approximation to hold). Another class of work has focused explicitly on finite populations, but only in the case where the environment varies stochastically from one generation to the next (25–31). Later work has extended this analysis to fluctuations on somewhat longer timescales, but this work is still restricted to the special case where selection cannot change allele frequencies significantly during an individual environmental epoch (9, 32, 33).

These studies have provided important qualitative insights into various aspects of environmental fluctuations. However, we still lack both a quantitative and conceptual understanding of more significant fluctuations, where selection in each environment can lead to measurable changes in allele frequency. This gap is particularly relevant because significant changes in allele frequency are the most clearly observable signal of variable selection in natural populations.

In this work, we analyze the fate of a new mutation that arises in an environment that fluctuates between two conditions either deterministically or stochastically on any timescale. We provide a full analysis of the fixation probability of a mutation when evolutionary and environmental timescales are comparable and allele frequencies can change significantly in each epoch. We find that even in enormous populations, natural selection is often very inefficient at distinguishing between mutations that are beneficial and deleterious on average. In addition, substitution rates of all mutations are dramatically increased by variable selection pressures. This can lead to counterintuitive results. For instance, mutations that result in a trade-off but are predominantly deleterious during their lifetime can be much more likely to fix than mutations that are always neutral or even beneficial. Thus, it may often be difficult for populations to maintain specialist traits, even when loss-of-function mutations are selected against on average. This can lead to important signatures on the genetic level, e.g., in elevated rates of nonsynonymous to synonymous substitutions (dN/dS) (34).

Model

We consider the dynamics of a mutation that arises in a haploid population in an environment that fluctuates over time. We assume the population has constant size N (neglecting potential seasonal changes in the size of the population) and denote the frequency of the mutant at time t as $x(t)$. In the diffusion limit, the probability density function of the frequency of the mutant, $f(x,t)$, evolves according to the standard single-locus diffusion equation with a time-varying selection coefficient (35)

$$\frac{\partial f}{\partial t} = -\frac{\partial}{\partial x}\left[s(t)x(1-x)f\right] + \frac{1}{2}\frac{\partial^2}{\partial x^2}\left[\frac{x(1-x)}{N}f\right]. \qquad [1]$$

We focus on the case where the environment fluctuates between two conditions, where the (log) fitness effects of the mutation are $s_1 = \bar{s} + s$ and $s_2 = \bar{s} - s$, respectively. Note that $\bar{s}$ is the arithmetic average of the log fitness, which corresponds to the geometric mean of the absolute fitness. We neglect longer-term changes in selection pressures, so that $s(t)$ will fluctuate between s_1 and s_2 in discrete environmental epochs (Fig. 1*A*). Through the bulk of our analysis we will focus on the case of a mutation with a strong pleiotropic trade-off, such that $s \gg |\bar{s}|$ and $Ns \gg 1$. In other words, selection in each epoch is strong compared with drift and compared with the time-averaged selection pressure. Although this will not be generically true, the effects of fluctuations will turn out to be most dramatic for those mutations that fall into this regime, and we consider violations of these assumptions in the *Supporting Information*. We note that this does not imply that the trait is nearly neutral on average because selection can still be strong in the traditional sense ($N|\bar{s}| \gg 1$).

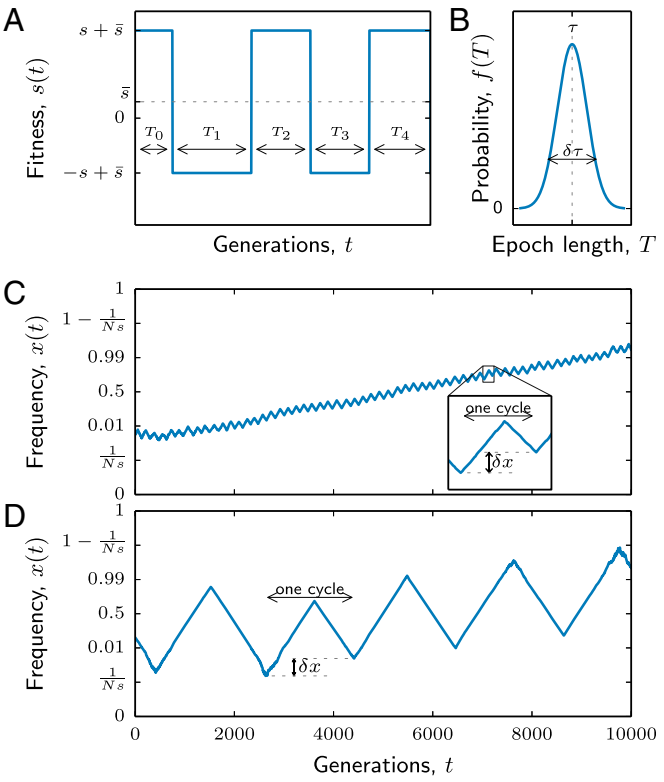

Fig. 1. Fitness and frequency trajectories. (*A*) Sample fitness trajectory. The mutation arises at a random point in time. (*B*) Epochs have average length $\langle T\rangle = \tau$ and variance $\mathrm{var}(T) = \delta\tau^2$. Examples of frequency trajectories for environmental fluctuations that are (*C*) fast and (*D*) slow compared with the timescale of selection. In *C* and *D* $N = 10^6$, $s = 10^{-2}$, $\delta\tau = 0.1$; in *C*, $\bar{s} = 10^{-3}$, $s\tau = 1$; and in *D*, $\bar{s} = 10^{-4}$, $s\tau = 10$.

We assume that the duration of each epoch is drawn at random from some distribution with mean τ and variance $\delta\tau^2$ (Fig. 1*B*). For simplicity, we assume that the distribution of epoch lengths is the same for both environments through most of the analysis, but our approach can easily be generalized to the asymmetric case as well (*Supporting Information*). Through most of our analysis we focus on the case where the mutation rate, μ, is low enough that we can ignore recurrent mutation between the allelic types ($N\mu \ll 1$). However, we show in the *Supporting Information* that our analysis and conclusions also extend to the regime in which the mutation rate is high ($N\mu \gg 1$). We discuss the relationship between our model and those used in previous work in more detail in the *Supporting Information*.

Timescales of Environmental Variation. The fate of a new mutation will crucially depend on how the characteristic timescale of environmental fluctuations, τ, compares to the typical lifetime of a new mutation. For example, in the extreme case where environmental fluctuations are very slow, each mutant lineage will either fix or go extinct during the epoch in which it arose. Thus, its fate is effectively determined in the context of a constant environment in which it is either strongly beneficial or strongly deleterious. The fixation probability of such a mutation has been well studied, and can be most easily understood as a balance between the competing forces of natural selection and genetic drift. We briefly review the key results here, because they will serve as the basis for the rest of our analysis below.

When the mutation is rare, genetic drift dominates over natural selection, and the mutant allele drifts in frequency approximately neutrally. When the mutation is more common, natural

selection dominates over genetic drift: a beneficial mutation increases in frequency deterministically toward fixation, and a deleterious mutation declines deterministically toward extinction. To determine the threshold between these two regimes, we ask whether significant changes in allele frequency are driven by selection or drift. According to Eq. **1**, natural selection changes the frequency of a rare allele substantially (i.e., by of order x; see ref. 36 for details) in a time of order $t = 1/s$ generations. In this time, genetic drift leads to a change in frequency of order $\sqrt{\frac{x}{2N}t} = \sqrt{\frac{x}{2Ns}}$. Thus, there is a critical frequency $x_{\text{sel}} = \frac{1}{2Ns}$ where these forces are comparable. Below x_{sel}, genetic drift drives substantial changes in allele frequencies before natural selection has time to act, and above x_{sel} natural selection dominates over drift.

In the drift-dominated regime where $x < x_{\text{sel}}$, the probability that a lineage at frequency x drifts to frequency x_{sel} before going extinct is approximately $\frac{x}{x_{\text{sel}}}$. Thus, a new mutation ($x = \frac{1}{N}$) will reach this threshold with probability of order $\frac{1}{N}\frac{1}{x_{\text{sel}}} = 2s$. If the mutation arose during a beneficial environment, it will then grow logistically $\left[x(t) = \frac{1}{s}e^{st}/\left(1 + \frac{1}{s}(e^{st} - 1)\right)\right]$ and will fix in about $\frac{2}{s}\log(Ns)$ generations. On the other hand, if the mutation arose during a deleterious environment, it cannot increase in frequency substantially above x_{sel} and will typically go extinct within $\mathcal{O}\left(\frac{1}{s}\right)$ generations. Given equal probabilities of arising in either environment, the net fixation probability is therefore

$$p_{\text{fix}} \approx \frac{1}{2} \cdot 2s = s. \qquad [2]$$

This will hold provided that the environment changes slowly enough that the mutation will have fixed or gone extinct by the end of that environmental epoch [$s\tau \gg 2\log(Ns)$]; see *Supporting Information* for further discussion and analysis of the correction due to finite epoch lengths.

In contrast, whenever $s\tau \ll 2\log(Ns)$, a mutant lineage will experience many beneficial and deleterious epochs before it can fix. In this case, environmental fluctuations can have a dramatic influence on the frequency trajectory of a new mutation (Fig. 1). For example, when $s\tau > 1$, selection within each epoch will drive the mutant frequency to very high and very low values, but because $s\tau \ll 2\log(Ns)$, the mutation will experience many of these dramatic reversals before it fixes or goes extinct (Fig. 1*D*).

An Effective Diffusion Process. Because we aim to predict the long-term fate of the mutation, we are primarily concerned with how multiple epochs combine to generate changes in the allele frequency. This suggests that we define an effective diffusion process which integrates Eq. **1** over pairs of environmental epochs, similar to the earlier approaches of refs. 9 and 32. This yields a modified diffusion equation,

$$\frac{\partial f}{\partial k} = -\frac{\partial}{\partial x}\left[\langle \delta x \rangle f(x,k)\right] + \frac{1}{2}\frac{\partial^2}{\partial x^2}\left[\langle \delta x^2 \rangle f(x,k)\right], \qquad [3]$$

where x now represents the frequency of a mutation at the beginning of a beneficial epoch, and time is measured in pairs of epochs (Fig. 1 *C* and *D*). Eq. **3** also leads to a corresponding backward equation,

$$0 = \langle \delta x \rangle \frac{\partial p(x)}{\partial x} + \frac{1}{2}\langle \delta x^2 \rangle \frac{\partial^2 p(x)}{\partial x^2}, \qquad [4]$$

for the fixation probability, $p(x)$, as a function of x (35). Here, $\langle \delta x \rangle$ and $\langle \delta x^2 \rangle$ are the first two moments of the change in frequency in a single time step, and must be calculated by integrating Eq. **1** over a pair of epochs. These functions will be independent of time, but will generally have a more complicated dependence on x than the coefficients in Eq. **1**. In this way, we can reduce the general problem of a time-varying selection pressure to a time-independent diffusion process of a different form. The only caveat is that this process describes the fate of a mutation starting from the beginning of a beneficial epoch, but mutations will actually arise uniformly in time. Thus, we must also calculate the frequency distribution of a mutation at the beginning of its first full beneficial epoch, so that we can compute the overall fixation probability p_{fix} by averaging $p(x)$ over this range of initial sizes.

In the following sections, we calculate $\langle \delta x \rangle$ and $\langle \delta x^2 \rangle$ and solve the resulting diffusion equation for p_{fix} as a function of $\bar{s}$, s, τ, $\delta\tau$, and N. We begin by analyzing the problem at a conceptual level to provide intuition for the more formal analysis that follows.

Heuristic Analysis

We first consider the simplest case of an on-average neutral mutation in a perfectly periodic environment ($\bar{s} = 0$, $\delta\tau = 0$). In this case, the effects of environmental fluctuations are primarily determined by how rapidly selection acts relative to the rate of environmental change. When τ is much less than $1/s$, selection barely alters the frequency of the mutation over the course of a single epoch. We can then add up the contribution of multiple epochs in a straightforward manner (*Supporting Information*), and we find that the coarse-grained process is indistinguishable from a neutral mutation in a constant environment (9, 32).

In contrast, when τ is much greater than $1/s$ (but still shorter than the fixation time), natural selection dramatically alters the frequency of a mutation within a single epoch, and the effects of environmental fluctuations will play a much larger role. For example, the fate of a mutation now crucially depends on the precise time at which it arises. If it arises early in a deleterious epoch, it will be driven to extinction long before the environment shifts. Because a deleterious mutation with cost s can survive for at most of order $1/s$ generations, the mutation must arise within the last $1/s$ generations of a deleterious epoch to avoid extinction. Similarly, if the mutation arises late in a beneficial epoch it might increase in frequency for a time, but these gains will be reversed in the subsequent deleterious epoch, when the fitness of the mutation switches to $-s$ (Fig. 2*A*). Therefore, the mutation must arise within the first $\sim 1/s$ generations of a beneficial epoch to avoid extinction (i.e., within the "window of opportunity"; Fig. 2*A*). We let $\tau_c = 1/s$ denote the length of the critical period in each epoch when a successful mutation can arise. Because mutations occur uniformly throughout each epoch, only a fraction $\tau_c/\tau \ll 1$ will arise at the "right" time; all others are certainly destined for extinction.

If a mutation does arise during this critical time, its future behavior is characterized by a series of dramatic oscillations in frequency, which can drive an initially rare mutant to high frequencies (and back) over the course of a single cycle (Fig. 1*D*). Because selection is efficient within each epoch ($Ns \gg 1$), the effects of genetic drift are dominated by the period within of order $\tau_c = 1/s$ generations of the beginning and end of each epoch, when either the mutant or the wild type becomes rare (Fig. 2*A*). However, provided that the mutation starts at a frequency $x \ll e^{-s\tau/2}$, the dominant contribution to genetic drift comes from periods where the mutant is rare, because the wild type remains above frequency x throughout the environmental cycle. As a result, the contributions from drift are dominated by the first $\sim \tau_c$ generations and the last $\sim \tau_c$ generations of the cycle, when the frequency of the mutant is still close to x. Thus, the overall magnitude of drift is reduced by a factor of τ_c/τ, but the dynamics of the mutation are otherwise neutral. This approximation breaks down when the frequency of the mutation is of order $e^{-s\tau/2}$, because genetic drift near the middle of the cycle (when the wild type is rare) starts to play a larger role. This drift, when propagated to the end of the cycle, ultimately leads to a net increase in the average frequency of the mutant and the effective diffusion process is no longer neutral (*Supporting Information*).

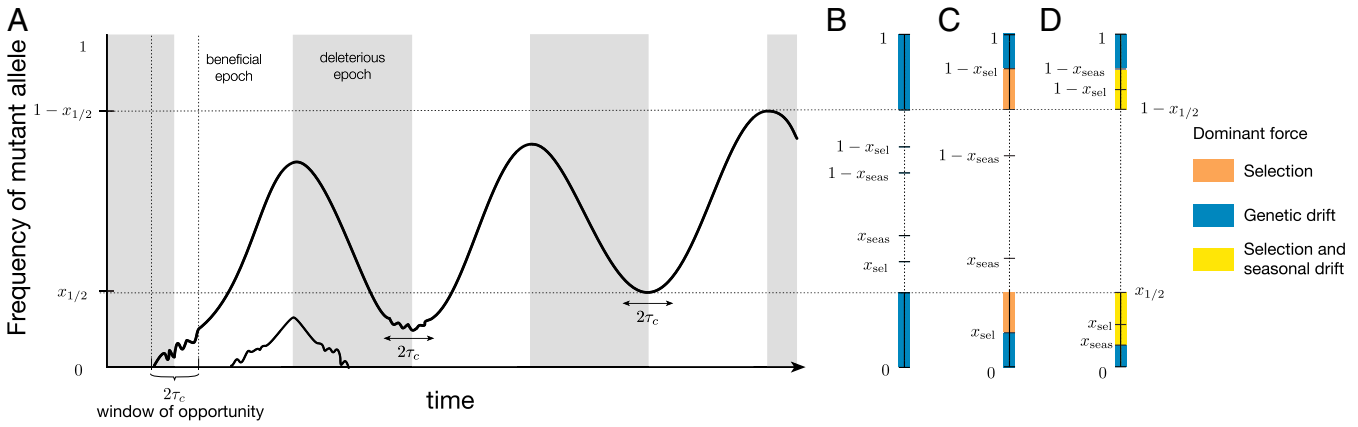

Fig. 2. A schematic illustration of the concepts in the heuristic section. (*A*) All mutations that arise outside of the window of opportunity near the beginning of a beneficial epoch are destined to go extinct. Within a pair of environmental epochs, genetic drift is strongest within $2\tau_c$ generations of the mutant being most rare as long as the frequency of the mutant is below $x_{1/2}$ at the beginning of the beneficial epoch. If the mutant starts the beneficial epoch at $x_{1/2}$, selection will take its frequency to $1-x_{1/2}$ by the end of that epoch. The dominant evolutionary force depends on the frequency of the mutation. (*B*) When the average selection pressure and the variation in epoch lengths are weak, genetic drift dominates all other evolutionary forces. The mutation thus drifts neutrally below $x_{1/2}$, at which point it has a fixation probability of 1/2. This picture applies regardless of whether x_{sel} is large or small compared with x_{seas}. (*C*) When the average selection pressure is sufficiently large, $x_{\text{sel}} \ll x_{1/2}$ and $x_{\text{sel}} \ll x_{\text{seas}}$. The mutation drifts neutrally below x_{sel}, after which its dynamics are deterministic and dominated by natural selection. This picture holds regardless of whether x_{seas} is large or small compared with $x_{1/2}$. (*D*) When the variation in epoch lengths is large enough, x_{seas} is less than both x_{sel} and $x_{1/2}$. The mutation first drifts neutrally below x_{seas}. Above this critical frequency, both natural selection and seasonal drift are potentially important, depending on the magnitudes of x_{seas}, x_{sel}, and $x_{1/2}$.

Fortunately, by the time that the mutation reaches an initial frequency of $e^{-s\tau/2}$, we know that it must have an equal chance of fixing or going extinct. In other words, $x_{1/2} = e^{-s\tau/2}$ is the special frequency at which $p(x_{1/2}) = 1/2$. This is a consequence of the inherent symmetry of the problem: when the mutant begins a beneficial epoch with frequency $x_{1/2}$, the wild type will have frequency $x_{1/2}$ at the end of that epoch, and the situation will be exactly reversed—hence, the mutant and wild type must have the same fixation probability (Fig. 2*A*).

Given that $p(x_{1/2}) = 1/2$, we can calculate the fixation probability of a new mutation when it is rare, without having to consider the dynamics above $x_{1/2}$. We have seen that there is a probability $\sim \tau_c/\tau$ that the mutation arises at the right time; otherwise it is certain to go extinct. Provided that it arises at the right time, the mutation has an initial frequency of $\frac{1}{N}$, and it drifts neutrally to frequency $x_{1/2}$ with probability $\approx \frac{1/N}{x_{1/2}}$ (Fig. 2*B*). Because it is equally likely to fix or go extinct at this point, the net fixation probability is simply

$$p_{\text{fix}} \approx \frac{\tau_c}{\tau} \cdot \frac{1/N}{x_{1/2}} \cdot \frac{1}{2} \approx \frac{2}{\pi N s \tau}, \qquad [5]$$

where we have also included an $\mathcal{O}(1)$ factor of $4/\pi$, which is derived in the formal analysis below. We note that the same line of reasoning can be applied to the fast switching ($s\tau \ll 1$) case as well, provided that we redefine $\tau_c = \tau$ and $x_{1/2} = 1/2$. With these definitions, we recover the standard result that $p_{\text{fix}} = 1/N$ when $s\tau \ll 1$ (32). In contrast, when $1 \ll s\tau \ll \log(Ns)$ the fixation probability in Eq. **5** is much larger than $1/N$ [and eventually saturates to s when $s\tau \gg \log(Ns)$]. In other words, an on-average neutral mutation in a fluctuating environment is much more likely to fix than a strictly neutral mutation. This has important implications for the maintenance of specialist phenotypes, which we revisit in more detail in the *Discussion*.

The Reduced Efficiency of Selection. It is straightforward to extend this picture to mutations that are beneficial or deleterious on average ($\bar{s} \neq 0$). As in the constant environment case, we must consider the relative contributions of selection and drift to the net change in the mutant frequency. Over a pair of epochs, the average selection pressure will alter the frequency of the mutation by a factor of order $e^{2\bar{s}\tau}$, which leads to small changes of order $2\bar{s}\tau x$ when $|\bar{s}|\tau \ll 1$. Thus, selection requires approximately $\frac{1}{2\bar{s}\tau}$ pairs of epochs to change the frequency of the mutation by of order x. Meanwhile, the contribution from drift over a single cycle is of order $\sqrt{\frac{2\tau_c x}{2N}}$, so the net drift that accumulates over $\frac{1}{2\bar{s}\tau}$ cycles is $\approx \sqrt{\frac{\tau_c x}{2N\bar{s}\tau}}$. By comparing the magnitudes of these terms, we find that there is a critical frequency $x_{\text{sel}} = \frac{1}{2N|\bar{s}|}\frac{\tau_c}{\tau}$ above which selection operates efficiently. If $|\bar{s}|$ is small enough that $x_{\text{sel}} \gg x_{1/2}$, then the average selection pressure will not have time to influence the fate of the mutation before it reaches $x_{1/2}$ (Fig. 2*B*), and it will fix with the probability in Eq. **5**. On the other hand, if $x_{\text{sel}} \ll x_{1/2}$, then the mutation will drift to frequency x_{sel} with probability $\approx \frac{\tau_c}{\tau} \cdot \frac{1/N}{x_{\text{sel}}} \approx 2|\bar{s}|$, and will then deterministically fix or go extinct depending on the sign of $\bar{s}$ (Fig. 2*C*). The threshold between these two behaviors occurs at $|\bar{s}| = s^*$, where we have defined

$$s^* \equiv \frac{\tau_c/\tau}{4Nx_{1/2}} \approx \begin{cases} \dfrac{1}{2N} & \text{if } s\tau \ll 1, \\ \dfrac{e^{s\tau/2}}{\pi N s\tau} & \text{if } s\tau \gg 1, \end{cases} \qquad [6]$$

which includes an additional factor of 1/2 derived in the formal analysis below. The total fixation probability is therefore given by

$$p_{\text{fix}} \approx \begin{cases} 2\bar{s} & \text{if } \bar{s} \gg s^*, \\ 2s^* & \text{if } |\bar{s}| \ll s^*, \\ 0 & \text{if } -\bar{s} \gg s^*. \end{cases} \qquad [7]$$

For mutations with $-s^* < \bar{s} < s^*$, the fixation probability does not depend on the average selection coefficient and can be much higher than the fixation probability of neutral mutations in a constant environment. When fluctuations are strong ($s\tau \gg 1$), this "drift barrier" at s^* is much larger than the traditional value of $s^* \sim \frac{1}{N}$ in a constant environment. Thus, we see that in addition to raising the overall fixation probability of nearly neutral mutations ($\bar{s} \ll s^*$), environmental fluctuations also elevate the minimum fitness effect required for selection to operate efficiently.

The Role of Seasonal Drift. Of course, environmental fluctuations in nature are never truly periodic, so it is natural to consider what happens when we allow for stochastic variation in the length of each epoch. To illustrate these effects, it is useful to first return to the case where $\bar{s}=0$. When the duration of consecutive epochs is no longer deterministic, the increase in frequency during a beneficial epoch may not always be balanced by the decrease in frequency during the following deleterious epoch. These imbalances change the frequency of the mutation by multiplicative factors of $e^{s\Delta T}$, which serve as an additional source of variation alongside genetic drift. However, the nature of this "seasonal drift" is very different from ordinary genetic drift, because it does not act on each individual independently. Instead, the $e^{s\Delta T}$ factors lead to correlated fluctuations across the whole mutant lineage. Thus, the relative changes from seasonal drift do not decrease at higher frequencies as they do for genetic drift. When $s\delta\tau \ll 1$, the seasonal drift over a pair of epochs leads to a change of order $s\delta\tau x$, and we have seen that the contribution from genetic drift over the same period is of order $\sqrt{2\tau_c x/2N}$. This means that there is a critical frequency $x_{\text{seas}} = \frac{\tau_c}{N(s\delta\tau)^2}$ above which seasonal drift dominates over genetic drift.

If $x_{\text{seas}} \gg x_{1/2}$, then seasonal drift will have little time to influence the fate of the mutation before it has an equal chance of fixing or going extinct (Fig. 2 *B* and *C*), and the fixation probability will remain the same as Eq. **5**. On the other hand, if $x_{\text{seas}} \ll x_{1/2}$, or

$$(s\delta\tau)^2 \gg \frac{\tau_c}{N x_{1/2}} \approx \begin{cases} \dfrac{2\tau}{N} & \text{if } s\tau \ll 1 \\ \dfrac{e^{s\tau/2}}{Ns} & \text{if } s\tau \gg 1, \end{cases} \qquad [8]$$

then there will be a broad range of frequencies where seasonal drift is the dominant evolutionary force (Fig. 2*D*). In large populations, this condition can be satisfied even when $s\delta\tau$ (and $s\tau$) are extremely small. For frequencies above x_{seas}, the multiplicative changes of seasonal drift cause the logarithm of the mutant frequency to undergo an unbiased random walk, so that the probability of reaching $x_{1/2}$ before returning to x_{seas} is approximately $\log(x/x_{\text{seas}})/\log(x_{1/2}/x_{\text{seas}})$. The probability that the mutation reaches the seasonal drift region (i.e., that it drifts to $c\cdot x_{\text{seas}}$ for some order one constant c) is proportional to $\frac{\tau_c}{\tau}\frac{1}{N}\frac{1}{x_{\text{seas}}} \sim \frac{(s\delta\tau)^2}{\tau}$. The total fixation probability is therefore of order

$$p_{\text{fix}} \sim p\left(\frac{1}{N} \to c\cdot x_{\text{seas}}\right)\cdot p\left(c\cdot x_{\text{seas}} \to x_{1/2}\right) \sim \frac{[s\delta\tau]^2}{\tau}\cdot\frac{1}{\log\left[N(s\delta\tau)^2 x_{1/2}/\tau_c\right]}. \qquad [9]$$

Because the right-hand side of Eq. **9** is much larger than $1/N$ in this regime, we see that just a small amount of seasonal drift can dramatically enhance the fixation of on-average neutral mutations, even when $s\tau \ll 1$. In addition, because p_{fix} now decays as a logarithm of N, the relative enhancement becomes even more pronounced in larger populations.

The addition of selected mutations ($\bar{s}\neq 0$) can be treated in an analogous manner, except that we must now compare the strength of selection with both genetic and seasonal drift. If $|\bar{s}|$ is sufficiently large that $x_{\text{sel}} \ll x_{\text{seas}}$, the mutation will reach frequency x_{sel} with probability $\approx 2|\bar{s}|$ and fix or go extinct deterministically as before (regardless of whether x_{seas} is large or small compared with $x_{1/2}$; Fig. 2*C*). On the other hand, when $x_{\text{sel}} \gg x_{\text{seas}}$, selection primarily operates in the seasonal drift regime (Fig. 2*D*), where the logarithm of the mutation frequency undergoes a biased random walk with mean $2\bar{s}\tau$ and variance $(s\delta\tau)^2$. When $\bar{s}=0$, seasonal drift requires roughly $\log^2(x_{1/2}/x_{\text{seas}})/(s\delta\tau)^2$ pairs of epochs to carry a mutation from x_{seas} to $x_{1/2}$. If the relative change due to $\bar{s}$ is small over this timescale, then the average selection pressure will barely bias the trajectory of the mutation before it reaches $x_{1/2}$, and the fixation probability will be identical to the on-average neutral case in Eq. **9**. This will be true provided $\bar{s} \ll s^*$, where we now have

$$s^* \equiv \frac{[s\delta\tau]^2}{4\tau}\frac{1}{\log\left[N(s\delta\tau)^2 x_{1/2}/\tau_c\right]}, \qquad [10]$$

which includes the appropriate factor of $1/2$ derived in the formal analysis below. On the other hand, if $\bar{s} \gg s^*$, then selection dominates over seasonal drift and the fixation probability again approaches either $2\bar{s}$ or 0. Thus, we see that seasonal fluctuations again lead to a fixation probability of the form in Eq. **7**, but with s^* now defined by Eq. **10**. In other words, seasonal drift also leads to an increase in the fitness effects required for natural selection to operate efficiently. But as we saw for the neutral fixation probability in Eq. **9**, this increase is even more pronounced when seasonal drift becomes important.

Formal Analysis

We now turn to a formal derivation of the results described above. We begin by calculating the moments of the effective diffusion process in Eq. **4**. As in the heuristic analysis above, we will work in the limit that $\bar{s}\tau \ll 1$ and $s\delta\tau \ll 1$. When either of these assumptions is violated, the change in frequency over a pair of epochs is no longer small and the effective diffusion approximation is no longer appropriate. We discuss violations of these assumptions in the *Supporting Information*.

To calculate the moments of the effective diffusion, we must integrate the dynamics in Eq. **1** over an entire environmental cycle. When environmental switching is fast ($s\tau \ll 1$), the frequency of the mutant lineage cannot change substantially within the cycle. The overall changes in the frequency of the mutant can therefore be obtained from a short-time asymptotic expansion of Eq. **1** derived in the *Supporting Information*. We can then average over the epoch lengths to obtain the moments of the effective diffusion equation

$$\begin{aligned} \langle \delta x\rangle &= x(1-x)\left[2\bar{s}\tau + (1-2x)(s\delta\tau)^2\right], \\ \langle \delta x^2\rangle &= x(1-x)\frac{2\tau}{N} + 2x^2(1-x)^2(s\delta\tau)^2. \end{aligned} \qquad [11]$$

In the absence of seasonal drift ($\delta\tau=0$), we recover the standard moments for a mutation with fitness effect $\bar{s}$ in a constant environment, where time is measured in units of 2τ generations. When $\delta t>0$, seasonal drift leads to additional terms in both the mean and variance of δx, consistent with the multiplicative random walk described in the heuristic section.

These short-time asymptotics break down when environmental switching is slow ($s\tau \gg 1$), because we can no longer assume that the frequency of the mutation is approximately constant during a cycle. In this case, however, we can now model the peaks of each cycle (when either the mutant or wild type is rare) using standard branching process methods, with asymptotic matching at intermediate frequencies. Provided that the mutant is not so common that it is likely to fix over the course of the cycle ($x \ll 1-e^{s\tau}/Ns$), we show in the *Supporting Information* that the moments of the effective diffusion equation are given by

$$\begin{aligned} \langle \delta x\rangle &= x(2\bar{s}\tau) + x(s\delta\tau)^2 + x^2\frac{2e^{s\tau}}{Ns}, \\ \langle \delta x^2\rangle &= 2x^2(s\delta\tau)^2 + \frac{2x}{Ns}\left(1+x^2e^{s\tau}\right). \end{aligned} \qquad [12]$$

When $x \ll x_{1/2}$, these moments are similar to the fast-switching regime above, except that genetic drift is reduced by a factor

of $\tau_c/\tau = 1/(s\tau)$. For $x \gtrsim x_{1/2}$, we see that additional terms arise due to genetic drift near the middle of the cycle, which increase both the mean and variance of δx.

To extend this solution to frequencies above $x \gtrsim 1 - e^{s\tau}/Ns$, it is useful to consider the corresponding diffusion process for the wild-type frequency. By construction, the moments of this effective diffusion process are identical to Eq. **12** (with $\bar{s} \to -\bar{s}$), and the two sets of moments now cover the entire range of mutant frequencies. We can then find the total fixation probability $p(x)$ by matching the corresponding solutions of Eq. **4** at some intermediate frequency where both sets of moments are valid (e.g., at $x = x_{1/2}$). Finally, we obtain the fixation probability of a new mutation by averaging over the frequency of the mutant lineage at the beginning of the first full cycle it encounters. We carry out these calculations in detail in the *Supporting Information*.

In both the fast and slow switching limits, we find that the fixation probability of a new mutant in a fluctuating environment satisfies a modified version of Kimura's formula,

$$p_{\text{fix}}(\bar{s}; N, s, \tau, \delta\tau) = \frac{2\bar{s}}{1 - e^{-\bar{s}/s^*}}, \qquad [13]$$

where s^* is defined in Eqs. **6** and **10**. Eq. **13** shows that the relevant fitness effect is the average fitness $\bar{s}$, but that environmental fluctuations lead to a modified drift barrier s^*, which is independent of $\bar{s}$ but depends on the other parameters: N, s, τ, and $\delta\tau$. We compare this predicted parameter collapse to the results of Wright–Fisher simulations in Fig. 3, and compare our predictions for s^* with simulations in Fig. 4. These results are in full agreement with our heuristic analysis: mutations with average fitness effect $|\bar{s}| \ll s^*$ will fix with a probability approximately equal to $2s^*$, beneficial mutations with $\bar{s} \gg s^*$ will fix with probability $2\bar{s}$, and deleterious mutations with $|\bar{s}| \gg s^*$ will have an exponentially small probability of fixation given by $2|\bar{s}|e^{-|\bar{s}|/s^*}$.

Discussion

In this work, we have analyzed how temporal fluctuations alter the dynamics and fixation probability of a new mutation. We find two main qualitative impacts. First, fluctuations reduce the efficiency of selection. This efficiency is commonly quantified by the ratio of fixation probabilities of beneficial and deleterious mutations, $p_{\text{fix}}(-\bar{s})/p_{\text{fix}}(\bar{s})$. We have shown here that this ratio continues to exhibit a simple exponential dependence on $\bar{s}$,

$$\frac{p_{\text{fix}}(-\bar{s})}{p_{\text{fix}}(\bar{s})} = e^{-\bar{s}/s^*}, \qquad [14]$$

even in the presence of environmental fluctuations. As in a constant environment, Eq. **14** implies that selection cannot distinguish between beneficial and deleterious mutations when $|\bar{s}|$ is less than the "drift barrier" s^*, and that selection becomes exponentially more efficient for mutations with $|\bar{s}| \gtrsim s^*$. We have shown here how environmental fluctuations increase the drift barrier s^*, broadening the range over which selection cannot distinguish between beneficial and deleterious mutations.

Given the similarity of Eq. **14** to the constant environment case, where $s^* = \frac{1}{2N_e}$, it is tempting to define an effective population size $N_e = 2/s^*$. This would attribute the decreased efficiency of selection to an increased variance in offspring number arising from variability in the environment. However, we have shown that this intuition is misleading, because the offspring number fluctuations caused by environmental variation do not affect individuals independently. This leads to behavior that cannot be captured by an effective population size [e.g., neutral fixation times which do not scale as N_e but rather as $N_e^2(s\delta\tau)^2/2\tau$].

These correlated fluctuations are also responsible for the second effect of environmental fluctuations: an overall increase in the fixation probability of all mutations. This increased rate of fixation can lead to counterintuitive results. For example, consider a mutation that is deleterious on average ($\bar{s} < 0$) in a fluctuating environment. As is apparent from Fig. 5, the fixation probability of such a mutation can be much larger than $1/N$ (the fixation probability of a mutation that is neutral in both environments, e.g., a strictly neutral synonymous mutation). In fact, a mutation that is on average deleterious can be more likely to fix than a mutation that is on average beneficial, depending on the statistics of environmental fluctuations relevant to the two (e.g., see crossover between blue and orange lines in Fig. 5). In particular, if we compare the deleterious mutation above to a beneficial mutation of the same magnitude

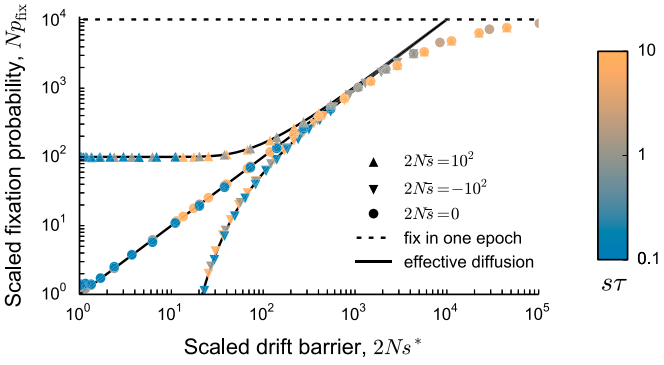

Fig. 3. The effects of environmental fluctuations on the fate of a new mutation are well summarized by a change in the drift barrier, s^*. Here, s^* is independent of the average fitness, $\bar{s}$, but depends on the population size and the dynamics of environmental fluctuations. Colored points show Wright–Fisher simulations of mutant lineages arising at random points in time, performed for a range of epoch lengths and variances in epoch time. Here $N = 10^6$, $s = 10^{-2}$, and $\text{var}(\tau)/\tau^2$ varies from 10^{-4} to 10. The different colors distinguish between simulations in which switching rates were different and the different shapes distinguish between mutations that are on average beneficial (upward triangles), neutral (circles) and deleterious (downward triangles). The full lines show the theoretical predictions for the fixation probability in the effective diffusion limit (Eq. **13**) and the dotted line shows the probability of fixation in a single environmental epoch (Eq. **2**).

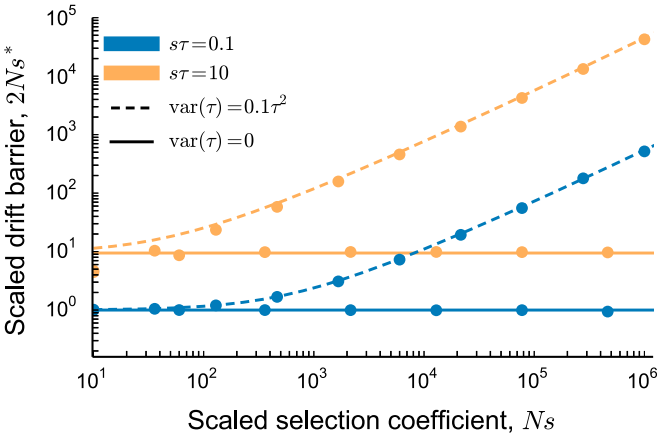

Fig. 4. The increase in drift barrier, s^*, relative to its value in a constant environment as a function of the strength of selection, Ns. The value of s^* was measured using Wright–Fisher simulations of an on average neutral mutant (symbols). Lines show theoretical predictions. Fast switching ($s\tau = 0.1$) is shown in blue and slow switching ($s\tau = 10$) in orange. Here $s = 10^{-2}$ and N ranges from 10^3 to 10^8 to obtain the values of Ns shown.

in a constant environment, the ratio of their fixation probabilities is given by

$$\frac{p(-\bar{s},\tau>0)}{p(\bar{s},\tau=0)}=\frac{1}{e^{\bar{s}/s^*}-1}=\begin{cases}\dfrac{s^*}{\bar{s}} & \text{if } \bar{s}\ll s^*,\\ e^{-\bar{s}/s^*} & \text{if } \bar{s}\gg s^*.\end{cases} \quad [15]$$

Due to the dramatic increase in s^* due to environmental fluctuations (Fig. 4), this ratio can often be much greater than one, reflecting a higher substitution rate of on-average deleterious mutations with a fluctuating selection coefficient compared with always beneficial mutations of the same average magnitude. The fate of a mutation can thus be more strongly influenced by the dynamics of environmental fluctuations than by its average fitness effect. At some level this is not surprising, as this behavior trivially arises whenever a deleterious mutation sweeps to fixation in a single beneficial epoch (and $p_{\text{fix}}\approx s$). However, our results show that this is still true even when environmental changes are rapid enough that the mutation experiences many beneficial and deleterious epochs in its lifetime. This implies that fluctuations can accelerate sequence divergence and increase quantities such as dN/dS even when the population is not adapting on average. This potential consequence of fluctuating selection on rates of adaptation has been pointed out previously in the context of slow environmental fluctuations, and analyzed using the concept of "fitness flux" (10).

Our findings have important implications for the maintenance of regulatory functions in the face of a changing environment. In contrast to previous work, which primarily focuses on traits that are essential in one of the two environments (7, 37), our analysis here applies to traits with more subtle costs and benefits (see ref. 38 for a recent review). For example, bacterial regulatory mechanisms can provide an important advantage in a specific environment, but are typically costly otherwise [e.g., in the case of the *lac* operon $s\approx\pm 10\%$ (39)]. Assuming that environmental changes occur on the order of a day ($\tau\approx 10$ generations) and that N can easily exceed 10^6, these populations will likely be in the regime where $1\lesssim s\tau\ll 2\log(Ns)$. Depending on the time spent in each environment, our analysis shows that the population can be extremely susceptible to invasion by loss-of-function mutations even if the regulatory mechanism provides an overall benefit across environmental conditions. This can make it much more difficult for a population to maintain the regulatory mechanism, leading to a Muller's-ratchet-like effect in which the time-averaged fitness declines over time. Furthermore, it may be equally difficult to maintain regulatory traits even in very large populations, because the drift barrier declines only logarithmically with N when environmental fluctuations are irregular.

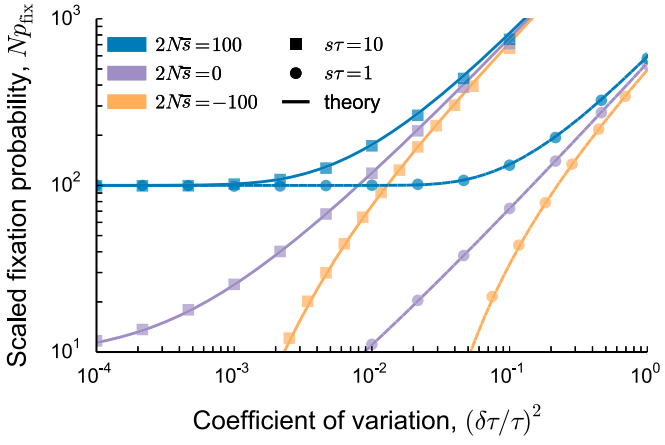

Fig. 5. The dependence of the fixation probability on the rate and regularity of environmental fluctuations. The fixation probability has been scaled by the fixation probability of a neutral mutation in a constant environment, $1/N$. In all simulations, $N=10^6$, $s=10^{-2}$, and the other parameters are shown in the plot. As the variance increases, the fixation probability becomes higher and the average fitness effect, $\bar{s}$, plays an increasingly smaller role. The fixation probability is also higher if the environmental changes are slower.

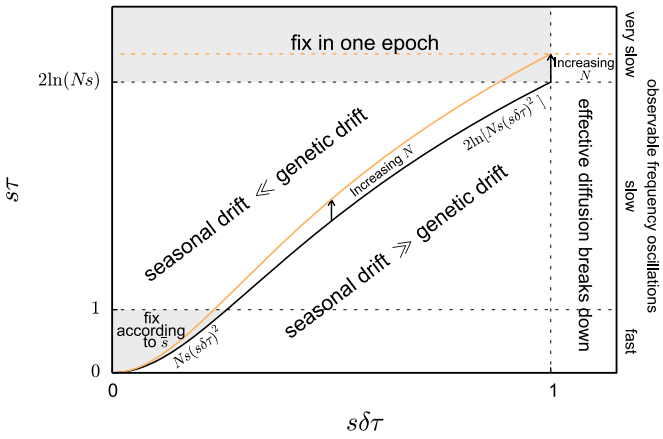

Fig. 6. Phase diagram showing the various regimes discussed in the paper, as a function of the magnitude of environmental fluctuations ($s\delta\tau$) and the average timescale of environmental fluctuations ($s\tau$). The shaded regions are the only ones in which the environmental fluctuations do not change the drift barrier, and so the effect of environmental fluctuations can be summarized by an effective fitness. The black line separates the region in which genetic drift is the dominant source of stochastic fluctuations in the lineage size from the region in which seasonal drift has a more significant effect. The effect of an increase in the population size on the boundaries of the regions is shown in orange.

In addition to predicting fixation probabilities, our results also specify the regimes in which the evolutionary process is altered as a result of changing environmental conditions. We might have assumed that the fate of a mutation is determined by its average strength of selection whenever it experiences many beneficial and deleterious epochs over the course of its lifetime [i.e., whenever $s\tau<2\log(Ns)$]. When environmental fluctuations are both rapid and extremely regular ($s\tau\ll 1$ and $s\delta\tau\ll\sqrt{\tau/N}$) this is indeed the case. However, our analysis shows that there is also a broad regime in which environmental fluctuations lead to dramatic changes in the evolutionary process that cannot be summarized by a simple change in the effective selection coefficient (Fig. 6). This can happen for two reasons: (*i*) either selection within each environment is strong enough, or the duration of each epoch is long enough, that $s\tau$ is no longer vanishingly small; or (*ii*) environmental fluctuations are sufficiently irregular that seasonal drift becomes important (Fig. 6).

It is not a priori clear which regime is most relevant for natural populations, largely due to the difficulty in measuring time-varying selection pressures in their native context. For a randomly chosen combination of s and τ, the rate of environmental fluctuations will often be either very fast or very slow, and the behavior described here will not apply. However, the region between these two limits becomes larger as the size of the population increases (Fig. 6), both because longer fixation times permit more extreme frequency oscillations and also because genetic drift becomes weaker relative to seasonal drift. Moreover, given a distribution of fitness effects of new mutations, it is natural to expect that some alleles will exhibit long-lived oscillations of the type studied here. Trade-offs in this regime are arguably the most likely to be directly observed in natural populations, precisely because they exhibit frequency changes that can be measured from time-course population sequences.

For example, a recent study has identified numerous polymorphisms in natural *Drosophila melanogaster* populations that undergo repeated oscillations in frequency over the course of the

year (10 generations) (2). Although the oscillations in many of these SNPs are likely driven by linkage to other seasonally selected sites, these data suggest that there are at least some driver alleles with $s\tau \approx 1$. The annual variation in the sizes of these populations may contribute important effects that our model does not consider, but in a population of $N \approx 10^5$ individuals, seasonal drift would be more significant than genetic drift as long as $\delta\tau/\tau \gg 0.01$, corresponding to a variance in the lengths of seasons on the order of a single day.

In our analysis so far, we have primarily discussed the case where mutations incur a strong pleiotropic trade-off and the average selection coefficient is much less than $1/\tau$. When either of these conditions is violated, the fate of a mutation is predicted by its time-averaged fitness effect and does not otherwise depend on the dynamics of environmental variation (*Supporting Information*). We have also assumed that the variance in epoch lengths is not too large, so that the changes due to seasonal drift in each cycle are small ($s\delta\tau \lesssim 1$). When this assumption is violated, the effective diffusion approximation in Eq. **3** can technically no longer be applied. However, many of our heuristic arguments remain valid, and we expect qualitatively similar behavior of the fixation probability. We leave a more detailed treatment of this regime for future work.

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