Fitness in time-dependent environments includes a geometric contribution

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Phenotypic evolution implies sequential fixations of new genomic sequences. The speed at which these mutations fixate depends, in part, on the relative fitness (selection coefficient) of the mutant vs. the ancestor. Using a simple population dynamics model we show that the relative fitness in dynamical environments is not equal to the fitness averaged over individual environments. Instead it includes a term that explicitly depends on the sequence of the environments. This term is geometric in nature and depends only on the oriented area enclosed by the trajectory taken by the system in the environment state space. It is related to the well-studied geometric phases in classical and quantum physical systems. We discuss possible biological implications of these observations, focusing on evolution of novel metabolic or stress-resistant functions.

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I. INTRODUCTION

Organisms react to long-term changes in environmental conditions by sequential fixation of new genome sequences, mostly corresponding to increasingly more adapted phenotypes. However, often environmental changes are faster than the characteristic time for mutation-selection cycles needed to evolve an optimal phenotype. In such cases, depending on the structure and time scales of the fluctuations, a dynamic environment creates dynamic fitness landscapes [1], promotes sensing [2], modularity [3, 4], switching [5], and can change the speed of adaptation [6, 7].

The effect of fluctuating selection and/or population size on the population-genetics dynamics has been extensively studied over the years [7, 8], starting with the introduction of the concept of adaptive topography by Wright [9]. More recently, the evolutionary dynamics of density regulated populations in fluctuating environments has been elucidated in ecologically realistic models [10, 11]. These bridge the gap between the classical population dynamics exhibiting very diverse responses to fluctuating environments [12, 13, 14] and classical population genetics models. However, a complete understanding of the effect of fluctuations on population and evolutionary dynamics has not been achieved yet.

Some of the relevant parameters describing evolutionary response of a population to a changing environment are the rate at which new genotypes are created (mutation rate), the relative fitness of new phenotypes, and the total population size. We concentrate on the case of environments changing on scales longer than an individual’s lifetimes. This is relevant, in particular, for bacterial populations confronted with daily environmental changes (natural or artificial) [15], for longer-living organism affected by seasonal variations, or for pathogens experiencing transmission, uncontrolled growth in a new host, and then effects of the host immune system. For example, in the now-classic long-term *E. coli* evolution experiment [16], bacterial cultures are diluted daily, and the environment (i.e., cell growth and death rates) changes during dilution events and between them due to depletion of resources, cell density growth, and cell-to-cell interactions. These experiments are a great model to study clonal competition [17]. Interestingly, the number of accumulated beneficial mutations is relatively small, considering that every single point and many possible double mutations have happened thousands of times in the 25-year history of the experiment. This discrepancy is likely largely accounted for by strong bottlenecks at dilution times, when most new mutations disappear by chance. However, all clones, even beneficial ones, experience additional huge fluctuations in their reproductive rates during the course of the experiment. It remains to be seen if such fluctuations can contribute to the slowing down of the evolutionary adaptation as well.

In this article, we make a step in this direction by studying effects of fluctuating environments (represented by birth and death rates) on the effective selection coefficient. Using analytic and computational tools, we investigate a model of a heterogeneous population (a background strain and a newly emergent mutant) under the assumption that the time scales of the clonal frequency dynamics on the one hand and the environment fluctuation on the other are both much larger than the division

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time, but not necessary well separated from each other. We start by showing that the selection coefficient in an infinitely slow changing environments is given by a time-average of static selection coefficients corresponding to each environment. However, for environments varying at a slow but finite rate, such time-average is not the whole story. A new contribution emerges. For example, in a cyclically oscillating environment, this contribution to the selection coefficient is independent of the speed of variation and depends only on the sequence of environments visited during each cycle. The contribution is non-zero only for nontrivial coupling between the environment and the population dynamics, represented as a multi-dimensional trajectory in the space of birth and death rates. The contribution changes sign when the sequence of the visited environments is reversed. It is largely independent on the speed of the dynamics. Finally, it scales quadratically with the amplitude of the environmental fluctuations. In other words, the contribution is geometric in nature. We believe that this has not been noticed before in the context of population dynamics.

We will focus on the deterministic approximation to population dynamics. Geometric effects are well-known for slowly changing deterministic dynamical systems \[18\] \[19\]. While evolutionary dynamics of a population driven together by forces of mutation, drift and selection cannot be accurately described deterministically, we believe that our model is meaningful even for a stochastic case for large population, low mutation rate, and strong selection. Indeed, the recent observation that stochastic dynamical systems are also subject to geometric corrections suggests that deterministic vs. stochastic treatment of population dynamics is not crucial for the phenomenon \[20\] \[21\].

In what follows, we develop our results in a relatively simple two species population model with bilinear, symmetric competition, which we believe is general enough to capture the main effects of fluctuations for a large class of related models. We first solve the system in the limit of small differences between the birth and the death rates of the competing species. We derive expressions for the selection coefficient in the limit of stationary, very slowly continuously, and infrequently discontinuously varying environments. The selection coefficient for arbitrary time scale of the environment fluctuations can be derived then using a perturbative approach.

\[ \] II. MODEL

Let \( x_i \) be the number of individuals of genotypes \( i, i = 1, 2 \), in a large asexual population. We assume that \( x_1 \gg 1 \), so that demographic (phenotypic) fluctuations and random genetic drift can be neglected. We refer to \( x_1 \) as an ancestral phenotype, and to \( x_2 \) as a mutant. The competition between the two is described by a driven two-dimensional Lotka-Volterra (logistic) model

\[
\dot{x}_1 = x_1 \left[ b_1(t) - d_1(t) (x_1 + x_2) \right], \\
\dot{x}_2 = x_2 \left[ b_2(t) - d_2(t) (x_1 + x_2) \right].
\] (1)

Here \( b_i(t) \) represents the birth rates, and \( d_i(t) \) parameterize the death rates for each of the genotypes. Generally, all parameters are time dependent.

Following classical models of ecological population genetics, we view our model as a particular form of the more general dynamics. Defining the total population size, \( x(t) = x_1(t) + x_2(t) \), we write

\[
\dot{x}_1 = x_1 g_1(x,t), \\
\dot{x}_2 = x_2 g_2(x,t).
\] (2)

Here \( g \) is the generalized growth rate. For this system of equations to represent the dynamics of a realistic self-sustaining population, \( g_i(x) \) must be negative for large \( x \), and it must have at least one zero. Our approach applies to a very general subset of such growth rate functions provided that the system, Eq. (3), has exactly one fixed point on each of the axes \( x_i = 0 \) in addition to the trivial unstable extinction point \( (0,0) \).

One traditionally takes \[12\]

\[
g_i = r_i(t) \left[ 1 - \frac{f(x)}{f(K_i(t))} \right],
\] (3)

where \( r_i \)'s are the intrinsic maximum growth rates of each genotype, if unconstrained by limited resources. The terms \( r_i f(x)/f(K_i(t)) \) represent the reduction of these rates due to competition for resources. This reduction depends only on the total population size \( x(t) \) and on \( K_i \), which are stable total populations of the isolated phenotypes \( i \) supported by stationary resource-limited environments. \( K_i \)'s are referred to as the carrying capacities. Our approach applies for any non-negative, monotonously increasing \( f(x) \), as explained above. However, for simplicity, we now concentrate on \( f(x) = x \). In this case, the competition is linear and symmetric, and the simple Lotka-Volterra model \[4\] is recovered with \( b_i(t) = r_i(t) \) and \( d_i(t) = r_i(t)/K_i(t) \).

We are interested in modeling competition of the ancestral genotype with the mutant one. The two are very close in the genotype space, essentially one mutation away. Since mutation effects are, in general, small \[17\], we assume that the differences between \( g_1 \) and \( g_2 \) are also small,

\[
\left| \frac{g_1(x,t) - g_2(x,t)}{g_1(x,t) + g_2(x,t)} \right| \leq \epsilon \ll 1.
\] (4)

This corresponds to small differences in the parameters \( b_i, d_i, r_i, K_i \). We assume this from now on. In particular, it is possible that differences between the mutant and the ancestor parameters at any particular time are much smaller than the variations of each of the parameters over time.
III. PRELIMINARIES

In order to determine the conditions under which the mutant, initially present in small numbers relative to the ancestor, invades the population, we explicitly integrate the model, Eq. (1). We write the dynamics of the total population size \( \dot{x} = x_1 + x_2 \):

\[
\dot{x} = x \left( b(t)x_1 + \frac{b_2(t)x_2}{x} \right) - \left( \frac{d_1(t)x_1}{x} + \frac{d_2(t)x_2}{x} \right) x,
\]

To the zeroth order in \( \epsilon \ll 1 \), this does not depend on the individual values \( x_1 \) and \( x_2 \):

\[
\dot{x} = x \left[ b(t) - d(t) x \right] + O(\epsilon),
\]

where we have defined

\[
b(t) = \frac{b_1(t) + b_2(t)}{2}, \quad d(t) = \frac{d_1(t) + d_2(t)}{2}.
\]

We also define

\[
p = \frac{x_2}{x_1 + x_2},
\]

the fraction of the mutant in the whole population. This obeys

\[
\dot{p} = p(1 - p) \left\{ \left[ b_2(t) - b_1(t) \right] - \left[ d_2(t) - d_1(t) \right] x \right\}.
\]

The model then reduces to

\[
\begin{align*}
\dot{x} &= x \left[ b(t) - d(t) x \right], \\
\dot{p} &= p(1 - p) \left[ \delta b(t) - \delta d(t) x \right],
\end{align*}
\]

where we have used the notation \( \delta(b, d) \) for small (order \( \epsilon \)) time dependent differences between the corresponding mutant and ancestral rates. To simplify the notation, for any pair of parameters \( (P_1, P_2) \) describing the ancestor and the mutant, we write \( \bar{P} = (P_1 + P_2)/2 \), and \( \delta \bar{P} = \bar{P} - P_1 \). In addition we always assume \( |\delta \bar{P}/\bar{P}| = O(\epsilon) \ll 1 \).

To the zeroth order in \( \epsilon \), the dynamics of the total population size defined by Eqs. (1) is now uncoupled from the dynamics of the mutant fraction

\[
x(t) = \frac{x(0)e^{\int_{\tau}^{t}\delta b(\tau)}}{1 + x(0)\int_{-\infty}^{t}dt'd(\tau')e^{\int_{t'}^{t}\delta b(\tau')}}.
\]

Due to the small variation assumption, Eq. (4), \( p(t) \) changes on time scales much longer than \( x(t) \). On these time scales, \( x(t) \) converges to a unique (up to the first order in \( \epsilon \)) attractor \( x_n(t) \), independent of the initial conditions,

\[
x_n(t) = \frac{1}{\int_{-\infty}^{t}dt'd(\tau')e^{\int_{t'}^{t}\delta b(\tau')}}.
\]

Then the slower dynamics of \( p \) is

\[
\logit p(t) = \logit p(0) + \int_{0}^{t}d\tau \left[ \delta b(\tau) - \delta d(\tau) x(\tau) \right],
\]

where \( \logit p = \log p - \log(1 - p) \). The obvious first lesson from this equation is that the clone with the largest average growth rate, \( \langle g_i \rangle \geq \frac{1}{T} \int_{0}^{T}dt \left[ b_i(t) - d_i(t)x(t) \right] \) for some large \( T \), will have an advantage.

IV. SELECTION COEFFICIENT

For coefficients varying periodically with a period \( T \), we write for the logarithmic change of the mutant-to-ancestor ratio, \( \logit p \), over time \( T \gg T \),

\[
\Delta(T) \equiv \logit p(T) - \logit p(0) = \frac{T}{T} \int_{0}^{T}d\tau \left[ \delta b(\tau) - \delta d(\tau) x(\tau) \right] \equiv sT,
\]

where the last equality defines the selection coefficient, \( s \). It is the sign of \( s \) that decides the stability of the fixed points \( p = 1 \) and \( p = 0 \). For example, for \( s > 0 \), \( p = 0 \) is unstable, and the mutant phenotype invades the population towards a stable fixed point \( p = 1 \).

In a constant environment, and for \( \epsilon \ll 1 \), the selection coefficient \( s \) can be rewritten in terms of the ecological parameters defined in Eq. (3)

\[
s \approx \frac{\delta K}{K}.
\]

We have a classical result that selection favors phenotypes with larger carrying capacities (larger \( K_i \)) independent of the magnitude of the intrinsic growth rates \( r_i \) [10, 11]. To derive this, we rely on the fact that the total population is given at all times by \( K \), and it is independent of the frequency of the mutants in the population.

In this paper, we are interested in the values of the selection coefficient for temporally varying environments. As a consequence, the selection coefficient is now given by the interaction between several varying quantities. To simplify the discussion, we focus on limiting cases of large time scale separation between the environment fluctuations and individual lifetimes.

In the regime of infinitely fast environmental fluctuations, for \( T \to \infty \), we approximate the general driven model, Eq. (2), as

\[
\begin{align*}
\dot{x}_1 &= x_1(g_1(x))_T, \\
\dot{x}_2 &= x_2(g_2(x))_T.
\end{align*}
\]

We assume here that the environment variation attains a well defined, constant average for every state \((x_1, x_2)\). We denote this by \( \langle \ldots \rangle_T \), where the subscript \( T \) stands for averaging over a period. We assume that \( x \) does not change appreciably over this time. For the specific case of the Lotka-Volterra model, the selection coefficient for fast fluctuations, \( s_f \), can be computed using the formula for the constant case, Eq. (4), keeping in mind that one has to use the average values of the relevant coefficients:

\[
s_f = \delta(r) - \delta(r/K) \frac{\langle r \rangle}{\langle r/K \rangle}.
\]
In the opposite limit of an infinitely slow parameter variation, the total population is equal to the carrying capacity at all times, \( x(t) = K(t) \). In this case, the quasi-stationary (qst) selection coefficient \( s \) is

\[
s_{\text{qst}} = \frac{1}{T} \int_0^T dt \frac{r(t)}{K(t)} \delta K(t) = \frac{1}{T} \int_0^T dt \, s(t),
\]

where the period \( T \) is much longer than the individual’s lifetime. This allows for a proper average to be attained.

In both limits, the sign of the selection coefficient does not depend on the average carrying capacity \([11, 12]\). Indeed, it is possible to have a slowly varying environment, in which the mutant has, on average, a larger carrying capacity but a lower fitness. In both limits, the selection coefficient becomes independent of the speed of environmental variations, and it is symmetric with respect to time reversal for the driving parameters.

\[ \text{V. CONTINUOUS, DETERMINISTIC, OSCILLATORY ENVIRONMENTS} \]

We now proceed to a more realistic case of an environment fluctuating slowly, but not infinitely slowly, compared to an individual’s lifetime. This condition allows us to derive a perturbative approximation for the selection coefficient valid when \( b(t), r(t) \gg \frac{1}{T} \) are satisfied at every \( t \). Our approximation is based on a simplified solution for the dynamics of the total population size \( x_a(t) \), Eq. [11]. By making a variable change \( y(t) = \int_0^t d\tau \, b(\tau) \), we write

\[
x_{a}(y) = \int_{-\infty}^{y} dz \frac{e^{-z}}{K(z)} = \int_{-\infty}^{y} dz \frac{1}{K(z)} e^{-y(z-z)}.
\]

In the limit of slow environmental changes, the carrying capacity \( K(y) \) varies slowly, and the integral in the denominator is dominated by the value of \( 1/K(z) \) around \( z = y \). In this regime,

\[
1 \frac{1}{K(z)} \simeq 1 \frac{K'(y)}{K^2(y)} (z-y) \quad \text{for} \quad (y-z) \ll y.
\]

Using Eq. [19], we now derive an approximation for the total population trajectory \( x_a \) valid in the qst regime. We denote it as \( x_{\text{qst}} \),

\[
x_{\text{qst}}(t) \simeq K(t) - \frac{K'(t)}{r(t)}.
\]

This solution represents the correction to the quasi-stationary result \( x_{\text{qst}}(t) = K(t) \) as a first order perturbation in the small ratio between the rate of change of the environment and the typical rate of change of the total population. Note that the approximation is consistent with the intuition that the instantaneous total population falls behind the instantaneous carrying capacity.

The selection coefficient can be expressed now as

\[ s = s_{\text{qst}} + s_{\text{geom}}, \]

where

\[
s_{\text{geom}} = \frac{1}{T} \int_0^T d\tau \left[ \frac{\delta r(\tau)}{r(\tau)} - \frac{\delta K(\tau)}{K(\tau)} \right] K'(\tau) \frac{s(t)}{K(t)}
\]

is a geometric contribution to the selection rate. The geometric nature of this term can be better understood if we express the change in the mutant-to-ancestor ratio as

\[
\Delta(T) = s_{\text{qst}} T + \Delta_{\text{geom}}(T).
\]

We note that, for any reparameterization of time, \( \lambda = \lambda(t) \), \( \Delta_{\text{geom}} \) can be written in a very similar form

\[
\Delta_{\text{geom}}(T) = \int_0^{\Lambda(T)} d\lambda \left[ \frac{\delta r(\lambda)}{r(\lambda)} - \frac{\delta K(\lambda)}{K(\lambda)} \right] K'_{\lambda} \frac{s(t)}{K(t)}
\]

which emphasizes that it depends on the trajectory itself, \( \lambda_{1,2}(\lambda) \), \( K_{1,2}(\lambda) \), rather than on how this trajectory is traversed. As any closed contour integral expression, this expression can be transformed into a surface integral over any 2D domain bounded by the trajectory \( [r_1(t), r_2(t), K_1(t), K_2(t)] \) in the parameter space. In particular, using variables

\[
\chi = \delta \log \frac{r}{K}, \quad \gamma = \log K
\]

and the Stokes theorem, we can equate \( \Delta_{\text{geom}}(T) \) with the oriented area bounded by the trajectory for times \( t \in (0, T) \) in the plane \( (\chi, \gamma) \).

In other words, \( \Delta_{\text{geom}} \) is a truly geometric term in the spirit of geometric phases in quantum or classical mechanics [15, 19]. The geometric nature of the change in the population composition over long times, Eq. (24), is the main result of the paper. It allows us to make important macroscopic predictions about the population dynamics that will hold generally irrespective of the microscopic details of the model. First, the geometric changes in the relative fraction of the mutant depend on the sequence of the environmental states in addition to their identity: same environmental states may have very different effects depending on the order in which the states are visited. At an extreme, a reversal of the order (time-reversal) would change the sign of the geometric contribution, which may make a deleterious mutation advantageous, and vice versa. To our knowledge, such dependence of the effective selection coefficient on the sequence of the environmental states has not been noticed before in population biology. Second, the contribution to \( \Delta_{\text{geom}} \) depends only on the oriented area covered in the parameter space (and thus, in particular, on the number of periodic oscillations), but not on the speed of traversal of the trajectory. Figure [13] illustrates these features: even when the environmental dynamics involves backtracking,
FIG. 1: Mutant fraction as a function of time for two sample environment trajectories \((X(t), Y(t))\): \(X_1(t) = 0.02\sin[\omega_1 t + \sin(\omega_1 t)]\), \(Y_1(t) = 1 + 0.1\cos[\omega_1 t + \sin(\omega_1 t)]\) and \(X_2(t) = 0.02\sin[\omega_2 t + 2.5\sin(\omega_2 t)]\), \(Y_2(t) = 1 + 0.1\sin[\omega_2 t + 2.5\sin(\omega_2 t)]\) where \(\omega_1/1.4 = \omega_2 = 2\pi/40\). (A) The two trajectories for \(Y = \log K\) are shown; the first has the frequency 1.4 times the second, and the second reverses twice before completing the full cycle. (B) Nonetheless, the shapes of the trajectories \((X(t), Y(t))\) are the same for both examples. (C) Instantaneous and one-period-averaged mutant fractions for both trajectories. The average growth of \(\Delta\), given completely by a geometric term, is linear. The slopes of the two curves are different by exactly 1.4, so that \(\Delta\) is only dependent on the number of elapsed periods. This is indicated by the horizontal line connecting the two averages delayed by the same number of periods. Thus the geometric contribution to the mutant fraction depends only on the shape of the contour in the parameter space and on the number of cycles, but is independent of the speed of the trajectory traversal.

FIG. 2: Illustration of the geometric nature of the mutant fraction dynamics. (A) Three different trajectories \((X(t), Y(t))\): \(X_1(t) = -0.02\cos(\omega t), \) \(Y_1(t) = 1 + 0.1\sin(\omega t), \) \(X_2(t) = 0.01\cos(\omega t), \) \(Y_2(t) = 1 + 0.1\sin(\omega t), \) \(X_3(t) = 0.02\cos(\omega t), \) \(Y_3(t) = 1 + 0.1\sin(2\omega t)\) where \(\omega = 2\pi/100\). The second trajectory (solid line) encloses exactly half the area of the first (dotted line), and the two are traversed in opposite directions. The oriented area enclosed by the third trajectory (dash-dotted) is zero. (B) The average mutant fraction change for the first trajectory is equal to the oriented area and is, therefore, twice that for the second one, and in the opposing direction. The quantity is zero for the third trajectory. The state occupied between \(t_a\) and \(t_{a+1}\) will be denoted by \(\mu_a\). We assume that the interval \((t_{a+1} - t_a)\) is long enough so that the total population \(x(t)\) reaches the carrying capacity long before the environment switches again, that is \(1/r_{\mu a} \ll (t_{a+1} - t_a)\). In this case one can derive the qst contribution as a sum over all of the environment states

\[
\Delta_{\text{qst}} = \sum_a r_{\mu a} \frac{\delta K^{\mu a}}{\bar{K}^{\mu a}} (t_{a+1} - t_a).
\]

At each switch, there is an extra contribution because \(x(t > t_a)\) reaches the value \(K^{\mu a}\) with a delay. That is, from Eq. (10), we derive:

\[
x(t_a < t < t_{a+1}) = K^{\mu a} \left[ \frac{K^{\mu a} - K^{\mu a-1}}{K^{\mu a-1}} - r^{\mu a}(t^* - t) \right]^{-1}.
\]

Integrating Eq. (27) results in a geometric contribution after \(M\) environment state changes

\[
\Delta_{\text{geom}}(T) = \sum_a \left[ \frac{\delta r^{\mu a}(\lambda)}{r^{\mu a}(\lambda)} - \frac{\delta K^{\mu a}(\lambda)}{K^{\mu a}(\lambda)} \right] \log \left[ \frac{K^{\mu a}(\lambda)}{K^{\mu a-1}(\lambda)} \right].
\]

The fact that Eq. (28) is independent of the actual time spent in each state and depends only on the sequence of environmental states is the signature of its geometric nature, illustrated in Fig. 3. Importantly, unlike in the continuous variation case, Eq. (24), \(\Delta_{\text{geom}}\) in Eq. (28) can have a finite value even if parameters change only between two states. Hence it is unclear if the contribution can be interpreted as an oriented area enclosed by the trajectory in the parameter space.

VI. SWITCHING AMONG DISCRETE ENVIRONMENT STATES

The approach can be extended to a more common model of piecewise constant environments, see e.g., Refs. [2, 7]. Consider the case of parameters abruptly changing between \(m\) sets indexed by \(\mu = 1 \ldots m\), \((r_1^\mu, r_2^\mu, K_1^\mu, K_2^\mu)\), at possibly random times \(t_a\).
Now using suitable continuity properties of the parameters’ trajectory, we transform the geometric contribution to
\[
\Delta_{\text{geom}}(T) = \int_0^T dt \sum_{\alpha=1}^A \sum_{\beta=\alpha+1}^A (\kappa_{\beta\alpha} - \kappa_{\alpha\beta}) \gamma_\alpha(t) \dot{\gamma}_\beta(t).
\]  

(31)

The geometric properties of \( \Delta_{\text{geom}} \) are clear from Eq. (31): \( \Delta_{\text{geom}}(T) \) depends only on the length of the parameters’ trajectory, is antisymmetric with respect to time reversals, and is nonzero only if multiple parameter vary simultaneously and incoherently. Note that Eq. (31) is valid only for parameter variations with small (bounded) speeds. Therefore, if the parameter dynamics, \( \gamma_\alpha(t) \), are modeled as multidimensional Wiener processes, care must be taken to regularize and properly define the stochastic integrals in Eqs. (29, 31).

Equations (29) and (31) represent a natural extension of the geometric correction to acyclic trajectories. While now the geometric term \( \Delta_{\text{geom}}(T) \) is aperiodic, for parameters dynamics with a stationary distribution of \( \gamma_\alpha \) and \( \dot{\gamma}_\alpha \), \( \Delta_{\text{geom}}(T) \) still has a mean linear dependence on \( T \) for large times:
\[
\lim_{T \to \infty} \frac{\Delta_{\text{geom}}(T)}{T} = \sum_{\alpha=1}^A \sum_{\beta=\alpha+1}^A (\kappa_{\beta\alpha} - \kappa_{\alpha\beta}) \left. \frac{dC_{\alpha\beta}(t)}{dt} \right|_{t=0},
\]

(32)

where \( C_{\alpha\beta}(t) = \langle \gamma_\alpha(0) \gamma_\beta(t) \rangle \) are time dependent correlations of the environment. Note that the derivatives \( \frac{dC_{\alpha\beta}(t)}{dt} \) are inversely proportional to the correlation times of the process. Moreover one can identify the terms in the rhs of Eq. (32) as products of the Berry curvature, \( \kappa_{\beta\alpha} - \kappa_{\alpha\beta} \), previously introduced in the classical and quantum geometric phases literature [18, 21], and, for \( \alpha \neq \beta \), the rates of growth of the oriented areas bounded by the process \( \frac{dC_{\alpha\beta}(t)}{dt} \) at \( t=0 \).

VIII. POSSIBLE EXPERIMENTAL EFFECTS

The existence of geometric corrections to fitness in a time dependent environment requires that changes in the environment are felt by the population on multiple time scales. In the model, Eq. (1), the immediate change in the growth rates and the delayed effect of the population reaching the carrying capacity provide these scales, but other mechanism would work as well. Similar effects will be encountered in almost any situation when a population responds to asynchronous changes in multiple external stresses or nutrient supplies. Therefore, the geometric effects must be considered when modeling emergence or fixation of new metabolic or stress-resistance functions in the presence of environmental changes. We suggest that the relative timing of fluctuations of extracellular nutrient/stressor concentrations will affect the relative fitness advantage of these functions.
FIG. 4: Simulated dynamics of the logarithm of the relative population size for two partially antibiotic resistant populations competing for the same consumable carbon source in a chemostat. The concentration of the antibiotic changes as \( A(t) = 0.1 + 0.1 \cos(\omega t + \phi) \). The nutrient is cleared by the chemostat and consumed by both strains in proportion to the population growth, resulting in the concentration \( \nu(t) \). The growth rate of either population is proportional to \( V (1 + A/K_A)^{-1} (1 + K_v/\nu)^{-1} \). \( V \) is the maximum growth rate, \( K_v \) is the Monod growth constant, and \( K_A \) is related to the minimal inhibitory concentration for the antibiotic. \( K_A \) for the more resistant strain is 14\% higher than for the less resistant one, but its \( V \) is 5\% smaller to account for the cost of resistance \[23\]. The numbers are chosen such that the average growth for very slow environmental changes (solid line) is almost the same for both strains. Depending on the phase \( \phi \) (dashed and dash-dotted lines), either the resistant or the non-resistant strain has the higher growth rate and will eventually take over the population. The “difference” line shows the nearly linear difference between the strain fractions for the two opposite environmental trajectories.

Of a particular interest is emergence of antibiotic resistance in bacteria. Mutations conferring antibiotic resistance often decrease ability of cells to grow in the absence of antibiotics, but provide a growth advantage in their presence \[24\]. At the same time, delivery of antibiotics is hardly ever uniform, and nutrient supplies also fluctuate. Focusing for simplicity on periodic nutrient and antibiotics concentration changes, we see that the time delay, or the phase lag, between the changing concentrations will join their amplitudes and the period in selecting whether a resistant strain will fix or not. We illustrate this in Fig. 4 depending on the phase difference between the nutrient and the antibiotic influx, either the resistant or the faster growing bacterium will be selected for. A robust prediction of our theory is that the difference in the logarithmic fractional population changes between an environmental trajectory and its time reversed counterpart will grow almost linearly in time with the number of periods. We emphasize that the effect is different from episodic selection \[25\], where only frequencies and magnitudes of antibiotic selection episodes determine fixation of the resistant strain.

Another experimental system where our predictions can be important is evolution of a metabolic pathway corresponding to a new metabolite, when both the old and the new metabolite concentrations change in time. In such a case, one would need to take into account possible effects of catabolite repression and di-auxic growth in addition to instantaneous effects of metabolite concentrations on the birth/death rates. Nevertheless we expect that careful modeling of these effects will also uncover the fitness sensitivity to the timing of pathway activation.

An important characteristic of the geometric effect is that it is much harder to be observed in typical serial dilution experiments, especially when the environment changes are only imposed at the dilution points. Such experimental protocols will miss important effects that may be relevant for wild-type conditions.

IX. DISCUSSIONS

Fixation dynamics of mutants in a large class of mathematical models is governed by a single effective parameter, the selection rate, obtained as a time average of the instantaneous growth rate difference between the mutant and the ancestral population. In population dynamics with symmetric competition, and in the limit of small differences between the mutant and the ancestor, the total population size is decoupled from changes in the population composition. Instead the total population enters the fixation dynamics only as a time dependent parameter. Then the population growth rates and the selection coefficient depend on the interplay between the time scales of the population dynamics and the environmental fluctuations. For infinite separation between the time scales, the selection depends only on values of environmental parameters. More specifically, here the fitness difference can be expressed as a function of growth rates and carrying capacities averaged over all of the environmental states and independent of the period of the fluctuations. Nonetheless, due to the non-linear dependence of the growth rates on the environmental parameters, the average fitness difference is not necessarily the same as the fitness difference for the average environment.

This quasi-steady state approximation breaks down for faster environmental changes. The mutant fraction dynamics is now dependent not only of the period of environmental changes but also on the sequence of successive environmental states. In particular the first non-adiabatic correction is always anti-symmetric with respect to time reversals, and it is geometric in nature. As long as the fluctuations in the parameters are large, this non-adiabatic correction can be of the same order of magnitude in the birth and death rates variation as the gradient contribution to the fitness difference. The geometric nature of this term constrains the effect that environment fluctuations can have on fitness differences. Indeed, as other geometric contributions \[18\] \[19\], this effect is independent of the instantaneous speed of variation of parameters. In ecological terms, this implies that
the geometric contribution to the mutant ratio drift does not depend on how fast the environment changes, but only on the sequence of environmental states. We illustrate this in Figs. 1, 3. Further, we note that the mutant fraction drift, $\Delta$, can be seen as a line integral in the parameter space, cf. Eq. (24). This implies that only multidimensional and off-phase parameter variations can give nonzero long-term contributions to the population dynamics.

For the results derived in this work, the assumption of an oscillatory environment is not essential. Our conclusions, and the concept of geometric phase in general, are valid for non-cyclic environment dynamics [23]. Typically such dynamics is represented with a Gaussian and, in general, uncorrelated noise [8, 11, 12]. While a detailed extension of the present results to random trajectories is beyond the scope of this paper, we have shown here that the geometric contribution to the selection coefficient is present generically if and only if the population dynamics contains multiple correlated parameters driven by a colored noise, cf. Eq. (32).

In this article we have focused on deterministic population dynamics with small parameter differences among the competing species, which is equivalent to frequency independent selection. We expect that a similar geometric phase contribution to the fixation dynamics is present in stochastic Fisher-Wright type models, as well as models that exhibit various frequency and density dependent selection effects.

The results in Eq. (24) allow us to make a conclusion that is independent of the exact variation of the parameters and the exact details of the model. Namely, for clones with the same mean fitness, the clone that has a higher growth rate when the environment is abundant (increasing carrying capacity) will have a selective advantage over the clone that performs well when the carrying capacity decreases. This is important during acquisition of new metabolic or stress-response functions, as discussed above. Further, in the case of the long-term E. coli evolution experiment [10], we point out that unless mutations manifest themselves in a positive way during the exponential growth phase following a serial dilution, daily variability of the environment would make it harder for mutations to fixate even without stochastic effects associated with the dilution bottlenecks.

We conclude with an observation that species with the fitness advantage in the average environment, with the average fitness advantage over all environments, and with the average fitness advantage for a particular time course of the environment are not necessarily the same species. In particular, a naively deleterious mutation can fixate in a population due to these temporal effects. We believe this to hold true independently of many of the simplifying assumptions of our toy model.

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