Population Genetics with Fluctuating Population Sizes

Thiparat Chotibut∗ and David R. Nelson†

Department of Physics, Harvard University,
Cambridge, Massachusetts 02138, USA

(Dated: August 30, 2016)

Abstract

Standard neutral population genetics theory with a strictly fixed population size has important limitations. An alternative model that allows independently fluctuating population sizes and reproduces the standard neutral evolution is reviewed. We then study a situation such that the competing species are neutral at the equilibrium population size but population size fluctuations nevertheless favor fixation of one species over the other. In this case, a separation of timescales emerges naturally and allows adiabatic elimination of a fast population size variable to deduce the fluctuations-induced selection dynamics near the equilibrium population size. The results highlight the incompleteness of the standard population genetics with a strictly fixed population size.

Keywords: Population Genetics, Fluctuating Population Sizes, Dynamical System, Stochastic Process

∗Electronic address: thiparatc@gmail.com
†Electronic address: nelson@physics.harvard.edu
I. INTRODUCTION

Evolutionary processes are ubiquitous in living systems. Organisms reproduce and pass on their genes to their descendants. Depending on environmental conditions and interactions among organisms in living populations, fitter organisms tend to reproduce faster by natural selection. However, fitter organisms in a particular generation may also give birth to fewer descendants by random chance; these noisy statistical fluctuations in the reproduction rates are termed genetic drift in population genetics [1,2]. In well-mixed competition experiments, in which different species of microbes grow in a vigorously shaken test tube or in a chemostat, both selection and genetic drift influence the evolutionary dynamics that determines the genetic composition of populations [3–5]. In this work, we neglect the less frequent changes due to additional spontaneous mutations, and focus as well on the dynamics of asexual organisms.

Although advances in experimental evolution have revealed the interplay between evolutionary dynamics and the dynamics of population size [5–8], standard theoretical frameworks are often limited to evolutionary dynamics in a strictly fixed population size [1,2,9,10]. Several population genetics works addressed how evolutionary dynamics is affected by a deterministically changing population size, such as during exponential, logistic, or cyclic population growth [11], and during the population bottlenecks inherent in serial transfer experiments [12,13] (for a review, see Ref. [14].) In this paper, we study instead evolutionary dynamics with a stochastically fluctuating population size and show that, even if two competing species are neutral at the equilibrium population size, the coupling between evolutionary dynamics and the dynamics of population size can lead to a fluctuation-induced selection mechanism that favors one species over the other, in a way that is inherited from the dynamics away from the equilibrium population size. Although the model we study is mathematically similar to those in Refs. [15–18], we exploit here the tools of statistical physics, which leads via Sec. IIIB to a number of novel predictions tabulated in Sec. IIIC.

We first review the standard model of neutral evolution in this introduction section. For two competing neutral species in a well-mixed environment, both species grow on average at the same rate and the genetic compositions remain unchanged in the limit of infinitely large population size. However, in finite populations, genetic compositions can also be influenced by fluctuating evolutionary forces from random birth and death events. Random
fluctuations in the reproductive rate, or genetic drift, is one of the central concepts in population genetics embodied in the foundational work of Fisher [19] and Wright [20]. In the Wright-Fisher model consisting of \( N \) neutral haploid individuals, random members of the parental generation are chosen to give birth via cell division to a generation of daughters. The generations are assumed non-overlapping, and the random sampling process culls the offspring to insure that the daughter generation still contains exactly \( N \) individuals. This random sampling with replacement simulates random birth and death events of the parental generation. For two neutral species 1 and 2, this process generates fluctuations in the species frequency (relative fraction) as follows: let \( X_t \) denote the number of species 1 in generation \( t \); the conditional probability that \( X_{t+1} = n \) given \( X_t = m \) is the binomial distribution:

\[
P(X_{t+1} = n|X_t = m) = \binom{N}{m} \left( \frac{m}{N} \right)^n \left( 1 - \frac{m}{N} \right)^{N-n}.
\]

Using properties of the binomial distribution, one finds that the mean species frequency remains unchanged. However, the species frequency \( f_t \equiv X_t/N \) fluctuates with a variance that depends on both the population size \( N \) and the species frequency of the parental generation \( f \) as

\[
\text{Var}(f_{t+1}|f_t = f) = \frac{f(1-f)}{N}.
\]

This discrete-time unbiased random walk in the genetic composition of populations exemplifies genetic drift, whose effect becomes more pronounced at smaller population size. Despite being neutral (identical reproduction rates on average), one of the species can take over the populations (fixation) by chance. Fig. [1] illustrates genetic drift for the Wright-Fisher model.

A variant of the Wright-Fisher model for genetic drift is the Moran model, which does not assume non-overlapping generations. Although the original model is formulated in discrete time [22, 23], we introduce the continuous time version here as it is more relevant to statistical physics in the context of the Master equation. Recall that, in a continuous-time discrete-state Markov process, the time evolution of the probability distribution \( P(n, t) \) for finding the system in a discrete state \( n \) at time \( t \) evolves according to the Master equation [24]:

\[
\partial_t P(n, t) = \sum_{n'} [W(n|n')P(n', t) - W(n'|n)P(n, t)],
\]

3
FIG. 1. (Color Online) Unbiased random walk in the allele frequency $f(t)$ due to genetic drift in neutral haploid asexual populations with the population size $N = 100$ (left) and $N = 1000$ (right). Each color of fluctuating paths represents different realizations of genetic drift simulated from the Wright-Fisher model. Initially, both populations consist of an equal mixture of two alleles (i.e., variants); however, microscopic fluctuations due to genetic drift lead to an eventual fixation, an irreversible macroscopic change in the compositions. The standard deviation of these fluctuations scales as $1/\sqrt{N}$, which, from the result of the first passage time of an unbiased random walk [21], implies the mean time to fixation scales as $N$.

where $W(n|n')$ is the transition rate from the configuration $n'$ to $n$. The Moran model is a Markov process that specifies the transition rate by a continuous-time sampling with replacement. In a finite population of size $N$ with $n$ representatives of species 1 and $N-n$ of species 2, two individuals are sampled at a rate $\mu$; one is chosen to reproduce and the other is chosen to die to ensure the population size remains constant. The transition rates for reproduction of species 1 (death of species 2) and for death of species 1 (reproduction of species 2) are thus given by, respectively,

$$W(n+1|n) = \mu \left(1 - \frac{n}{N}\right) \left(\frac{n}{N}\right),$$

$$W(n-1|n) = \mu \left(1 - \frac{n}{N}\right) \left(\frac{n}{N}\right).$$

The Master equation describing the dynamics of species 1 in the Moran model reads

$$\frac{\partial}{\partial t} P(n,t) = [W(n+1|n)P(n+1,t) + W(n|n-1)P(n-1,t)]$$

$$- [W(n+1|n)P(n,t) + W(n-1|n)P(n,t)],$$  \hspace{1cm} (6)
where the transition rates are given by Eqs. (4) and (5).

In the large $N$ limit, we may promote the species frequency $f = n/N$ to a continuous variable and approximate the discrete Master equation (6) by the Fokker-Planck equation in $f$. Two systematic methods for deriving the Fokker-Planck approximation to the discrete Master equation are the Kramers-Moyal expansion and the Van-Kampen’s system size expansion [24, 25]. Both methods require that we Taylor expand Eq. (6) to $O(1/N^2)$:

$$
\partial_t P(f, t) = \mu \left( f - \frac{1}{N} \right) \left( 1 - f + \frac{1}{N} \right) \left( 1 - \frac{1}{N} \partial_f + \frac{1}{2N^2} \partial_f^2 \right) P(f, t) \\
+ \mu \left( f + \frac{1}{N} \right) \left( 1 - f - \frac{1}{N} \right) \left( 1 + \frac{1}{N} \partial_f + \frac{1}{2N^2} \partial_f^2 \right) P(f, t) \\
- 2\mu f(1 - f)P(f, t) + O(1/N^3).
$$

Upon defining one generation time as $\tau_g = N\mu^{-1}$, which represents $N$ random sampling events, the final result is a Fokker-Planck equation for genetic drift:

$$
\partial_t P(f, t) = \frac{1}{\tau_g} \partial_f^2 \left[ \frac{D_g(f)}{N} P(f, t) \right],
$$

(7)

where the frequency-dependent genetic diffusion coefficient is

$$
\frac{D_g(f)}{N} = \frac{f(1 - f)}{N},
$$

(8)

similar to the variance per generation time of Eq. (2) in the Wright-Fisher model. The Fokker-Planck equation (7) describes genetic drift as an unbiased random walk in the frequency space, provided the two competing species are neutral.

By absorbing $\tau_g$ into the unit of time, one obtains a stochastic differential equation associated with Eq. (7) that reveals the underlying continuous time stochastic dynamics

$$
\frac{df}{dt} = \sqrt{\frac{2\mu D_g(f)}{N}} \Gamma(t),
$$

(9)

where $\Gamma(t)$ is the Gaussian white-noise with zero mean $\langle \Gamma(t) \rangle$ and unit variance $\langle \Gamma(t)\Gamma(t') \rangle = \delta(t - t')$ [25, 26]. To recover the unbiased Fokker-Planck equation (7) of population genetics, where the fluctuations in a given generation are entirely determined by the statistics of the
preceding generation, the Ito’s interpretation of Eq. (9) must be employed [25, 27]. The
stochastic differential equation (9) implies that once the system reaches either $f = 0$ or
$f = 1$, the dynamics completely stop; the genetic drift, whose strength is proportional to
the diffusion coefficient $D_g(f)/N = f(1-f)/N$, vanishes at these states. Since fluctuations
can drive the system into but not away from $f = 0$ and $f = 1$, these are absorbing states.

Two important quantities quantify the fate of the surviving species: the fixation proba-
bility $u(f)$ and the mean fixation time $\tau(f)$. These are, respectively, the probability that
a species of interest takes over the population and the average time required for this to
happen, given an initial composition $f$. Throughout this paper, we shall refer to fixation
as the situation when species 1 takes over, which is equivalent to the situation that the
system eventually reaches the absorbing state $f = 1$. This first passage problem is more
conveniently studied in a backward time formulation (backward Kolmogorov equation) with
a target state in mind, rather than the forward time formulation in the Fokker-Planck equa-
tion (forward Kolmogorov equation) [21, 25, 27]. The backward Kolmogorov equation for
the fixation probability and the mean fixation time associated with Eq. (9) are, respectively,

$$\frac{D_g(f)}{N} \frac{d^2}{df^2} u_{neutral}(f) = 0,$$
(10)

$$\frac{D_g(f)}{N} \frac{d^2}{df^2} \tau_{neutral}(f) = -\frac{1}{\mu},$$
(11)

subject to the boundary conditions $u_{neutral}(0) = 0, u_{neutral}(1) = 1$ and $\tau_{neutral}(0) = \tau_{neutral}(1) = 0$ [24, 27]. Integrating Eqs. (10) and (11) yields the standard results

$$u_{neutral}(f) = f,$$  
(12)

and

$$\tau_{neutral}(f) = -\left(\frac{N}{\mu}\right) \left[f \ln f + (1-f) \ln(1-f)\right].$$  
(13)

Although the effect of genetic drift in neutral evolution as embodied in the Moran or the
Wright-Fisher model are well studied, this framework enforces a strictly fixed population size
$N$ through a strictly enforced growth condition: the birth of one species necessitates the
death of the other, somewhat like the canonical ensemble in equilibrium statistical mechan-
ics. In evolution experiments, as well as in natural environments, population size fluctuations away from a preferred carrying capacity often arise [5]. In Section 2, we discuss a two-species competitive Lotka-Volterra model that accounts for natural population growth and encompasses neutral evolution at the equilibrium population size. Instead of artificially enforcing a strictly fixed population size $N$, the population size becomes a dynamical variable $N(t)$ (like the grand canonical ensemble of statistical mechanics) and couples to the evolutionary dynamics $f(t)$. In Section 3, we show that, while $N(t)$ fluctuates around a fixed stable equilibrium size $N$, neutral evolution with genetic drift of Eq. (9) can acquire a fluctuation-induced selection bias as a result of the coupling between $f(t)$ and $N(t)$. Species with a selective disadvantage in the dilute limit far from the equilibrium population size acquire a selective advantage for competitions at long times near $N$. After adiabatic elimination of the fast population size variable, the effective evolutionary dynamics of quasi-neutral evolution near the equilibrium population size $N$ is determined, and the classical population genetics results of Eqs. (12) and (13) are modified.

II. NEUTRAL EVOLUTION FROM A COMPETITIVE LOTKA-VOLTERRA MODEL

The two-species competitive Lotka-Volterra model assumes that each species $S_i$ grows under dilute conditions with rates

$$S_i \xrightarrow{\mu_i} S_i + S_i,$$

and competes for limited resources under crowded conditions with rates

$$S_i + S_j \xrightarrow{\lambda_{ij}} S_j.$$

In an infinitely large population and in the absence of interspecies competition ($\lambda_{ij} = 0$ for $i \neq j$), population of species $i$ eventually saturates at its carrying capacity $N_i^* \equiv \mu_i/\lambda_{ii}$, which is the stable fixed point of the logistic growth process for species $i$. We assume identical carrying capacities $N = N_1^* = N_2^*$ throughout this paper.

In finite populations, microscopic rates in (14) and (15) define the Markov process for the stochastic dynamics in the number $N_i$ of species $i$. In the limit of large carrying capacity $1/N \ll 1$, the discrete Master equation for the joint probability distribution $P(N_1, N_2, t)$,
associated with (14) and (15), can now be approximated by a continuous two-variable Fokker-Planck equation in the rescaled coordinates $c_i \equiv N_i/N$:

$$\partial_t P(c, t) = \sum_{i=1}^{2} \left(-\partial_{c_i}[v_i(c)P(c, t)] + \frac{1}{2N}\partial_{c_i}^2[D_i(c)P(c, t)]\right), \quad (16)$$

where the deterministic drift and $N$-independent diffusion coefficients read

$$v_1(c) = \mu_1 c_1 (1 - c_1 - c_2) + \mu_1 \beta_1 c_1 c_2, \quad (17)$$
$$v_2(c) = \mu_2 c_2 (1 - c_1 - c_2) + \mu_2 \beta_2 c_1 c_2, \quad (18)$$
$$D_1(c) = \mu_1 c_1 (1 + c_1 + c_2) - \mu_1 \beta_1 c_1 c_2, \quad (19)$$
$$D_2(c) = \mu_2 c_2 (1 + c_1 + c_2) - \mu_2 \beta_2 c_1 c_2, \quad (20)$$

and $\beta_1 \equiv 1 - \left(\frac{\lambda_{12}}{\lambda_{21}}\right)\left(\frac{\mu_2}{\mu_1}\right)$ and $\beta_2 \equiv 1 - \left(\frac{\lambda_{21}}{\lambda_{11}}\right)\left(\frac{\mu_1}{\mu_2}\right)$ are the rescaled parameters [28, 29].

The inverse of the carrying capacity $1/N$ controls the relative strength of deterministic to fluctuating dynamics such that when $N \to \infty$ the dynamics is entirely deterministic and given by the coupled dynamical equations: $dc_i/dt = v_i(c)$. When $\beta_1 = \beta_2 = 0$ and when both species grow at the same rate under dilute conditions ($\mu = \mu_1 = \mu_2$), the stochastic dynamics associated with the Fokker-Planck equation (16) describes neutral evolution with genetic drift without fixing the population size variable $c_T \equiv c_1 + c_2$; the population size now fluctuates around the equilibrium size at $N$ ($c_T = 1$) at long times [28, 30]. This can be seen by prescribing the Itô stochastic differential equations associated with the Fokker-Planck equation (16) to obtain coupled Langevin’s dynamics in the frequency $f \equiv c_1/(c_1 + c_2)$ and the population size variable $c_T = c_1 + c_2$ [28]:

$$\frac{df}{dt} = \sqrt{\frac{\mu D_g(f)}{N}} \left(\frac{1 + c_T}{c_T}\right) \Gamma_f(t), \quad (21)$$
$$\frac{dc_T}{dt} = \mu v_G(c_T) + \sqrt{\frac{\mu c_T(1 + c_T)}{N}} \Gamma_{c_T}(t), \quad (22)$$

where $\Gamma_i(t)$ is a Gaussian white noise with $\langle \Gamma_i(t)\Gamma_j(t') \rangle = \delta_{ij}\delta(t - t')$ and $\langle \Gamma_i(t) \rangle = 0$, $D_g(f) = f(1-f)$ is the frequency-dependent genetic drift coefficient, $v_G(c_T) \equiv c_T(1-c_T)$ is the logistic growth function. Eq. (22) reveals that the population size variable undergoes $f$-independent stochastic logistic growth dynamics such that, at long times, slow fluctuations
with variance $1/N$ around the equilibrium at $c_T = 1$ take over (the equilibrium population size is $N$). Near $c_T = 1$, the frequency dynamics of Eq. (21) resembles neutral evolution with genetic drift of Eq. (9). In this case, the numerical fixation probability $u(f)$ and the mean fixation times $\tau(f)$ starting along the equilibrium line $c_T = c_1 + c_2 = 1$ obtained via the Gillespie algorithm show excellent agreement with the standard population genetics results of Eqs. (12) and (13) [29, 30]. Thus, the competitive Lotka-Volterra model generalizes neutral evolution with genetic drift to include independent population size fluctuations around the equilibrium size without changing the essential results of neutral evolution, provided $\beta_1 = \beta_2 = 0$ and $\mu_1 = \mu_2$.

III. FLUCTUATION-INDUCED SELECTION IN QUASI-NEUTRAL EVOLUTION

We now discuss the scenario such that $\beta_1 = \beta_2 = 0$ but $\mu_1/\mu_2 \neq 1$. As opposed to when $\mu_1/\mu_2 = 1$ in the previous section, the two competing species no longer grow at an equal rate at low population densities. Consequently, the mean frequency of each species is not fixed as the population size grows up from small values and equilibrates at $c_T = 1$. This can be seen as follows: In the limit $N \to \infty$, the dynamics are deterministic and are given by

\[
\frac{dc_1}{dt} = \mu_1 c_1 (1 - c_1 - c_2),
\]
\[
\frac{dc_2}{dt} = \mu_2 c_2 (1 - c_1 - c_2).
\]

The overall population size variable $c_T = c_1 + c_2$ grows and equilibrates at $c_T = 1$ according to $dc_T/dt = (\mu_1 c_1 + \mu_2 c_2)(1 - c_T)$. Moreover, every point on the line $c_T = c_1 + c_2 = 1$ is a fixed point (thus defining a fixed line). This limit defines neutral evolution at the equilibrium population size since the frequency $f$ at the equilibrium size is unchanged. Away from the equilibrium size, however, as the population size saturates, $c_1(t)$ and $c_2(t)$ change to conserve the variable

\[
\rho \equiv c_2(t)/c_1(t)^{(\mu_2/\mu_1)},
\]

9
since \( dp/dt = 0 \) follows from Eqs. (23) and (24). Upon defining the *selective advantage in the dilute limit* (selective advantage near the origin) \( s_o \) as \((1 + s_o) \equiv \mu_1/\mu_2\), we can rewrite the conserved variable \( \rho \) in terms of \( f \) and \( c_T \) as

\[
\rho = c_T(t)^{s_o/(1+s_o)}[1 - f(t)]/f(t)^{1/(1+s_o)}.
\]  

(26)

Eq. (26) and the conservation of \( \rho \) imply that the frequency of a species with a selective advantage in the dilute limit increases (decreases) as \( c_T(t) \) grows from \( c_T(t) < 1 \) (declines from \( c_T(t) > 1 \)) to \( c_T = 1 \). This competition scenario with selective advantage away from, but neutral at, the equilibrium size (*quasi*-neutral evolution) is illustrated by the bent deterministic trajectories that intersect the fixed line \( c_T = 1 \) in Fig. 3(b); the deterministic trajectory is bent toward the axis of the species with a selective advantage in the dilute limit. If both species are also neutral in the dilute limit \( (s_o = 0) \), the relative frequency is conserved and the deterministic trajectory leading to the equilibrium fixed line \( c_T = 1 \) is a straight trajectory of fixed \( f \); see Fig. 3(a).

We now study the interesting limit of finite populations, in which, as a result of the feedback between \( f \) and \( c_T \), fluctuation-induced selection at the equilibrium population size emerges, even though the competing species are completely neutral at the equilibrium size. Without loss of generality, we assume that species 1 has a selective advantage in the dilute limit \((1 + s_o = \mu_1/\mu_2 > 1)\), and define \( \mu \equiv \mu_2 \) for brevity. Following Appendix A. of Ref. [28] and absorbing \( \mu \) into the unit of time, we find the coupled stochastic dynamics for \( f \) and \( c_T \) near \( c_T = 1 \) in the limit \( 1/N \ll 1 \):

\[
\frac{df}{dt} = v_R(f, c_T) + \sqrt{\frac{D_g(f)}{N} \left(1 + \frac{c_T}{c_T}\right)(1 + s_o(1 - f))} \Gamma_f(t),
\]

(27)

\[
\frac{dc_T}{dt} = (1 + s_o f) v_G(c_T) + \sqrt{\frac{c_T(1 + c_T)}{N}(1 + s_o f)} \Gamma_{c_T}(t),
\]

(28)

where \( v_R(f, c_T) = s_o f(1 - f) \left[(1 - c_T) - \frac{1}{N} \left(\frac{1 + c_T}{c_T}\right)\right] \) is the deterministic drift due to the selective advantage near the origin \( s_o \) and \( v_G(c_T) = c_T(1 - c_T) \) is the usual logistic growth of population size. Here, \( \Gamma_f(t) \) and \( \Gamma_{c_T}(t) \) are uncorrelated Gaussian white noise with zero means and \( \langle \Gamma_{\alpha}(t)\Gamma_{\beta}(t)\rangle = \delta_{\alpha\beta}\delta(t - t') \), interpreted according to Ito’s prescription. In the standard neutral evolution, when \( s_o = 0 \), Eqs. (27) and (28) reduce to the Moran model
for neutral evolution with a fluctuating population size given by Eqs. (21) and (22). In quasi-neutral evolution, when $s_o \neq 0$, however, fluctuations of population size becomes $f$-dependent with variance proportional to $(1 + s_o f)/N$, while $f$ acquires an intriguing deterministic drift at $c_T = 1$ of the form $v_R(f, c_T = 1) = -2s_o f (1 - f)/N$, which actually favors the fixation of the species with a selective disadvantage near the origin ($s_o < 0$). The presence of non-vanishing deterministic drift is in striking contrast to the unbiased random walk behavior of neutral evolution along the equilibrium line $c_T = 1$ displayed in Eq. (21).

For the generalization of Eqs. (27) and (28) that reveals the role of a non-vanishing selection in other non-neutral scenarios, such as mutualism, see [28]. As this paper was nearing completion, we learned of related work in the context of public goods game by Constable et al. [31], who studied the effect of two opposing selections: non-vanishing deterministic selection that favors one species and the fluctuations-induced selection that favors the other species. Such a scenario with two opposing selection pressures also arose in the competitive Lotka-Volterra model studied in Ref. [28], when $\beta_1$ and $\beta_2$ have opposite signs, $|\beta_1| \ll 1$, $|\beta_2| \ll 1$, and $1/N \ll 1$. In this situation, fluctuation-induced selection can reverse the direction of deterministic selection and alleviate the public good dilemma of cooperation [31].

Eq. (28) drives small excursions from $c_T = 1$ which changes the dynamics of $f$. To understand in more detail how quasi-neutral evolution with a selective advantage near the origin $s_o$ differs from the classic Moran model, we seek an effective dynamics of $f$ near the fixed equilibrium population size $c_T = 1$. Several works addressed similar problems in the context of evolution [15, 16], ecology [17], and epidemiology [18], and deduced an effective dynamics at the equilibrium line $c_T = 1$, using asymptotic expansions in powers of $1/N$ [17, 18]. A more systematic framework for studying an effective dynamics for stochastic dynamical systems with timescale separations is discussed in Ref. [32]. However, here, we present an alternative (and, for us, more intuitive) argument based on adiabatic elimination of a fast variable which exploits an appropriate choice of coordinates. As we shall see in Sec. III C, this choice of coordinates allows the fate of competitions to be inferred for an arbitrary population size, rather than constraining the description to $c_T \approx 1$, i.e., near the equilibrium size. With the effective dynamics in hand, we then calculate the fixation probability as well as the mean fixation time and verify the results with numerical simulations. Our stochastic simulations employ the Gillespie algorithm to efficiently simulate the discrete
Master equation associated with the microscopic rates (14) and (15). The simulated fixation probabilities and the mean fixation times for each initial condition are constructed from 10^4 realizations of fixation events.

A. A Naive Approximation

In the limit 1/N ≪ 1, one strategy to close Eq. (27) for f is to substituting c_T = 1 and ignore weak population size fluctuations of order 1/N. This naive approximation yields

\[
\frac{df}{dt} = -\frac{2s_o}{N} f(1-f) + \sqrt{2D_g(f)} \left(1 + s_o(1-f)\right) \Gamma_f(t).
\]  

(29)

Upon solving the associated backward Kolmogorov equations (similar to solving Eqs. (10) - (11) associated with the stochastic differential equation (9)), we determine s_o-dependent corrections to the fixation probability and the mean fixation time,

\[
u(f) = \frac{\nu_{neutral}(f)}{1 + s_o(1-f)},
\]

(30)

\[
\tau(f) = \frac{\tau_{neutral}(f)}{1 + s_o(1-f)},
\]

(31)

where \( \nu_{neutral}(f) \) and \( \tau_{neutral}(f) \) are given by Eqs. (12) and (13). Although at \( s_o = 0 \) we recover the results of the Moran model, dashed lines in Fig. 2 show that these approximations are poor when \( s_o = 0.5 \) and \( s_o = 1.5 \). These errors stem from neglecting overall population size fluctuations of the term \( s_o f(1-f)(1-c_T) \), which (as we shall see) actually contribute a deterministic drift of order \( s_o/N \) comparable to the term kept in Eq. (29).

B. Effective Evolutionary Dynamics Near The Equilibrium Population Size

We now employ adiabatic elimination of a fast variable to deduce an effective evolutionary dynamics for an approximately fixed population size close to N. Motivated by the approximate conservation of the composite variable \( \rho \) neglecting number fluctuations (see Eq. (25)), we calculate the stochastic dynamics of \( \rho \) from Ito’s change of variable formula (24) (27), and find

\[
\frac{d\rho}{dt} = \frac{v_\rho(f,c_T)}{N} + \sqrt{\frac{2D_\rho(f,c_T)}{N}} \Gamma_\rho(t),
\]

(32)
FIG. 2. (Color Online) The fixation probability (top) and the mean fixation time in the units of $\mu/N$ (bottom) as a function of the initial frequency $f$ with the initial overall population size along the fixed line $c_T = 1$. Predictions from adiabatic elimination of a fast variable shown in solid lines are in excellent agreement with simulations shown in symbols, while dashed lines are predictions from our “naive approximation,” which exaggerates the deviations from the classical results of Eqs. (12) and (13). The fixation probability is $N$-independent while the mean fixation time scales linearly with $N$, which are also features of unbiased random walk (genetic drift.) Population size fluctuations, however, induce selection that disfavors a species that grows faster near the origin ($s_o > 0$), resulting in a decline in the fixation probability as well as a reduced mean fixation time.

where

$$v_p(f, c_T) = \frac{1}{2} \left( \frac{2 + s_o}{1 + s_o} \right) \left( 1 - \frac{f}{f} \right) \left( 1 + \frac{c_T}{c_T} \right) \left( \frac{c_T^{s_o}}{f} \right)^{1/(1+s_o)},$$  

(33)

$$D_p(f, c_T) = \frac{1}{2} \left( \frac{1 + s_o f}{1 + s_o} \right) \left( 1 - \frac{f}{f} \right) \left( 1 + \frac{c_T}{c_T} \right) \left( \frac{c_T^{s_o}}{f} \right)^{2/(1+s_o)},$$  

(34)
FIG. 3. (Color Online) Schematic phase portraits of deterministic neutral evolution in (a) (left) and quasi-neutral evolution in (b) (right) where species 1 is assumed to have a selective advantage near the origin \((s_o > 0)\). Blue curves represent deterministic trajectories of dynamical systems in Eqs. (23)-(24) that eventually reach the red fixed line \(c_T = 1\). Different curves correspond to different values of the deterministically conserved variable \(\rho\) of Eq. (25). For neutral evolution, the trajectories toward the equilibrium population size \(c_T = 1\) are straight lines that fix the fraction \(f\), while the trajectories in quasi-neutral evolution bend toward the axis of the species that grow faster in the dilute population limit (species 1 in this figure). In finite populations, a combination of slow population size fluctuations and fast relaxation toward \(c_T = 1\) along a warped trajectory \(c_2 = (\rho c_1)^{1+s_o}\) of conserved \(\rho\), depicted by the blue curves, generates an effective selection at \(c_T \approx 1\), depicted by the faint orange arrow on the right. Remarkably, fluctuation-induced selection disfavors fixation of species with a selective advantage near the origin (the faint orange arrow points away from the axis of the species with \(s_o > 0\)). The effective stochastic dynamics of \(f\) when \(c_T \approx 1\) after adiabatic elimination of the fast variable \(c_T\) is given by Eq. (39). The effective selection term \(\tilde{v}(f)\) given by Eq. (37) differs from the naive approximation \(v_R(f,c_T = 1)\) in Eq. (29) by a factor of \(2(1+s_o f)/(1+s_o)\), leading to the improved agreement between simulation and theory when \(O(s_o) \sim 1\) in Fig. 2.

and \(\langle \Gamma_\rho(t)\Gamma_\rho(t')\rangle = \delta(t-t')\). Eqs. (32)-(34) reveal that \(\rho\) varies on a slow timescale of order \(1/N \ll 1\) everywhere in our domain of interest. On the other hand, the dynamics of the overall population size given by Eq. (28) exhibits a fast relaxation toward \(c_T \approx 1\), after which slow fluctuations of order \(1/N\) take over. Since \(\rho = (c_2/c_1)^{(\mu_2/\mu_1)}\) and \(c_T = c_1 + c_2\) together completely specify the state of the system, the dynamics of the system starts with a rapid quasi-deterministic relaxation toward \(c_T \approx 1\) along a trajectory of fixed \(\rho\); then the slow residual dynamics of \(\rho\) takes over. The slow dynamics of the coordinate \(\rho\) generates an effective dynamics of \(f\) when \(c_T \approx 1\). Fig. 3(a) depicts the fluctuation-induced selection emerging from the slow stochastic dynamics of \(\rho\) near \(c_T = 1\).

To explicitly eliminate the fast variable, we integrate out \(c_T\) in the joint probability distribution of \(c_T\) and \(\rho\) at time \(t\), \(P(c_T,\rho,t)\), and obtain the marginal probability distribution \(\tilde{P}(\rho,t) \equiv \int P(c_T,\rho,t) dc_T\). The Fokker-Planck equation for the marginal probability
distribution dictates the effective dynamics of the remaining slow variable $\rho$. Motivated by the separation of timescales, we factorize $P(c_T, \rho, t) = P_{st}(c_T)P_{\rho}(\rho, t)$, assuming $c_T$ rapidly relaxes to $c_T = 1$ and forms a quasi-stationary distribution $P_{st}(c_T)$ before $\rho$ varies significantly. In other words, $c_T$ is slaved to $\rho$ \cite{27}. Upon substituting this factorization into the Fokker-Planck equation associated with Eqs. (28) and (32), we find

$$\partial_t P(c_T, \rho, t) = -\vec{\nabla} \cdot \vec{J}(c_T, \rho, t) = -\left[ \frac{1}{N} \partial_{c_T} v(c_T) P_{\rho}(\rho, t) - \frac{1}{N} \partial_{\rho}^2 D_{\rho}(c_T) P_{\rho}(\rho, t) \right] P_{st}(c_T),$$

where the probabilistic current in the $c_T$ direction vanishes by the assumption of stationarity. Integrating out $c_T$ then leads to

$$\partial_t \tilde{P}(\rho, t) = -\frac{1}{N} \partial_{\rho} v(\rho, \langle c_T \rangle) \tilde{P}(\rho, t) + \frac{1}{N} \partial_{\rho}^2 D(\rho, \langle c_T \rangle) \tilde{P}(\rho, t), \quad (35)$$

where $\langle \cdot \rangle$ denotes an expectation value. The effective Langevin dynamics associated with Eq. (35) is precisely Eq. (32) with the substitution $c_T = \langle c_T \rangle$, which is here simply the equilibrium population size $\langle c_T \rangle = 1$.

We can now determine the effective evolutionary dynamics when $c_T \approx 1$ by substituting $\rho(f)$ for $c_T \approx 1$, i.e. (using Eq. (26)) we have $\rho = (1 - f)/f^{1/(1+s_0)}$. The Fokker-Planck equation for $\rho$ can be converted to the Fokker-Planck equation for $f$ along the line $c_T = 1$ via the chain rule $d/d\rho = -[(1 + s_0)f(1 - f)/((1 + s_0 f)\rho)]d/df$. The calculation is more easily carried out using the backward Kolmogorov equation, since derivatives only act on the probability distribution. A straightforward calculation leads to an effective Fokker-Planck equation of $f$ for $c_T \approx 1$; namely,

$$\partial_t \tilde{P}(f, t) = -\partial_f \tilde{v}(f) \tilde{P}(f, t) + \frac{1}{N} \partial^2_f \tilde{D}(f) \tilde{P}(f, t), \quad (36)$$

where

$$\tilde{v}(f) = -\left( \frac{1}{N} \right) s_0(1 + s_0) \frac{f(1 - f)}{(1 + s_0 f)^2}, \quad (37)$$

and

$$\tilde{D}(f) = D_g(f) \left( \frac{1 + s_0}{1 + s_0 f} \right). \quad (38)$$
Hence, the effective dynamics of $f$ reads

$$\frac{df}{dt} = \tilde{v}(f) + \sqrt{\frac{2\tilde{D}(f)}{N}} \Gamma_f(t),$$

(39)

where $\tilde{v}(f)$ is given by Eq. (37) and describes fluctuation-induced selection term (displayed as the faint orange arrow in Fig. 3(b), and $\tilde{D}(f)$ is the effective genetic drift coefficient given by Eq. (38). Eq. (39) reduces to the Moran model for neutral evolution at $s_o = 0$. For $s_o \neq 0$, not only does fluctuation-induced selection appear, but we also obtain an effective genetic drift that differs from the Wright-Fisher sampling by a frequency-dependent factor $(1 + s_o)/(1 + s_o f)$.

The fixation probability and the mean fixation time with an initial condition on the equilibrium line $c_T = 1$ now follow immediately from solving the Backward Kolmogorov equations associated with Eq. (39):

$$u(f) = \frac{(2 + s_o f)}{(2 + s_o)} u_{\text{neutral}}(f),$$

(40)

$$\tau(f) = -\left(\frac{N}{\mu}\right) \left[ \left(1 + \frac{s_o f}{2} \right) f \ln f + \left(1 + \frac{s_o(1-f)}{2} \right) (1-f) \ln(1-f) + \frac{s_o^2}{2(1 + s_o)(2 + s_o)} f(1-f) \right].$$

(41)

Eqs. (39)-(41) are in agreement with the results of Refs. [15–17] after an appropriate change of variable. At small $s_o$, both Eq. (40) and Eq. (30) give $u(f) = [1 - s_o(1-f)] u_{\text{neutral}}(f) + \mathcal{O}(s_o^2)$ while both Eq. (41) and Eq. (31) give $\tau(f) = [1 - s_o(1-f)] \tau_{\text{neutral}}(f) + \mathcal{O}(s_o^2)$, reducing to the standard results of the Moran model when $s_o = 0$. The differences appear only at $\mathcal{O}(s_o^2)$. Fig. 2 shows the predictions from Eq. (40) and (41) are in excellent agreement with our stochastic simulations.

Upon inoculating an equal mixture of each species and assuming species 1 has a selective advantage near the origin $s_o$, the fixation probability of species 1 is $1/4 + 1/(4 + 2s_o)$ which monotonically decreases from $1/2$ when $s_o = 0$ to $1/4$ as $s_o \to \infty$. Moreover, by defining $\tilde{f}$ such that the fixation probability $u(\tilde{f}) = 1/2$, we find $\tilde{f} = (2 + s_o)/(2 + \sqrt{4 + 2s_o(2 + s_o)})$ which rises monotonically from $\tilde{f} = 1/2$ when $s_o = 0$ to $\sqrt{2}/2$ as $s_o \to \infty$. Consequently,
the faster growing species near the origin is only more likely to survive provided the initial fraction is biased in its favor, \( f \in [\sqrt{2}/2, 1] \approx [0.707, 1] \) for \( c_T = 1 \), confirming that population size fluctuations disfavor the ultimate survival of a species with a selective advantage near the origin.

C. Dimensional Reduction: the Fixation Probability and the Mean Fixation Time

FIG. 4. (Color Online) Dimensional reduction from 2 variables to 1 variable by adiabatic elimination of the fast population size variable for \( s_o = 1 \) and \( N = 100 \). In all figures, solid lines are analytical predictions constructed in Sec. III B while symbols are simulation results. (a) and (c) show the fixation probability and the mean fixation time as a function of initial frequency \( f \) in a dilute (\( c_T = 0.5 \)), optimal (\( c_T = 1 \)), and overcrowded (\( c_T = 1.5 \)) initial population size. When replotted against the slow variable \( \rho \), (b) and (d) show data collapse of the fixation probability and the mean fixation time onto \( u_{s_o=1}(\rho) \) and \( \tau_{s_o=1}(\rho) \). (a) demonstrates that population size degree of freedom plays a crucial role in determining the fate of competition; a wise strategy for the species with a selective advantage near the origin is to start with a dilute population size. On the other hand, a species with a selective disadvantage near the origin is better off starting in an overcrowded population size.
Since the dynamics also contains the overall population size degree of freedom, the initial frequency $f^0$ and the initial population size $c_T^0$ will both in general enter the fixation probability $u(f^0, c_T^0)$ and the mean fixation time $\tau(f^0, c_T^0)$. To keep the notation simple, we now continue with the practice of setting $f \equiv f^0$ and $c_T \equiv c_T^0$. Separation of dynamical timescales, in fact, implies the fixation probability and the mean fixation time are universal functions of the slow variable $ho = (1 - f)f^{-1/(1+s_o)}c_T^{s_o/(1+s_o)}$, provided $1/N \ll 1$. In other words, $u(f, c_T) = u(f', c_T') = u(\rho)$ and $\tau(f, c_T) = \tau(f', c_T') = \tau(\rho)$ if $\rho(f, c_T) = \rho(f', c_T') = \rho$. These simplifications arise from a rapid quasi-deterministic relaxation of the population size, with $\rho$ fixed, toward the line $c_T = 1$, after which the slow stochastic dynamics of $\rho$ dictates the outcome.

In principle, $u(\rho)$ and $\tau(\rho)$ follow from rewriting $f$ as a function of $\rho$ in Eqs. (40) and (41). For an arbitrary $s_o$, however, $f$ cannot easily be expressed as a function of $\rho$ at $c_T = 1$ because they are related by an $s_o$-dependent transcendental equation

$$\rho(f, c_T = 1) = (1 - f)f^{-1/(1+s_o)}c_T^{s_o/(1+s_o)}.$$  

One can nevertheless extract $u(\rho)$ and $\tau(\rho)$ from Eqs. (40) and (41) by numerically solving Eq. (42).

Consider the particularly simple case $s_o = 1$, where the physically relevant closed-form solution associated with Eq. (42) is $f(\rho) = 1 + \frac{1}{2} \left( \rho^2 - \rho \sqrt{\rho^2 + 4} \right)$. Substituting $f(\rho)$ into Eqs. (40) and (41) now yields analytical results of $u_{s_o=1}(\rho)$ and $\tau_{s_o=1}(\rho)$. It is also possible to reconstruct $u_{s_o=1}(f, c_T)$ and $\tau_{s_o=1}(f, c_T)$ for arbitrary $f$ and $c_T$ from $u_{s_o=1}(\rho)$ and $\tau_{s_o=1}(\rho)$ by a direct substitution $\rho = (1 - f)f^{-1/2}c_T^{1/2}$. To test these predictions, we simulated $10^4$ fixation events per each initial condition, with $N = 100$ and with $c_T = 0.5$, $c_T = 1$, $c_T = 1.5$ representing dilute, optimal, and overcrowded initial population sizes with $s_o = 1$. Figs. 4(a) and 4(c) show excellent agreement between $u_{s_o=1}(f, c_T)$ as well as $\tau_{s_o=1}(f, c_T)$ and the simulations. Figs. 4(b) and 4(d) show data collapse of the fixation probability and the mean fixation time onto $u_{s_o=1}(\rho)$ and $\tau_{s_o=1}(\rho)$ constructed above. These results demonstrate that population size degree of freedom can play a crucial role in determining the results of competition, here through the composite variable $\rho = (1 - f)f^{-1/(1+s_o)}c_T^{s_o/(1+s_o)}$. 

18
IV. CONCLUSION

We began by reviewing standard theory of neutral evolution of well-mixed systems with a fixed population size in population genetics using the language of statistical physics. A competitive Lotka-Volterra model that exhibits both neutral evolution and independent fluctuations in the population size was introduced. Relaxing the fixed population size assumption leads to interesting fluctuation-induced phenomena, such that the feedback between evolutionary dynamics and population size fluctuations induces a selective advantage for the species that grow faster in the dilute population even when the two competing species are neutral at the equilibrium size. In this situation, there is a natural separation of timescales between the fast population size variable $c_T$ and the slow composite variable $\rho$ that depends on both the relative frequency $f$ and the population size $c_T$. Because of this separation of timescales, the effective evolutionary dynamics near an equilibrium population size can be deduced by means of adiabatic elimination of a fast variable, which reveals a fluctuation-induced selective advantage and unusual genetic drift of a non-Wright-Fisher (or non-Moran) type. In addition, we found that the fixation probability and the mean fixation time are universal functions of the slow composite variable $\rho$, allowing the fate of competitions at an arbitrary initial population size to be deduced. Given a fixed initial frequency $f$, a better strategy for the species that grows fast in the dilute limit to ultimately fix (i.e., take over the populations) is to begin with both populations dilute ($c_T < 1$), rather than overcrowded populations ($c_T > 1$). Unlike the generalization from canonical ensemble to grand canonical ensemble in equilibrium statistical mechanics, replacing the population size by its average value does not yield the accurate description due to the intricate coupling between the frequency and the population size. These findings indicate the importance of the population size variable in population genetics results for the fixation probability and the fixation time.

It is a pleasure to dedicate this paper to the memory of Leo Kadanoff. One of us (drn) owes a particular debt to Leo, for a collaboration (J. V. José et. al., Physical Review B16, 1217 (1977)) that provided an inspiring example of how to do theoretical physics early in his scientific career.
ACKNOWLEDGMENTS

This work was supported in part by the National Science Foundation (NSF) through Grants No. DMR-1608501 and DMR-1306367 and by the Harvard Materials Research Science and Engineering Laboratory, through MRSEC Grant No. DMR-1420570. Portions of this research were conducted during a stay at the Center for Models of Life at the Niels Bohr Institute, the University of Copenhagen. Computations were performed on the Odyssey cluster supported by the FAS Division of Science Research Computing Group at Harvard University.

[1] J. H. Gillespie, Population Genetics: A Concise Guide (JHU Press, 2010), ISBN 1421401703.
[2] W. J. Ewens, Mathematical Population Genetics: I. Theoretical Introduction (Springer, 2004), ISBN 0387201912.
[3] S. F. Elena and R. E. Lenski, Nature Reviews Genetics 4, 457 (2003).
[4] M. M. Desai, Journal of Statistical Mechanics: Theory and Experiment 2013, P01003 (2013).
[5] J. E. Barrick and R. E. Lenski, Nature Reviews Genetics 14, 827 (2013).
[6] L. Dai, D. Vorselen, K. S. Korolev, and J. Gore, Science 336, 1175 (2012).
[7] A. Sanchez and J. Gore, PLoS biology 11, e1001547 (2013).
[8] A. S. Griffin, S. A. West, and A. Buckling, Nature 430, 1024 (2004).
[9] M. A. Nowak, Evolutionary Dynamics: Exploring the Equations of Life (Harvard University Press, 2006).
[10] D. L. Hartl, A. G. Clark, et al., Principles of Population Genetics, vol. 116 (Sinauer Associates Sunderland, 1997).
[11] S. P. Otto and M. C. Whitlock, Genetics 146, 723 (1997), ISSN 0016-6731, http://www.genetics.org/content/146/2/723.full.pdf, URL http://www.genetics.org/content/146/2/723.
[12] L. M. Wahl, P. J. Gerrish, and I. Saika-Voivod, Genetics 162, 961 (2002), URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1462272/.
[13] L. M. Wahl and P. J. Gerrish, Evolution 55, 2606 (2001), URL http://dx.doi.org/10.1111/j.0014-3820.2001.tb00772.x
[14] Z. Patwa and L. Wahl, Journal of The Royal Society Interface 5, 1279 (2008), URL http://dx.doi.org/10.1098/rsif.2008.0248
[15] T. L. Parsons, C. Quince, and J. B. Plotkin, Theoretical Population Biology 74, 302 (2008), URL http://dx.doi.org/10.1016/j.tpb.2008.09.001
[16] T. L. Parsons and C. Quince, Theoretical Population Biology 72, 468 (2007), URL http://dx.doi.org/10.1016/j.tpb.2007.04.002
[17] Y. T. Lin, H. Kim, and C. R. Doering, Journal of Statistical Physics 148, 647 (2012).
[18] O. Kogan, M. Khasin, B. Meerson, D. Schneider, and C. R. Myers, Physical Review E 90 (2014), URL http://dx.doi.org/10.1103/physreve.90.042149
[19] R. A. Fisher, The Genetical Theory of Natural Selection: a Complete Variorum Edition (Oxford University Press, 1930).
[20] S. Wright, Genetics 16, 97 (1931).
[21] S. Redner, A Guide to First-passage Processes (Cambridge University Press, 2001).
[22] P. A. P. Moran, in Mathematical Proceedings of the Cambridge Philosophical Society (Cambridge Univ Press, 1958), vol. 54, pp. 60–71.
[23] P. A. P. Moran et al., The Statistical Processes of Evolutionary Theory. (1962).
[24] N. G. Van Kampen, Stochastic Processes in Physics and Chemistry, vol. 1 (Elsevier, 1992).
[25] H. Risken, Fokker-Planck Equation (Springer, 1984).
[26] K. Korolev, M. Avlund, O. Hallatschek, and D. R. Nelson, Reviews of Modern Physics 82, 1691 (2010).
[27] C. Gardiner, Handbook of Stochastic Processes (1985).
[28] T. Chotibut and D. R. Nelson, Physical Review E 92 (2015), URL http://dx.doi.org/10.1103/physreve.92.022718
[29] S. Pigolotti, R. Benzi, P. Perlekar, M. H. Jensen, F. Toschi, and D. R. Nelson, Theoretical Population Biology 84, 72 (2013).
[30] G. W. A. Constable and A. J. McKane, Phys. Rev. Lett. 114 (2015), URL http://dx.doi.org/10.1103/physrevlett.114.038101.
[31] G. W. A. Constable, T. Rogers, A. J. McKane, and C. E. Tarnita, Proceedings of the National Academy of Sciences p. 201603693 (2016), URL http://dx.doi.org/10.1073/pnas.1603693113
[32] T. L. Parsons and T. Rogers, arXiv preprint arXiv:1510.07031 (2015).