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The 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 variable environment depends on the dynamics of environmental fluctuations 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 tradeoff 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.

INTRODUCTION

Evolutionary tradeoffs 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 tradeoffs apply to any specialist phenotype or regulatory system which incurs a general cost in order to confer benefits in specific environmental conditions [7]. But despite the ubiquity of these tradeoffs, it is not always easy to predict when a specialist phenotype can evolve and persist. How useful must a trait be on average in order to be maintained? How regularly does it need to be useful? How much easier is it to maintain in a larger population compared to 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 [9–11]. 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 which 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

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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 [9, 12–22]. 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 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 [23–29]. 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 [10, 30, 31].

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 the first 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 tradeoff but are strongly deleterious on average can be much more likely to fix than mutations that are always neutral or even beneficial. This implies that it may often be difficult for populations to maintain specialist traits, even when their loss leads to a decline in time-averaged fitness. Our results also have important implications for patterns of molecular evolution in variable environments. They imply that temporal fluctuations can lead to an increase in the ratio of nonsynonymous to synonymous substitutions (dN/dS) even when the population is not adapting on average.

ANALYSIS

We consider the dynamics of a mutation that arises in a population of N haploid individuals, in an environment that fluctuates over time. We 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:

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

We focus on the case where the environment fluctuates between two conditions, where the fitness effects of the mutation are $s_1 = \bar{s} + s$ and $s_2 = \bar{s} - s$, respectively. Thus $s(t)$ fluctuates between these two values in discrete environmental epochs (Fig. 1A). The effects of environmental fluctuations will turn out to be most dramatic for 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 to drift and compared to the time-averaged selection pressure. We will focus on this case throughout the bulk of our analysis, although we consider violations of these assumptions in Appendix A. Note that this does not imply that the trait is nearly neutral on average; we consider both the case where the trait is strongly selected on average (i.e. $N|\bar{s}| \gg 1$) and the case where it is neutral on average (i.e. $N|\bar{s}| \ll 1$). We assume that the length of each epoch is drawn at random from some distribution with mean τ and variance $\delta\tau^2$. Deterministic switching is included as a special case of this model when $\delta\tau = 0$. For simplicity, we assume that the epoch length distribution is the same for both environments through most of the analysis, but our approach can easily be generalized to the asymmetric case as well (see Appendix A).

The fate of a new mutation in such a model will crucially depend on how the characteristic timescale of environmental fluctuations 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. While 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 towards fixation, and a deleterious mutation declines deterministically towards extinction.

To calculate the threshold between these two regimes, we can analyze the relative contributions of natural selection and genetic drift to the change in frequency of the mutant allele. Since the effects of drift and selection depend on time in different ways, we must choose the appropriate timescale on which to make this comparison. The relevant timescale is the one on which the frequency

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x of the allele changes substantially (i.e. by of order x; see [32]). We wish to understand whether these changes are primarily driven by selection or genetic drift. Natural selection takes of order $1/s$ generations to change the frequency x of a lineage by an amount of order x. Over this same time period, genetic drift leads to a change in frequency of order $\sqrt{\frac{x}{2N}t} = \sqrt{\frac{x}{2Ns}}$. By comparing the magnitudes of these two terms, we find that there is a critical frequency $x_{\text{sel}} = \frac{1}{2Ns}$ above which selection dominates over drift, and below which selection is negligible.

The probability that a lineage at frequency $x < x_{\text{sel}}$ drifts to frequency x_{sel} before going extinct is $\frac{x}{x_{\text{sel}}}$. Thus a new mutation that has initial frequency $x = \frac{1}{N}$ will reach this threshold with probability $\frac{1}{N}\frac{1}{x_{\text{sel}}} = 2s$. 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

$$p_{\text{fix}} = \frac{1}{2} \cdot 2s \cdot \left[1 + \mathcal{O}\left(\frac{\log(Ns)}{s\tau}\right)\right]. \tag{2}$$

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 ($\tau + \delta\tau \gg \frac{2}{s}\log(Ns)$); see Appendix B for further discussion and analysis of the correction due to finite epoch lengths.

In contrast to this extreme limit, 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 $s\tau \gtrsim 1$, 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. 1C).

In principle, such large swings in allele frequency can make it difficult to solve Eq. (1) directly. However, because we are interested in predicting the long-term fate of the mutation, the precise dynamics of these frequency swings are not of immediate interest. Instead, we are primarily concerned with how these epochs combine to generate long-term changes in the mutation frequency. This suggests that we define an *effective* diffusion process which integrates the dynamics over *pairs* of environmental epochs, similar to the earlier approaches of Takahata et al. [30] and Gillespie [10]. This yields a modified diffusion equation,

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

where x now represents the frequency of a mutation at the *beginning* of a beneficial epoch, and time is measured

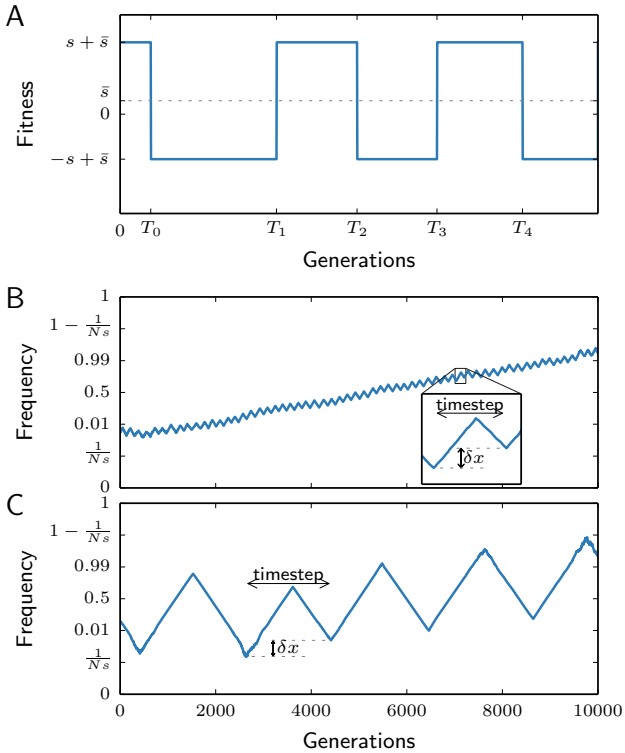

FIG. 1. Fitness and frequency trajectories. (A) Sample fitness trajectory. The mutation arises at a random point in time and at $T_0 \geq 0$ experiences the first deleterious epoch. Epochs have average length $\langle T \rangle = \tau$ and variance $\text{var}(T) = \delta\tau^2$. (B),(C) Examples of frequency trajectories for environmental fluctuations that are (B) fast and (C) slow compared to the timescale of selection. ($N = 10^6, s = 10^{-2}, \delta\tau = 0.1$; $\bar{s} = 10^{-3}, s\tau = 1$ in in panel B and $\bar{s} = 10^{-2}, s\tau = 10$ in panel C).

in pairs of epochs (i.e. from the start of one beneficial epoch to the beginning of the next beneficial epoch, see Fig. 1B,C). This leads to a corresponding equation

$$0 = \langle \delta x \rangle \frac{\partial p_{\text{fix}}(x)}{\partial x} + \frac{1}{2}\left\langle \delta x^2 \right\rangle \frac{\partial p_{\text{fix}}(x)}{\partial x^2} \tag{4}$$

for the fixation probability of a mutation as a function of x. Here, $\langle \delta x \rangle$ and $\left\langle \delta x^2 \right\rangle$ are the first two moments of the change in frequency in a single timestep, 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 have reduced 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, while mutations will actually arise uniformly in time. Thus, we must also calculate the frequency of a mutation at the beginning of its first full beneficial epoch, so that we can average the results of Eq. (4) over this range of initial sizes.

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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 first analyzing the problem at a conceptual level. This will allow us to derive many of our key results, and provide significant 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 (see Appendix C), and we find that the coarse-grained process is indistinguishable from a neutral mutation in a constant environment [10, 30].

In contrast, when τ is much greater than $1/s$, 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 drift to extinction long before the environment shifts. Since a deleterious mutation with cost s can survive for at most $\mathcal{O}(1/s)$ 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 $-s$. Therefore, the mutation must arise within the first $1/s$ generations of a beneficial epoch in order to avoid extinction. We let $\tau_c = 1/s$ denote the length of the critical period in each epoch when a successful mutation can arise. Since 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 very high frequencies (and back) over the course of a single cycle (Fig. 1C). Since selection is efficient within each epoch ($Ns \gg 1$), genetic drift primarily accumulates within $\tau_c = 1/s$ generations of the beginning and end of each epoch, when either the mutant or the wildtype becomes rare. 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, since the wildtype remains above frequency x throughout the environmental cycle. As a result, the contributions from drift are dominated by the first τ_c generations and the last τ_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 mutation starts at a frequency $x \sim e^{-s\tau/2}$, since genetic drift near the middle of the cycle (while the wildtype 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 (see Appendix D).

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 $p_{\text{fix}}(x_{1/2}) = 1/2$. 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.

Given that $p_{\text{fix}}(x_{1/2}) = 1/2$, we can calculate the fixation probability of a new mutation without having to consider the dynamics above $x_{1/2}$. We have seen that there is a probability τ_c/τ 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 $\frac{1/N}{x_{1/2}}$ (Figure 2A). Since it is equally likely to fix or go extinct at this point, the net fixation probability is simply

$$p_{\text{fix}} \approx \frac{\tau_c}{\tau} \cdot \frac{1/N}{x_{1/2}} \cdot \frac{1}{2} \approx \frac{2e^{s\tau/2}}{\pi N s \tau}, \tag{5}$$

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 $s\tau \ll 1$ [30]. In contrast, when $s\tau \gg 1$ the fixation probability in Eq. (5) is much larger than $1/N$. 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.

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

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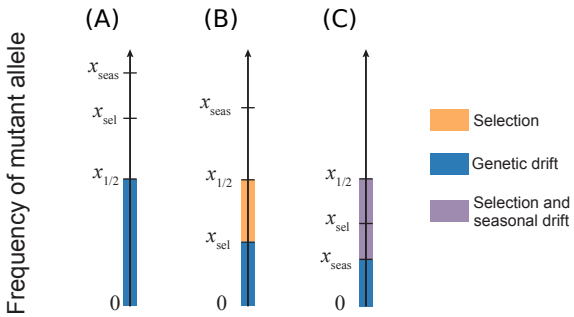

FIG. 2. Schematic of the key parameter regimes. (A) When the average selection pressure and the variation in epoch lengths are weak, genetic drift dominates all other evolutionary forces. The mutation thus drifts neutrally below $x_{1/2}$, at which point it has a fixation probability of 1/2. This picture applies regardless of whether $x_{\rm sel}$ is large or small compared to $x_{\rm seas}$. (B) When the average selection pressure is sufficiently large, $x_{\rm sel} \ll x_{1/2}$ and $x_{\rm sel} \ll x_{\rm seas}$. The mutation drifts neutrally below $x_{\rm sel}$, after which its dynamics are deterministic and dominated by natural selection. This picture holds regardless of whether $x_{\rm seas}$ is large or small compared to $x_{1/2}$. (C) When the variation in epoch lengths is large enough, $x_{\rm seas}$ is less than both $x_{\rm sel}$ and $x_{1/2}$. The mutation first drifts neutrally below $x_{\rm seas}$. Above this critical frequency, both natural selection and seasonal drift are potentially important, depending on the magnitudes of $x_{\rm seas}$, $x_{\rm sel}$ and $x_{1/2}$.

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 cumulative drift that accumulates over $\frac{1}{2\bar{s}\tau}$ cycles is $\sqrt{\frac{\tau_c x}{2N\bar{s}\tau}}$. By comparing the magnitudes of these terms, we find that there is a critical frequency $x_{\rm sel} = \frac{1}{2N|\bar{s}|}\frac{\tau_c}{\tau}$ above which selection operates efficiently. If $x_{\rm sel}$ is larger than $x_{1/2}$, then selection will barely have time to influence the fate of the mutation (Figure 2A), and it will fix with the same probability as Eq. (5). On the other hand, if $|\bar{s}|$ is large enough that $x_{\rm sel} \ll x_{1/2}$, then the mutation will drift to frequency $x_{\rm sel}$ with probability $\frac{\tau_c}{\tau}\cdot\frac{1/N}{x_{\rm sel}} \approx 2|\bar{s}|$, and will then deterministically fix or go extinct depending on the sign of $\bar{s}$ (Figure 2B). This will happen whenever $|\bar{s}| \gg s^*$, where we have defined

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

The total fixation probability is therefore given by

$$p_{\rm fix}(\bar{s}) \approx \begin{cases} 2\bar{s} & \text{if } \bar{s} \gg s^*, \\ s^* & \text{if } |\bar{s}| \ll s^*, \\ 0 & \text{if } -\bar{s} \gg s^*. \end{cases} \tag{7}$$

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" threshold 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 neutral mutations, environmental fluctuations also elevate the minimum fitness effect required for selection to operate efficiently.

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, since the $e^{s\Delta T}$ factors lead to correlated fluctuations across the whole mutant lineage. Because of these correlations, 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 $s\delta\tau x$, while 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 $x_{\rm seas} \sim \frac{\tau_c}{N(s\delta\tau)^2}$ above which seasonal drift dominates over genetic drift.

If $x_{\rm seas} \gg x_{1/2}$, 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 (Figure 2A), and the fixation probability will remain the same as Eq. (5). On the other hand, if $x_{\rm seas} \ll x_{1/2}$, or

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

then there will be a broad range of frequencies where seasonal drift is the dominant evolutionary force (Figure 2C). In large populations, this condition can be satisfied even when $s\delta\tau$ (and $s\tau$) are extremely small. For frequencies above $x_{\rm seas}$, 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 $x_{\rm seas}$ is simply $\log\left(x/x_{\rm seas}\right)/\log\left(x_{1/2}/x_{\rm seas}\right)$. The probability that the mutation first enters this seasonal drift regime (i.e. that it neutrally drifts to $c\cdot x_{\rm seas}$ for some order one constant c) is $\frac{\tau_c}{\tau}\frac{1}{N}\frac{1}{cx_{\rm seas}} \sim \frac{(s\delta\tau)^2}{\tau}$. The total fixation probability can therefore be approximated by

$$\begin{aligned} p_{\rm fix} &\approx p\left(\tfrac{1}{N} \to c\cdot x_{\rm seas}\right)\cdot p\left(c\cdot x_{\rm seas} \to x_{1/2}\right) \\ &\sim \frac{[s\delta\tau]^2}{\tau}\cdot\frac{1}{\log\left[N(s\delta\tau)^2 x_{1/2}/\tau_c\right]}. \end{aligned} \tag{9}$$

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Since 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, since $p_{\rm fix}$ 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 $x_{\rm sel} \ll x_{\rm seas}$, the mutation will reach frequency $x_{\rm sel}$ with probability $2|\bar{s}|$ and fix or go extinct deterministically as before (regardless of whether $x_{\rm seas}$ is large or small compared to $x_{1/2}$; Figure 2B). On the other hand, when $x_{\rm sel} \gg x_{\rm seas}$, selection primarily operates in the seasonal drift regime (Figure 2C), where the logarithm of the mutation frequency undergoes a *biased* random walk with mean $\bar{s}\tau$ and variance $(s\delta\tau)^2$. When $\bar{s} = 0$, seasonal drift requires roughly $\log^2(x_{1/2}/x_{\rm seas})/(s\delta\tau)^2$ pairs of epochs to carry a mutation from $x_{\rm seas}$ to $x_{1/2}$. If the relative change due to selection is small over this timescale, then selection 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

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

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.

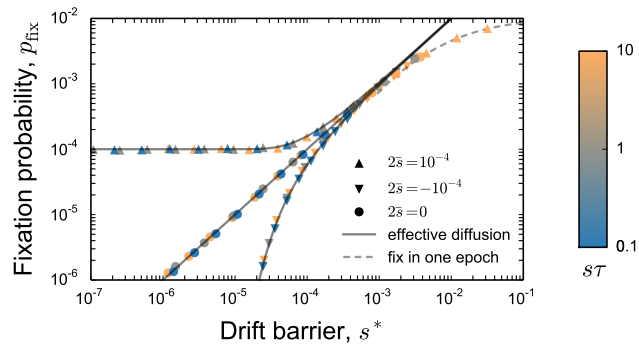

FIG. 3. The effects of environmental fluctuations on the fate of a new mutation are well summarized by a change in the drift barrier, s^*. Here, s^* is independent of the average fitness, $\bar{s}$, but depends on the population size and the dynamics of environmental fluctuations. Colored points show Wright-Fisher simulations of mutant lineages arising at random points in time, performed for a range of epoch lengths and variances in epoch time ($N = 10^8$, $s = 10^{-2}$, $\mathrm{var}(\tau)/\tau^2$ 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 within a single epoch.

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 Appendix A.

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 Appendix C. We can then average over the epoch lengths to obtain the moments of the effective diffusion equation

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

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 ($s\tau \gg 1$), since 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 wildtype 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 Appendix D that

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the moments of the effective diffusion equation are given by

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

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.

In order 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 *wildtype* frequency, starting from what is from its own perspective a beneficial epoch. 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 size of the mutant lineage at the beginning of the first full cycle it encounters. We carry out these calculations in detail in Appendix D.

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,

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

where s^* is defined in Eqs. (6) and (10). Equation (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 s^*, 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 $2|\bar{s}|e^{-2|\bar{s}|/s^*}$.

DISCUSSION

In this work, we have analyzed how temporal fluctuations in the environment alter the process by which new mutations come to dominate the population, and calculated the probability that these mutations fix. We find

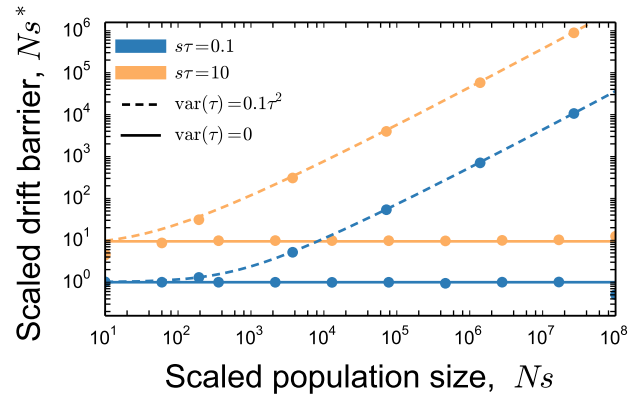

FIG. 4. The increase in drift barrier, s^*, relative to its value in a constant environment as a function of the strength of selection, Ns. Colored symbols show the results derived from Wright-Fisher simulations for an on average neutral mutant ($\bar{s} = 0$), in a changing environment, with and without variance in the epoch lengths. Lines show theoretical predictions. Fast switching ($s\tau = 0.1$) is shown in blue and slow switching ($s\tau = 10$) in orange.

that fluctuations can have a significant impact over a broad range of parameters, and our results predict how the fixation probability of a mutation depends on its fitness in each environment, the rate and predictability of environmental change, and the size of the population.

We find two main qualitative impacts of environmental fluctuations. First, fluctuations make selection less efficient at distinguishing between beneficial and deleterious mutations. This efficiency is commonly quantified by the ratio of fixation probabilities of beneficial and deleterious mutations, $p_{\rm fix}(-\bar{s})/p_{\rm fix}(\bar{s})$. We have shown here that this ratio continues to exhibit a simple exponential dependence on $\bar{s}$,

$$\frac{p_{\rm fix}(-\bar{s})}{p_{\rm fix}(\bar{s})} = e^{-2\bar{s}/s^*}, \tag{14}$$

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 the statistics of the 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 $s^* = \frac{1}{N}$, it is tempting to define an "effective population size" $N_e = 1/s^*$. This would attribute the decreased efficiency of selection to an increased variance in offspring number arising from uncertainty in the environment. However, we have shown that this intuition is misleading, since the offspring number

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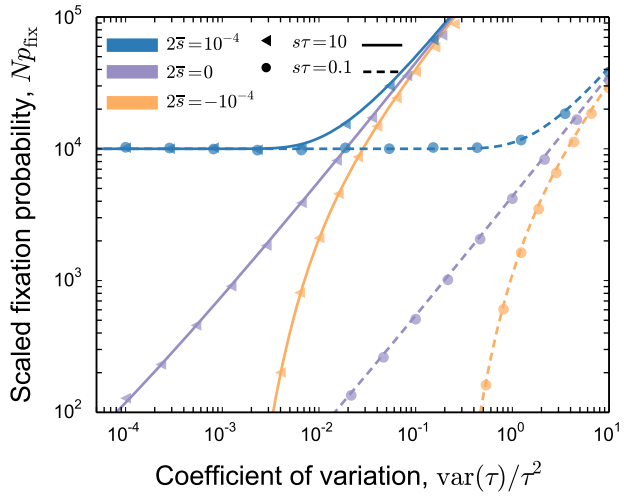

FIG. 5. The dependence of the fixation probability on the rate and regularity of environmental fluctuations. The fixation probability has been scaled by the fixation probability of a neutral mutation in a constant environment, $1/N$. In all simulations, $N = 10^8$, $s = 10^{-2}$. As the variance increases, 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.

fluctuations caused by environmental variation are highly correlated — they are the same for all mutant individuals at any given time. This leads to behavior which 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 counter-intuitive 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). This means that fluctuations can accelerate sequence divergence and increase quantities such as dN/dS even when the population is not adapting on average. 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 in a constant environment, the ratio of their fixation probabilities is given by

$$\frac{p(-\bar{s},\tau>0)}{p(\bar{s},\tau=0)} = \frac{1}{e^{\frac{2\bar{s}}{s^*}}-1} \approx \begin{cases} \frac{s^*}{2\bar{s}} & \text{if } \bar{s} \ll s^*, \\ e^{-\frac{2\bar{s}}{s^*}} & \text{if } \bar{s} \gg s^*. \end{cases} \quad (15)$$

Due to the dramatic increase in s^* by 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 to always beneficial mutations of the same average magnitude. The fate of a mutation can thus be more significantly determined by the dynamics of environmental fluctuations than by its average fitness effect, even when environmental changes are rapid enough that the mutation experiences many beneficial and deleterious epochs in its lifetime.

Our findings have important implications for the maintenance of regulatory functions in the face of a changing environment. Regulatory mechanisms (e.g. the *lac* operon) can provide an important advantage when an organism encounters a stressful environmental condition, but are typically costly otherwise [33]. Our analysis shows that even if the regulatory mechanism provides an overall benefit across environmental conditions, it can be extremely susceptible to invasion by loss-of-function mutations, since environmental fluctuations can dramatically increase the rate at which these mutations fix in the population. This can make it much more difficult for a population to maintain the regulatory phenotype, leading to a "Muller's ratchet"-like effect in which the environment-averaged fitness declines over time. Furthermore, even in very large populations it may be equally difficult to maintain regulatory traits, since the drift barrier declines only logarithmically with N when environmental fluctuations are irregular.

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 fate of a mutation is determined by its average strength of selection $N\bar{s}$ whenever it experiences *many* beneficial and deleterious epochs over the course of its lifetime (i.e. whenever $s\tau < \log(Ns)$). Our analysis, however, shows that this is only the case in a very narrow regime where environmental fluctuations are both very rapid ($s\tau \ll 1$) and extremely regular ($s\delta\tau \ll \sqrt{\tau/N}$) (see Figure 6). Whenever environmental fluctuations are long enough for there to be easily observable oscillations in frequency ($s\tau \gtrsim 1$), these lead to dramatic changes in the evolutionary process that cannot be summarized by a simple change in the effective selection coefficient. This is also true even in the opposite case when fluctuations are very rapid ($s\tau \lesssim 1$), provided that seasonal drift (which arises from the randomness in the lengths of environmental epochs) is stronger than genetic drift. Since genetic drift is weak in large populations, even very small variances in epoch lengths can lead to drastic effects. For example, recent work by Bergland et al. [2] identified numerous polymorphisms that undergo repeated seasonal oscillations

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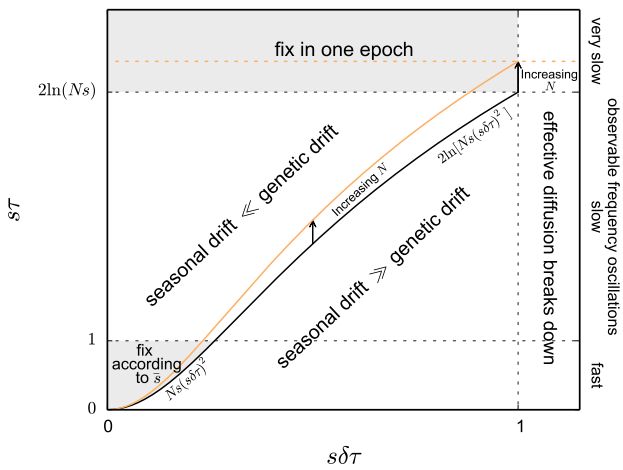

FIG. 6. Phase diagram showing the various regimes discussed in the paper, as a function of the magnitude of environmental fluctuations ($s\delta\tau$) and the average timescale of environmental fluctuations ($s\tau$). The shaded regions are the only ones in which the environmental fluctuations do not 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 natural *D. melanogaster* populations, with selective effects at least of order $Ns \sim 10^4$ in each season. For these polymorphisms, seasonal drift is thus much more significant than genetic drift as long as $\delta\tau/\tau \gg 0.01$, corresponding to variance in the length of seasons of the order of a single day.

The parameter regime in which fluctuations are important becomes broader as the population size increases (Figure 6). This occurs for two main reasons. First, fixation times are longer in larger populations, so the fates of mutations may be profoundly altered by even longer lived environmental fluctuations. Second, since genetic drift is weaker in larger populations, the regime in which seasonal drift is stronger than genetic drift broadens with an increase of the population size.

In our analysis so far, we have primarily discussed the case where mutations incur a strong pleiotropic tradeoff and the average selection coefficient is much less than $1/\tau$. When either of these conditions are violated, variable environmental conditions will often have a much more limited impact (see Appendix A). 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 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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Appendix A: Regimes not described in the main text

Extension to unequal epoch length distributions in the two environments

We have thus far assumed that the epoch length distribution is the same for both of the environments. Our approach can be extended to the asymmetric case by a redefinition of variables. Let the means of epoch lengths in the two environmental conditions be τ_1 and τ_2, with variances $\delta\tau_1$ and $\delta\tau_2$. We can then define $2\tau = \tau_1+\tau_2$, $2\bar{s}\tau = s_1\tau_1+s_2\tau_2$, $2(s\delta\tau)^2 = (s_1\delta\tau_1)^2+(s_2\delta\tau_2)^2$. As long as $\bar{s}\tau \ll s_1\tau_1, s_2\tau_2$ and $\bar{s}\tau, s\delta\tau \ll 1$, the effective diffusion equation is unchanged and all derived results extend exactly to the case of unequal epoch length distributions.

Selection pressures for which the trajectory of the mutation cannot be described as a coarse-grained diffusion process

For any choice of selection pressures, depending on the typical timescales of environmental fluctuations, there are two extreme limits. When environmental fluctuations are extremely slow, each mutant lineage fixes or goes extinct in the epoch in which it arose. In the opposite limit of extremely fast fluctuations, the mutant lineage fixes according to its average fitness. For any other timescale, the fixation probability must fall between these two limits

$$\pi(\bar{s}, N) \leq p_{\text{fix}}(s_1, s_2, N, \tau_1, \tau_2) \leq \frac{\pi(s_1, N)\tau_1 + \pi(s_2, N)\tau_2}{\tau_1 + \tau_2}. \tag{A1}$$

In the main text, we described how the probability of fixation depends on the timescale of fluctuations for a trait with a strong pleiotropic tradeoff ($s_1 > 0, s_2 < 0$, $Ns_1, N|s_2| \gg 1$), such that the change in frequency over the course of a pair of epochs due to the average fitness effect $\bar{s}$ is small ($\bar{s}(\tau_1 + \tau_2) \ll 1$). Here, we consider the cases when these conditions are violated.

No fitness tradeoff between environments

For mutations that are strongly beneficial in both environments ($Ns_1, Ns_2 \gg 1$), the fixation probabilities in the two limits and equal to $2\bar{s}$ up to exponential corrections and so the rate of substitutions ($R \propto Np_{\text{fix}}$) is independent of environmental fluctuations.

Similarly, mutations that are strongly beneficial in one environment and effectively neutral in the other ($Ns_1 \gg 1, N|s_2| \ll 1$) will fix with probability p_{fix} that is bounded by

$$\frac{\tau_1}{\tau_1 + \tau_2} 2s_1 \leq p_{\text{fix}} \leq \frac{\tau_1}{\tau_1 + \tau_2} 2s_1 + \frac{\tau_2}{\tau_1 + \tau_2} \frac{1}{N}. \tag{A2}$$

The difference between the fixation probabilities in these two limits is thus small in large populations. We can place an even lower bound on the difference between these two limits whenever the timescales of fluctuations are shorter than N (i.e. whenever the mutation has a chance to experience more than one environment). In that case, the fixation probability in the neutral environment falls exponentially with N/τ_2,

$$\frac{\tau_1}{\tau_1 + \tau_2} 2s_1 \leq p_{\text{fix}} \leq \frac{\tau_1}{\tau_1 + \tau_2} 2s_1 + \frac{\tau_2}{\tau_1 + \tau_2} \exp\left(-\frac{N}{\tau_2}\right). \tag{A3}$$

The fates of mutations that are always beneficial or occasionally neutral are thus unaffected by environmental fluctuations up to exponentially small corrections.

For mutations that are strongly deleterious in both environments ($s_1, s_2 < 0,\ N|s_1|, N|s_2| \gg 1$), Eq. (A1) becomes

$$\exp\left(-N|s_1|\frac{\tau_1}{\tau_1 + \tau_2} - N|s_2|\frac{\tau_2}{\tau_1 + \tau_2}\right) \leq p_{\text{fix}} \leq \frac{\tau_1}{\tau_1 + \tau_2} \exp\left(-N|s_1|\right) + \frac{\tau_2}{\tau_1 + \tau_2} \exp\left(-N|s_2|\right). \tag{A4}$$

Though the relative difference between these two limits can be quite large, both are exponentially small, and so the substitution rate is negligible in both of the limits, independent of the dynamics of environmental fluctuations. The evolutionary process is thus essentially independent of the fluctuations.

Similarly, mutations that are strongly deleterious in one environment, and effectively neutral in the other ($N|s_2| \gg 1, N|s_1| \ll 1$) also have negligible substitution rates whenever the timescales of fluctuations are shorter than N

$$\exp\left(-N|s_2|\frac{\tau_2}{\tau_1 + \tau_2}\right) \leq p_{\text{fix}} \leq \frac{\tau_1}{\tau_1 + \tau_2} \exp\left(-\frac{N}{\tau_1}\right) + \frac{\tau_2}{\tau_1 + \tau_2} \exp\left(-N|s_2|\right). \tag{A5}$$

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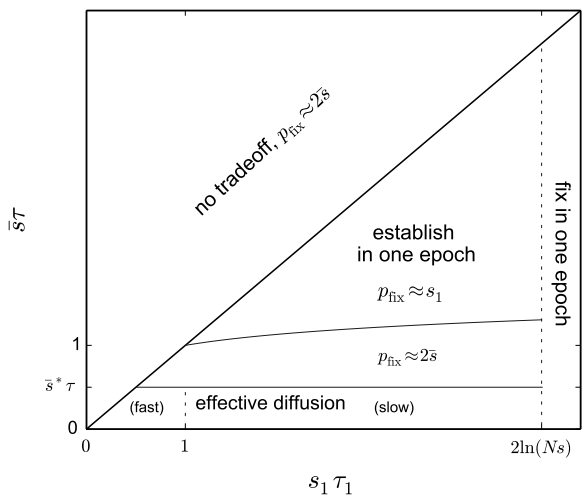

FIG. S1. Phase diagram showing the various regimes discussed in this section, as a function of $\bar{s}\tau$ and $s_1\tau_1$.

In summary, unless there is a strong tradeoff between the two environments, the substitution rate is either negligible or independent of environmental fluctuations up to exponentially small terms, and so the effects of environmental fluctuations are of limited significance.

Strong selection due to $\bar{s}$ over a pair of epochs ($|\bar{s}|\tau \gtrsim 1$)

Provided there is a strong tradeoff, $|\bar{s}|\tau \ll 1$ can be violated only in the slow switching regime ($s_1\tau_1, |s_2|\tau_2 \gg 1$) (see Fig. S1). When this happens, the effective diffusion process breaks down. Extrapolating from our previous results, we can predict that a mutation for which $\bar{s}\tau \gg 1$ will always fix once it has reached establishment, since the strength of the average selection coefficient guarantees that the frequency will deterministically increase over pairs of epochs. If $\bar{s}\tau \gg 1$ the probability of fixation is thus equal to the probability of establishment. Similarly, the frequency of a mutation for which $\bar{s}\tau \ll -1$ will deterministically decrease over pairs of epochs and its probability of fixation will be exponentially small.

A more rigorous argument can be made as follows. When the rate of environmental switching is slow, a mutation will go extinct if it arises in a deleterious epoch. If it arises in a beneficial epoch, its frequency at the end of that epoch, conditioned on establishment and averaged over the possible arising times, will be

$$x = \frac{1}{Ns_1}\frac{e^{s_1\tau_1}}{s_1\tau_1}. \tag{A6}$$

The extinction probability at the end of the next deleterious epoch can be calculated from Eq. (D4),

$$p_{\rm ext} = \exp\left[-\frac{Nsx\,\exp(s_2\tau_2)}{\exp(s_2\tau_2)-1}\right] = \exp\left[-\frac{\exp(2\bar{s}\tau)}{s_1\tau_1\left(\exp(s_2\tau_2)-1\right)}\right]. \tag{A7}$$

The mutation will deterministically go extinct by the end of the first deleterious epoch when $\bar{s}\tau \ll -1$. If $\bar{s}\tau \gg 1$, conditioned on non-extinction by the end of the first beneficial epoch, the mutation has an exponentially small probability of extinction and will deterministically grow from that point on. The probability of fixation of such a mutant is thus equal to the probability of arising and establishing in a beneficial epoch ($p_{\rm fix} = 2s_1\frac{\tau_1}{\tau_1+\tau_2}$) .

As $\bar{s}\tau$ gets smaller, this argument breaks down once the average selection coefficient is not strong enough to guarantee that the mutation will never reach the drift barrier again. This happens when $2\bar{s}\tau \sim \log(s_1\tau_1)$. Below this limit, the fixation probability is approximately $2\bar{s}$.

Note that $\bar{s} \ll s$ is a weaker condition than $\bar{s}\tau \ll 1$ and that $\bar{s} \ll s$ is thus a necessary but not sufficient condition for the effective diffusion process to be valid. For the sake of clarity in presentation, we also required that $\bar{s} \ll s$ in the fast switching case in the main text. We emphasize however that in the fast switching case, the effective diffusion process is valid independent of the relative sizes of $\bar{s}$ and s, as long as both $\bar{s}\tau \ll 1$ and $s\tau \ll 1$ are satisfied. Our fast switching results from the main text thus extend to a part of the regime in which $\bar{s} \gg s$.

The various regimes as a function of $s_1\tau_1$ and $\bar{s}\tau$ are presented in Figure S1.

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Appendix B: Extremely slow environmental switching, $\log(Ns) < s\tau$

Even in the limit of very long but finite environmental epochs, not all mutations that arise within a beneficial epoch have an equal opportunity to fix. In order to fix before the environment changes, a strongly selected mutation must arise at least of order $2\log(Ns)/s$ generations before the end of that epoch. Mutations that arise later than that will be driven to extinction during the subsequent deleterious epoch. Let T_0 denote the time from arising to the end of a beneficial epoch. The probability of fixation of a mutation is thus

$$p_{\text{fix}} = \underbrace{\frac{1}{2}}_{\substack{\text{probability that mutation arises}\\ \text{in a beneficial epoch and not a deleterious one}}} \times \overbrace{P\left[T_0 > 2\log(Ns)/s\right]}^{\text{probability that it arises early enough in epoch}} \times \underbrace{2s}_{\substack{\text{probability of fixation of}\\ \text{a new mutation with fitness } s}}. \tag{B1}$$

The the distribution of T_0 can be calculated from the distribution of epoch lengths as follows. Let the cumulative distribution of the epoch lengths be given by $F(x) = F(x, \tau, \delta\tau)$, with probability density (*pdf*) $f(x) = F'(x)$. If we assume that mutations arise uniformly in time, then mutations are more likely to arise in long epochs. The length of the epoch in which the mutation has arisen, which we denote T', thus has a *pdf* that is weighted by its length,

$$p(T') = \frac{T' f(T')}{\int_0^\infty T' f(T')} = \frac{T' f(T')}{\tau}. \tag{B2}$$

Conditioned on having arisen in an epoch of length T', the time until the end of the epoch is uniformly distributed within the epoch. The conditional *pdf* of T_0 is thus

$$p(T_0|T') = \begin{cases} \frac{1}{T'}, & T' \geq T_0 \\ 0, & T' < T_0 \end{cases}. \tag{B3}$$

Averaging over epoch lengths, we obtain the unconditional *pdf* of T_0

$$p(T_0) = \int_0^\infty p(T_0|T')p(T')dT' = \int_{T_0}^\infty \frac{1}{\tau} f(T')dT' = \frac{1 - F(T_0)}{\tau}. \tag{B4}$$

It follows that the probability of fixation of a new mutation is given by

$$p_{\text{fix}} = s\int_{2\log(Ns)/s}^\infty \frac{1 - F(x)}{\tau}dx = s\left[1 - \int_0^{2\log(Ns)/s} \frac{1 - F(x)}{\tau}dx\right]. \tag{B5}$$

There is a similar correction for mutations that arise late enough within a deleterious epoch to be able to survive until the beginning of the ensuing beneficial epoch. However, since deleterious mutations with cost s can survive at most $\mathcal{O}\left(\frac{1}{s}\right)$ generations before going extinct, this correction is of the order $\frac{1}{|s|\tau} < \frac{1}{2\log(Ns)s} \ll 1$ and can thus be neglected.

Appendix C: Fast switching, $s\tau \ll 1 \ll \log(Ns)$

For convenience, we rewrite the diffusion equation as a Langevin equation [34],

$$\frac{dx}{dt} = x(1-x)s(t) + \sqrt{\frac{x(1-x)}{N}}\eta(t), \tag{C1}$$

where $\eta(t)$ represents the noise term and has the properties $\langle\eta(t)\rangle = 0$, $\langle\eta(t)\eta(t')\rangle = \delta(t-t')$. In the Itô interpretation, this can be rewritten in the following differential form

$$dx = x(1-x)s(t)dt + \sqrt{\frac{x(1-x)\ dt}{N}}\eta(t). \tag{C2}$$

When the timescales of of environmental fluctuations are shorter than the timescale of selection, $\delta x = \int_{\text{epoch}} dx \ll x$, so we can assume that x is approximately constant over the course of a pair of epochs and coarse grain Eq. (C2) over

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an environmental cycle

$$\begin{aligned}\delta x =& \frac{x(1-x)\left(e^{(s+\bar{s})T_1+(-s+\bar{s})T_2}-1\right)}{1+x\left(e^{(s+\bar{s})T_1+(-s+\bar{s})T_2}-1\right)} + \sqrt{\frac{x(1-x)(T_1+T_2)}{N}}\eta \\ \approx& 2\bar{s}T_2\ x(1-x) + s(T_2-T_1)x(1-x) + \frac{1}{2}s^2(T_2-T_1)^2x(1-x)(1-2x) \\ &+ \sqrt{\frac{x(1-x)(T_1+T_2)}{N}}\eta.\end{aligned} \tag{C3}$$

Averaging over T_1 and T_2, we find the first two moments of δx

$$\begin{aligned}\langle\delta x\rangle &= x(1-x)2\bar{s}\tau + x(1-x)(1-2x)(s\delta\tau)^2 \\ \left\langle\delta x^2\right\rangle &= x(1-x)\frac{2\tau}{N} + 2x^2(1-x)^2(s\delta\tau)^2,\end{aligned} \tag{C4}$$

which can be rewritten as

$$\begin{aligned}\langle\delta x\rangle &= x(1-x)\frac{\tau}{N}\left[\frac{1}{x_{\text{sel}}} + \frac{1}{x_{\text{seas}}}(1-2x)\right] \\ \left\langle\delta x^2\right\rangle &= x(1-x)\frac{2\tau}{N}\left[1 + \frac{1}{x_{\text{seas}}}x(1-x)\right].\end{aligned} \tag{C5}$$

The backward equation for the fixation probability of a mutant at frequency x is thus [35]

$$\left[\frac{1}{x_{\text{sel}}} + \frac{1}{x_{\text{seas}}}(1-2x)\right]\frac{\partial p}{\partial x} + \left[1 + \frac{1}{x_{\text{seas}}}x(1-x)\right]\frac{\partial^2 p}{\partial x^2} = 0, \tag{C6}$$

which can be rearranged as

$$\partial_x \log\left[\partial_x p(x)\left|1 + \frac{1}{x_{\text{seas}}}x(1-x)\right|\right] = -\frac{\frac{1}{x_{\text{sel}}}}{1+\frac{1}{x_{\text{seas}}}x(1-x)}. \tag{C7}$$

It will be convenient to define $x_\pm$ to be the roots of $1 + x(1-x)/x_{\text{seas}}$ (i.e. $x_\pm = (1 \pm \sqrt{1+4x_{\text{seas}}})/2$). Integrating Eq. (C7), we obtain

$$\partial_x p(x) = C\frac{1}{|(x-x_+)(x-x_-)|}\left|\frac{x_+-x}{x-x_-}\right|^\lambda = C\frac{|x_+-x|^{\lambda-1}}{|x-x_-|^{\lambda+1}}, \tag{C8}$$

where we have defined $\lambda = \frac{1}{x_{\text{sel}}(x_+-x_-)}$. Finally, integrating Eq. (C8) and requiring that $p(0) = 0$ and $p(1) = 1$ gives

$$p(x) = \frac{1-\left|\frac{1-x/x_+}{x/x_- - 1}\right|^\lambda}{1-|x_-/x_+|^{2\lambda}}. \tag{C9}$$

To find the typical size of the mutant lineage at the beginning of the first full beneficial epoch it encounters, we must average over the arising times. Let t be the arising time of the mutation, either within either a beneficial epoch of length T_1 or within a deleterious epoch of length T_2. We have

$$\langle x\rangle = \frac{1}{2}\times\underbrace{\left\langle\int_0^{T_1}\frac{1}{N}e^{st-sT_2}dt\right\rangle}_{\substack{\text{mutation arises}\\ \text{in beneficial epoch}}} + \frac{1}{2}\times\underbrace{\left\langle\int_0^{T_2}\frac{1}{N}e^{-st}dt\right\rangle}_{\substack{\text{mutation arises}\\ \text{in deleterious epoch}}} \approx \frac{1}{N} + O\left(\bar{s}\tau, sdt\right). \tag{C10}$$

Since $\langle x\rangle / x_\pm \ll 1$, we can Taylor expand the expression in the numerator of Eq. (C9) to arrive at

$$p(x) \approx \frac{\lambda\ x\ \frac{x_+-x_-}{x_-x_+}}{1-|x_-/x_+|^{2\lambda}} = \frac{2\bar{s}Nx}{1-\exp\left(2\lambda\log\left|\frac{x_-}{x_+}\right|\right)}. \tag{C11}$$

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The fixation probability of a new mutation is thus

$$p_{\text{fix}} = \langle p(x) \rangle = p(\langle x \rangle) = \frac{2\bar{s}}{1 - e^{-2\bar{s}/s^*}}, \tag{C12}$$

where

$$\frac{1}{s^*} = \frac{2\tau}{(s\delta\tau)^2} \frac{1}{\sqrt{1 + \frac{4\tau}{N(s\delta\tau)^2}}} \log\left[\frac{\sqrt{1 + \frac{4\tau}{N(s\delta\tau)^2}} + 1}{\sqrt{1 + \frac{4\tau}{N(s\delta\tau)^2}} - 1}\right] = \begin{cases} N, & \frac{N(s\delta\tau)^2}{\tau} \ll 1 \\ \frac{2\tau}{(s\delta\tau)^2} \log\left(\frac{N(s\delta\tau)^2}{\tau}\right), & \frac{N(s\delta\tau)^2}{\tau} \gg 1 \end{cases}. \tag{C13}$$

Appendix D: Slow switching, $1 \ll s\tau \ll \log(Ns)$

Starting from the standard single-locus diffusion equation (Eq. (1)), we can take into account the nonlinear effects of selection over the course of a cycle by introducing the change of variable $\chi = x/(1-x)$, which transforms the original diffusion equation into the form

$$\frac{\partial f}{\partial t} = -\frac{\partial}{\partial \chi}\left[s(t)\chi f\right] + \frac{1}{2}\frac{\partial^2}{\partial \chi^2}\left[\frac{\chi(1+\chi)^2}{N} f\right]. \tag{D1}$$

The drift term is important only at very high and very low frequencies (corresponding to $\chi \ll (Ns)^{-1}$ and $\chi \gg Ns$), so we introduce a negligible error at frequencies for which $\chi \ll Ns$ by ignoring the nonlinear component in the drift term

$$\frac{\partial f}{\partial t} = -\frac{\partial}{\partial \chi}\left[s(t)\chi f\right] + \frac{1}{2}\frac{\partial^2}{\partial \chi^2}\left[\frac{\chi}{N} f\right]. \tag{D2}$$

We can derive an analogous equation that is valid whenever the frequency of the wildtype is not too high by the change of variable $\chi' = 1/(1-x)$

$$\frac{\partial f}{\partial t} = -\frac{\partial}{\partial \chi'}\left[-s(t)\chi' f\right] + \frac{1}{2}\frac{\partial^2}{\partial \chi'^2}\left[-\frac{\chi'}{N} f\right]. \tag{D3}$$

Over the course of a pair of epochs, the frequency of a mutation takes both low and high values, but we can account for the change in frequency over the entire cycle by using Eq. (D2) when $\chi \leq 1$ and Eq. (D3) when $\chi' \leq 1$ and matching the two processes at $\chi = \chi' = 1$, where they are both valid.

Concretely, let $\chi = \chi_0 \ll 1$ at the beginning of a beneficial epoch of length T_1. We would like to calculate the moments of $\delta\chi$, the total change in χ by the end of the following deleterious epoch, which has length T_2. The moment generating function of $\chi(t)$, defined as $H_\chi(z,t) = \langle \exp(-z\chi(t)) \rangle$, conditioned on $\chi(0) = \chi_0$, for an arbitrary $s(t)$ is given by [12]

$$H_\chi(z|\chi_0) = \exp\left[\frac{-z\ \chi_0\ e^{\int_0^t s(t')dt'}}{1 + \frac{z}{2N}\ e^{\int_0^t s(t')dt'} \int_0^t e^{\int_0^{t'} -s(t'')dt''} dt'}\right]. \tag{D4}$$

Thus, at some time t after the beginning of the beneficial epoch, such that $\frac{1}{s} \ll t \ll T_1$, the generating function of χ is

$$H_\chi(z, t\,|\chi_0) = \exp\left[-\frac{z\chi_0 e^{(s+\bar{s})t}}{1 + \frac{z}{2Ns} e^{(s+\bar{s})t}}\right]. \tag{D5}$$

It will be convenient to define the random variable ν_1 as $\chi(t) = \nu_1 e^{(s+\bar{s})t}$. Note that ν_1 captures all the non-deterministic changes in χ. The generating function of ν_1 is

$$H_{\nu_1}(z,t|\chi_0) = \langle \exp(-z\nu_1)\,|\chi_0\rangle = H_\chi\left(ze^{-(s+\bar{s})t}, t\,|\chi_0\right) \approx \exp\left[-\frac{z\chi_0}{1 + \frac{z}{2Ns}}\right], \tag{D6}$$

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and its mean and variance are

$$\langle \nu_1 \rangle = \chi_0, \quad \mathrm{var}\,(\nu_1) = \frac{\chi_0}{Ns}. \tag{D7}$$

The mutation reaches $\chi = 1$ at some random time $\frac{-\log(\nu_1)}{s+\bar{s}}$, or $T_1 + \frac{\log(\nu_1)}{s+\bar{s}}$ generations before the end of the beneficial epoch. From this moment on, the wildtype is the rare allele and we switch over to diffusion in χ'. Analogously to ν_1, we define a second random variable ν_2 that satisfies $\chi'(t') = \nu_2 e^{(s-\bar{s})t'}$, where t' is the time measured from the beginning of the *deleterious* epoch from the perspective of the mutation (i.e. the middle of the cycle). Subject to the initial condition that $\chi' = 1$ at $(T_1 + \log(\nu_1)/(s+\bar{s}))$ generations before the environmental shift, the generating function for ν_2 at some time t', such that $\frac{1}{s} \ll t' \ll T_2$ is

$$H_{\nu_2}(z, t|\nu_1, T_1) = \exp\left[-\frac{z\frac{1}{\nu_1}e^{-(s+\bar{s})T_1}}{1+\frac{z}{Ns}}\right], \tag{D8}$$

from which we obtain the conditional mean and variance of ν_2

$$\langle \nu_2|\nu_1, T_1\rangle = \frac{1}{\nu_1}e^{-(s+\bar{s})T_1}, \quad \mathrm{var}\,(\nu_2|\nu_1, T_1) = \frac{2}{\nu_1 Ns}e^{-(s+\bar{s})T_1}. \tag{D9}$$

Finally, we compute the generating function for χ at the end of the deleterious epoch, conditioned on it having initial value 1, $T_2 + \log(\nu_2)/(s-\bar{s})$ generations before the end of the deleterious epoch. We find

$$H_\chi\left(z|T_1, T_2, \nu_1, \nu_2\right) = \exp\left[-\frac{z\frac{1}{\nu_2}e^{(-s+\bar{s})T_2}}{1+\frac{z}{2Ns}}\right]. \tag{D10}$$

The generating function of $\delta\chi$ can be obtained from Eq. (D10) by noting that $H_{\delta\chi}(z,t) = e^{z\chi_0}H_\chi(z,t)$, which yields the conditional moments of $\delta\chi$

$$\begin{aligned}\langle \delta\chi|T_1, T_2, \nu_1, \nu_2\rangle &= \frac{1}{\nu_2}e^{-(s+\bar{s})T_2} - \chi_0,\\ \left\langle \delta\chi^2|T_1, T_2, \nu_1, \nu_2\right\rangle &= \frac{x_0}{Ns} + \frac{2}{2Ns}\left(\frac{1}{\nu_2}e^{-(s+\bar{s})T_2} - \chi_0\right) + \left(\frac{1}{\nu_2}e^{-(s+\bar{s})T_2} - \chi_0\right)^2.\end{aligned} \tag{D11}$$

The unconditional moments are obtained by averaging over ν_1, ν_2, T_1, and T_2. In doing this we note that T_1, T_2 and ν_1 are independent, and that T_2 and ν_2 are independent. We make use of the fact that the the standard deviations of all variables are much smaller than their means as long as $\bar{s}\tau \ll 1$ and $s\tau \ll 1$. To lowest order

$$\begin{aligned}\langle \delta\chi\rangle &= \chi_0\left[2\bar{s}\tau + (s\delta\tau)^2 + \frac{2e^{s\tau}}{Ns}\chi_0\right]\\ \left\langle \delta\chi^2\right\rangle &= 2\chi_0\left[\chi_0(s\delta\tau)^2 + \frac{1}{Ns}\left(1+\chi_0^2 e^{s\tau}\right)\right].\end{aligned} \tag{D12}$$

When $x \ll 1$, $\chi \approx x$, so the moments of δx in this limit are

$$\begin{aligned}\langle \delta x\rangle &= x\left[2\bar{s}\tau + (s\delta\tau)^2 + x\frac{2e^{s\tau}}{Ns}\right]\\ \left\langle \delta x^2\right\rangle &= 2x\left[x(s\delta\tau)^2 + \frac{1}{Ns}\left(1+x^2 e^{s\tau}\right)\right],\end{aligned} \tag{D13}$$

which we rewrite as

$$\begin{aligned}\langle \delta x\rangle &= x\frac{\tau}{N}\frac{\tau_c}{\tau}\left[\frac{1}{x_{\mathrm{sel}}} + \frac{1}{x_{\mathrm{seas}}} + 2\frac{x}{x_{1/2}^2}\right]\\ \left\langle \delta x^2\right\rangle &= 2x\frac{\tau}{N}\frac{\tau_c}{\tau}\left[1 + \frac{x}{x_{\mathrm{seas}}} + \left(\frac{x}{x_{1/2}}\right)^2\right].\end{aligned} \tag{D14}$$

The expressions for the moments of the effective diffusion in the slow and fast switching limits (given by Eq. (D14) and Eq. (D14)) are equivalent up to the term proportional to $x_{1/2}^{-2}$. This term arises from the amplification of the

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effects of drift in the middle of the environmental cycle and is thus negligible in the fast switching limit. To solve the backward equation and obtain an expression for $p(x)$, we proceed analogously to Appendix C. Defining $x_\pm$ as the roots of the polynomial $1+\frac{x}{x_{\rm seas}}+\left(\frac{x}{x_{1/2}}\right)^2$ and $\lambda=\frac{x_{1/2}^2}{x_{\rm sel}(x_+-x_-)}$, we arrive at

$$p(x)=C\left(\frac{1-\frac{x}{x_-}}{1-\frac{x}{x_+}}\right)^\lambda+D. \tag{D15}$$

Applying the boundary condition $p(0)=0$ and requiring that at $x_{1/2}$ the probability of fixation of the mutation (and its derivative) is continuous with the probability of extinction of the wildtype at the same frequency, we arrive at

$$p(x)=\frac{\left(\frac{1-\frac{x}{x_-}}{1-\frac{x}{x_+}}\right)^\lambda-1}{\left(\frac{1-\frac{x_{1/2}}{x_-}}{1-\frac{x_{1/2}}{x_+}}\right)^{2\lambda}-1}, \tag{D16}$$

which reduces to

$$p(x)=\frac{\frac{x}{x_{\rm sel}}}{\left(\frac{1-\frac{x_{1/2}}{x_-}}{1-\frac{x_{1/2}}{x_+}}\right)^{2\lambda}-1} \tag{D17}$$

when $x\ll 1$.

To find the probability of fixation of a new mutation arising at an arbitrary point in time, we must again average over the possible frequencies at the beginning of the first deleterious epoch. In the slow switching limit, $s\delta\tau\ll 1$ and $s\tau\gg 1$ imply $\delta\tau\ll t$. To first order in $\delta\tau/\tau$, the time from when the mutation arises to the first switch is uniformly distributed

$$p^*(T)=\frac{\theta(\tau-T)}{\tau}. \tag{D18}$$

Following the same approach as in Appendix C, the typical frequency of the mutation at the beginning of the first full beneficial epoch it encounters is

$$\langle\chi\rangle=\frac{1}{2}\times\underbrace{\left\langle\int_0^{T_1}\frac{dt}{\tau}\frac{1}{N}e^{sT_1-sT_2}\right\rangle}_{\text{mutation arises in beneficial epoch}}+\frac{1}{2}\times\underbrace{\left\langle\int_0^{T_2}\frac{dt}{\tau}\frac{1}{N}e^{-st}\right\rangle}_{\text{mutation arises in deleterious epoch}}=\frac{1}{Ns\tau}+O\left(\bar{s}\tau,\delta\tau s,\frac{\delta\tau}{\tau}\right). \tag{D19}$$

The fixation probability of a new mutation is therefore

$$p_{\rm fix}=p(\langle x\rangle)=\frac{2\bar{s}}{1-e^{-2\bar{s}/s^*}}, \tag{D20}$$

where

$$\frac{1}{s^*}=\frac{2Ns\tau x_{1/2}^2}{x_+-x_-}\log\left[\frac{1-\frac{x_+}{x_{1/2}}}{1-\frac{x_-}{x_{1/2}}}\right]=\begin{cases}\frac{\pi}{4}\,2Ns\tau e^{-s\tau/2} & \text{if } (s\delta\tau)^2\ll\frac{e^{s\tau/2}}{Ns}\\ \frac{2\tau}{(s\delta\tau)^2}\log\left(Nse^{-s\tau/2}(s\delta\tau)^2\right) & \text{if } (s\delta\tau)^2\gg\frac{e^{s\tau/2}}{Ns}\end{cases}. \tag{D21}$$