The dynamics of adapting, unregulated populations and a modified fundamental theorem

James P. O’Dwyer

Santa Fe Institute, Santa Fe, NM, USA

A population in a novel environment will accumulate adaptive mutations over time, and the dynamics of this process depend on the underlying fitness landscape: the fitness of and mutational distance between possible genotypes in the population. Despite its fundamental importance for understanding the evolution of a population, inferring this landscape from empirical data has been problematic. We develop a theoretical framework to describe the adaptation of a stochastic, asexual, unregulated, polymorphic population undergoing beneficial, neutral and deleterious mutations on a correlated fitness landscape. We generate quantitative predictions for the change in the mean fitness and within-population variance in fitness over time, and find a simple, analytical relationship between the distribution of fitness effects arising from a single mutation, and the change in mean population fitness over time: a variant of Fisher’s ‘fundamental theorem’ which explicitly depends on the form of the landscape. Our framework can therefore be thought of in three ways: (i) as a set of theoretical predictions for adaptation in an exponentially growing phase, with applications in pathogen populations, tumours or other unregulated populations; (ii) as an analytically tractable problem to potentially guide theoretical analysis of regulated populations; and (iii) as a basis for developing empirical methods to infer general features of a fitness landscape.

1. Introduction

A population of organisms encountering a novel environment will adapt via the processes of mutation and selection: when a beneficial mutation arises in an individual, it confers a selective advantage, leading to an expected increase in mean fitness of the population over time. However, the details of this adaptive process depend on the fitness landscape: the description of the fitness of all possible genotypes of the organism in this environment, and the number of mutational steps needed to move from one genotype to another [1,2]. There are then two clear objectives in developing theory to describe this phenomenon. First, to predict the dynamics of an adapting population given some knowledge of the fitness landscape, and second to go back in the other direction and infer features of the landscape from empirical data. These objectives are complicated by two significant hurdles. We have both limited knowledge of fitness landscapes from empirical data, and at the same time deriving theoretical predictions from a fitness landscape has made slow progress. Many important results are known in the case of uncorrelated, ‘rugged’ landscapes [3–6], where the fitness of a given genotype is uncorrelated with its neighbouring genotypes, but exploring more general landscapes has proved to be a substantial challenge. At the same time, as this theoretical problem has come to the fore, interest has been growing in the adaptation of unregulated populations, which are not of fixed size but may increase or decrease in size over time, according the fitness of individuals in the population. Many populations in nature and experimental studies [7–9] undergo exponential, unregulated growth phases, and recent work has focused on the application of evolutionary theory to the adaptation
of tumour cells [10,11]. In this manuscript, we address both issues: the dynamics of an unregulated population, and the question of inferring a fitness landscape from data.

A novel approach to describing the fitness landscape was introduced by Gillespie, and subsequently developed by others [12–15]. Instead of trying to make very general predictions, the focus is on populations already near a peak in the fitness landscape, where extreme value theory can extract universal features of the adaptive process. At the core of the analysis is the distribution of fitness effects arising from a single mutation, also termed the neighbourhood fitness distribution (NFD). The NFD is a way to statistically encode the properties of a fitness landscape, and our key assumption is that the same NFD is shared by all genotypes with the same fitness: we assume that the possible consequences of a mutation are primarily determined by the fitness of the parent, and that the impact of differences in parental genotypes with the same fitness is negligible. This description can capture the effects of epistasis by allowing this distribution to change as a function of fitness. For example, negative epistasis [16], thought to be common in real systems, can be characterized by a decreasing likelihood of a given increment in offspring fitness as a function of increasing parental fitness.

Kryazhimskiy et al. [17] have applied this description in terms of an NFD with a focus on a weak mutation limit, for a monomorphic population of fixed size, with the aim of classifying the possible behaviours arising from a range of NFDs. In parallel, other studies have gone beyond the weak mutation limit for populations of fixed size [18–25], but without explicitly distinguishing between different kinds of NFD; to obtain analytical results typically each mutation is assumed to produce the same jump in fitness. This crucial limitation means that we have so far been unable to explore the impact of more general fitness landscapes, and in particular epistatic landscapes, on the dynamics of adapt populations. We therefore have two orthogonal theoretical descriptions arising from Gillespie’s original framework. First, monomorphic populations where we can explicitly solve for the increase in mean fitness as a function of NFD, but are limited to the limit of weak mutation; and polymorphic populations, where it is much harder to explicitly solve for the dynamics arising from a given fitness landscape, and we have primarily been limited to the analysis of beneficial mutations of fixed effect.

We present a model of stochastic population dynamics for an unregulated, polymorphic, adapting population of asexual organisms, and derive analytical solutions for dynamics in various parameter regimes. Our results have three applications: first, we make predictions for a range of possible dynamics of unregulated populations. Second, while our results are applicable to the case of an unregulated population, some qualitative features may be relevant in guiding our understanding of populations subject to competition, and our theoretical framework has the potential to be generalized to tackle this more complicated situation when competition is relatively weak. Finally, we are able analytically to connect mean population fitness to the NFD. In particular, we find that the longer unregulated growth is maintained, the finer the detail of the fitness landscape that is unveiled, signalling that future work on mapping the fitness landscape may benefit from an increased focus on the dynamics of unregulated populations.

2. Results

Our approach is based on a multi-type branching process, arising from the stochastic processes of birth, death and mutation. We begin our analysis with a master equation [26] describing the stochastic evolution of an unregulated population evolving on a discrete fitness landscape. On this landscape, we initially take fitness to be a discrete quantity, with fitness classes labelled by indices i; at time t the population is described by the probability $P(n_1, n_2, \ldots, t)$ that the system has $n_i$ individuals in each of the fitness classes, $i$. In our model, there are then three distinct processes: individuals can die, they can reproduce identical individuals or they can produce mutated individuals. From these three rules, we present the appropriate master equation in our appendix, and subsequently take the limit of discrete fitness classes forming a continuum, $x$. For an individual in fitness class $x$, the key parameters in this problem are the per capita rate of mortality, $d(x)$, the per capita rate of reproduction of non-mutated individuals, $b(x)$ and the per capita rate of production of mutated individuals, $\mu(x)$. We characterize the impact of mutations by the distribution of fitness effects, or NFD $Q(x,y)$: the outcome of a mutation in the offspring of an individual in fitness class $x$ is the production of a new individual in fitness class $y$, occurring with probability $Q(x,y)$.

In his manuscript, we analyse the lowest two moments of the resulting probability distribution, with our focus primarily on the lowest moment, the expectation value of the distribution of fitness classes in a population: $\langle n(x,t) \rangle$. This is the expected number of individuals in a population with fitness class between $x$ and $x + dx$. The mean of this distribution will characterize the mean fitness of a population, while variation around this mean characterizes the level of polymorphism in the population. In the appendix, we derive the following integro-differential equation for $\langle n(x,t) \rangle$:

$$\frac{\partial}{\partial t} \langle n(x,t) \rangle = \int dy [Q(y,x) - \delta(x-y)] \mu(y) \langle n(y,t) \rangle + r(x) \langle n(x,t) \rangle,$$

where $r(x) = b(x) + \mu(x) - d(x)$ is the total net number of individuals produced per capita per unit time by individuals in fitness class $x$. We define $r(x)$ to be the fitness of an individual in fitness class $x$, and equation (2.1) is the central equation for our analysis of the average properties of populations on a given fitness landscape. In the appendix, we also extend this analysis to the two-point correlation function, which can be thought of as characterizing fluctuations around the expectation value $\langle n(x,t) \rangle$ and their correlations across fitness classes.

We now explore a series of results arising from equation (2.1). In §1, our overarching assumption is to focus on a certain subset of possible fitness landscapes, where the NFD takes the form $Q(x,y) = Q(x - y)$ [17,27]. This special case means that fitnesses are correlated, and that the distribution of possible fitness classes arising from a mutation is the same for all genotypes, implying a lack of any epistatic effects. With this assumption, we are able to derive a general solution for the expected distribution of fitness classes $\langle n(x,t) \rangle$ in a population, and the between-population variation in fitness, $c(x_1, x_2, t)$. We are also able to relate mean population fitness through time directly to the NFD $Q(x-y)$, and we find a stochastic generalization of Fisher’s fundamental theorem.
In §2.2, we consider more general NFDs, potentially incorporating the negative epistatic effects commonly reported in real populations [28,29]. These epistatic effects may be encoded as a rule of diminishing returns, so that the mean fitness jump arising from a single mutation decreases with increasing fitness. We do not report general solutions for the distribution of fitnesses in this case, but we are able to further generalize Fisher’s fundamental theorem: we provide a quantitative result for the rate of change of population fitness in terms of selection and mutation. We also give an explicit solution for an extreme case of negative epistatic interactions, and contrast the behaviour with non-epistatic results.

2.1. Non-epistatic landscapes

Our analysis of non-epistatic landscapes can be divided into two distinct scenarios, depending on whether mutation rate \( \mu(x) \) is constant, or is scaling with fitness class \( x \). We focus primarily on the first case, which is realistic when either (i) mutations occur spontaneously, irrespective of replication rate (e.g. owing to radiation) or (ii) when there is a constant rate of mutation per replication, \( \mu(x) \approx \mu(x) \), but where mutations act solely to increase or reduce mortality rate, \( d(x) \). Under the latter assumption, both \( b(x) \) and hence \( \mu(x) \) are constant for all individuals. Our second scenario is when per capita mutation rate depends explicitly on fitness class, \( x \), considered in the appendix. This is appropriate when two assumptions are fulfilled: mutations are coupled to birth events, \( \mu(x) \approx b(x) \), and \( b(x) \) in turn depends on fitness class \( x \): i.e. mutations act to increase or decrease the fertility of organisms. In this case, individuals in higher fitness classes have higher reproductive rates, and hence give rise to more mutation events.

We parametrize the dependence of fitness \( r(x) \) on fitness class \( x \) as a linear relationship: \( r(x) = r_0 + r_1x \). With this parametrization and with the assumptions that \( Q(x,y) = Q(x-y) \) and \( \mu(x) = \mu_0 \), we find that equation (2.1) reduces to

\[
\frac{\partial}{\partial t} \langle n(x,t) \rangle = \mu_0 \int dy (Q(x-y) - d(x-y)) \langle n(y,t) \rangle
+ (r_0 + r_1x) \langle n(x,t) \rangle.
\]

(2.2)

Both birth and mortality in our unregulated population are linear in population size, and so we can isolate and solve this expectation value independently of the higher order moments. We now take the Fourier transform of equation (2.2), defining

\[
\hat{n}(k,t) = \int dx e^{ikx} \langle n(x,t) \rangle.
\]

(2.3)

where we have dropped the angled brackets from the Fourier transformed distribution for convenience. With this definition

\[
\frac{\partial}{\partial t} \hat{n}(k,t) = \mu_0 \hat{Q}(k) - 1 \hat{n}(k,t) + (r_0 + r_1 \frac{\partial}{\partial k}) \hat{n}(k,t),
\]

(2.4)

where \( \hat{Q}(k) \) is the Fourier transform of \( Q(x) \). This Fourier transformed equation has the analytical solution

\[
ir_1 \log \frac{\hat{n}(k,t)}{\hat{n}(k,0)} = \int_{k_{-r_1t}}^{k} dk' (\mu_0 \hat{Q}(k') + r_0 - \mu_0).
\]

(2.5)

This solution entirely characterizes the time evolution of the population, and can be inverse Fourier transformed to obtain the expected distribution of fitness classes, \( \langle n(x,t) \rangle \).

2.1.1. Fitness through time traces the landscape

Before inverse transforming equation (2.5), we immediately have a general analytical solution for the mean fitness per individual for an initially monomorphic population of \( N_0 \) individuals with fitness \( r_0 \). We define mean fitness as

\[
\frac{F(t) = \int dx (r_0 + r_1x) \langle n(x,t) \rangle}{\int dx \langle n(x,t) \rangle}.
\]

(2.6)

In the appendix, we derive the following, general result relating mean fitness to the shape of the NFD:

\[
F(t) = r_0 - \mu_0 \mu_0 Q(-ir_1t),
\]

(2.7)

where \( \hat{Q}(-ir_1t) \) is defined by analytic continuation of \( \hat{Q}(k) \). This analytical continuation breaks down if the NFD drops off slower than exponentially: in such cases the function \( \hat{Q}(-ir_1t) \) diverges for all times \( t > 0 \). In real systems, we would expect long-tailed distributions to be cut-off at a finite fitness class, but if such distributions are relevant in nature then \( F(t) \) is clearly not a useful quantity: while the defining equation (2.2) for \( \langle n(x,t) \rangle \) remains valid, the moments of \( \langle n(x,t) \rangle \) are not well-defined such cases. On the other hand, for exponentially or faster decaying distributions, we have directly the functional form of the Fourier transformed NFD from the mean fitness of an unregulated population. In this manuscript, we do not seek to present an explicit experimental protocol, but this result strongly hints that certain features of the fitness landscape may be accessible by keeping track of the fitness of an unregulated population. The longer the timescale one can maintain a lack of population regulation in an experimental context, the higher the frequency one can potentially reach in this Fourier transform.

2.1.2. Variance through time, fundamental theorem and Price equation

The expected within-population variation in population fitness \( V(t) \) characterizes the degree of polymorphism in a population, and we define it in terms of the width of the distribution \( \langle n(x,t) \rangle \):

\[
V(t) = \frac{\int dx (r_0 + r_1x)^2 \langle n(x,t) \rangle}{\int dx \langle n(x,t) \rangle} - \left( \frac{\int dx (r_0 + r_1x) \langle n(x,t) \rangle}{\int dx \langle n(x,t) \rangle} \right)^2
\]

\[
= -r_1^2 \hat{n}(k=0) \log \hat{n}(k=0) \bigg|_{k=0}.
\]

(2.8)

Using this result, we find that for an initially monomorphic population

\[
\int dx Q(x) (\langle n(x,t) \rangle - \mu_0 \langle n(x,t) \rangle - \mu_0 \langle n(x,t) \rangle)
\]

and

\[
\frac{dF}{dt} = V(t) - ir_1 \mu_0 \frac{dQ}{dk} \bigg|_{k=-r_1t}.
\]

(2.9)

The first term corresponds to what we would expect from Fisher’s ‘fundamental theorem’ [30] in the absence of mutations, where we would expect the rate of change of population fitness to be proportional to its variance. The second term extends the theorem to account for the net impact of mutations:

\[-ir_1 \mu_0 \frac{dQ}{dk} \bigg|_{k=-r_1t} = r_1 \mu_0 \int dz zQ(z). \]
so that the rate of change of fitness is equal to population variance plus the average increment in fitness arising from a single mutation.

This extension of Fisher’s theorem is completely analogous to the connection between quasi-species equations and their moments, detailed explicitly in the study of Page & Nowak [31] and Nowak & Sigmund [32]. In this context, equation (2.9) can be thought of as the Price equation with quantitative character chosen to be fitness class [33], and the fitness landscape \( Q(x,y) \) is what then fixes the form of the terms in this equation. The distinction between our results and quasi-species dynamics is that we directly connect the form of these equations to features of the fitness landscape, and that we focus on unregulated stochastic population dynamics rather than a deterministic population of fixed size.

2.1.3. Fitness and variance: explicit examples

We now explore explicitly the fitness dynamics arising from three symmetric neighbourhood fitness distributions, exponential, Gaussian and the ‘jump’ distribution \( Q(z) = \frac{1}{2} (\delta(z + \Delta) + \delta(z - \Delta)) \) where all mutations result in the same increment up or down in fitness class, \( \Delta \). Applying equation (2.7), the resulting dynamics are

\[
Q(z) = a e^{-a|z|} \Rightarrow F(t) = r_0 - \mu_0 t + \left( \mu_0 a^2 / (a^2 - r_1 t) \right) \\
Q(z) = \sqrt{a / \pi} e^{-a z^2} \Rightarrow F(t) = r_0 - \mu_0 t + \mu_0 \sqrt{\pi} a z / a \\
\text{and jump } : Q(z) = \frac{1}{2} (\delta(z + \Delta) + \delta(z - \Delta)) \Rightarrow F(t) = r_0 - \mu_0 t + \mu_0 \cosh(\Delta r_1 t).
\]

(2.10)

In the exponential case, we see a blow-up at finite time. The jump distribution is the closest case to that explored by Desai and collaborators [22,23] for fixed population size; in contrast to the linear behaviour \( F(t) \sim t \) found there, we find an exponential increase in fitness at late times for unregulated populations, and no finite-time blow-up as in the exponential case. The reason for this qualitative difference is that for a sufficiently large population, even exponentially suppressed mutational effects will occur, and these large mutational effects will come to dominate if they increase fitness. In contrast, for the jump NFD the maximum jump in fitness is explicitly bounded by \( \Delta \). We plot fitness and variance through time for each of these three cases in figure 1.

2.1.4. Fitness distribution in the diffusion approximation

For general functional forms of the NFD, our solution for the Fourier transform of \( \langle n(x,t) \rangle \), equation (2.5) will need to be inverse-transformed numerically. Therefore, to gain some analytical insight into the functional form of \( \langle n(x,t) \rangle \) we take a diffusion approximation, retaining only the first two moments of the distribution \( Q(x - y) \):

\[
v = \int dz \, z Q(z) \\
\text{and } \sigma^2 = \int dz \, z^2 Q(z).
\]

(2.11)

We note that by diffusion approximation we refer to the ‘diffusion’ of individuals from one fitness class to another, rather than the diffusion approximations often used in population genetics to approximate the dynamics of a probability distribution. Dropping all higher moments beyond those in equation (2.11), we can solve explicitly for \( \langle n(x,t) \rangle \) in closed form in terms of initial fitness, \( r_0 \), the rate of change of fitness with fitness class, \( r_1 \), and the mean and variance of the NFD, \( \nu \) and \( \sigma \):

\[
\langle n(x,t) \rangle = \frac{N_0 e^{\nu t} / \sigma^2 t + \nu t + (r_1 x / 2) (\nu^2 / \sigma^2) + (x^2 / 2\sigma^2) - (x^2 / 4\mu_0)}{\sqrt{2\mu_0 \sigma^2 t}}.
\]

(2.12)

The result is plotted in figure 2. We also have the following limits for the mean fitness per individual and variance in population fitness:

\[
F(t) = r_0 + \mu_0 r_1 t^2 + \mu_0 \sigma^2 / 2
\]

and

\[
V(t) = 2\mu_0 \sigma^2 t \nu.
\]

(2.13)

special cases of equations (2.7) and (2.9). This diffusion approximation might also be thought of as the limit in which all mutational jumps are infinitesimal, and gives us an intuitive sense of how the fitnesses in an unregulated, adapting population evolve over time. On the other hand, the apparent avoidance of the much faster increases in fitness found above is only valid at early times, when the contributions from higher order moments of \( \dot{Q} \) to \( F(t) \) and \( V(t) \) are negligible.

2.2. Epistatic landscapes

In this section, we present some preliminary results extending our analysis to more general landscapes, defined by NFDs \( Q(x,y) \). We first derive an extension of Fisher’s fundamental theorem, finding that it depends on the mean fitness jump for a single mutation. We then consider an explicit example of very strong negative epistasis, solving exactly for the expected distribution of fitness classes as a function of time, and for between population variation. We see that in this case, and in contrast to the case of a non-epistatic landscape, the population reaches a steady state.

Figure 1. The mean fitness and variance through time for three NFDs; thick lines indicate fitness and thin lines indicate variance. In red, an exponentially decaying NFD, \( Q(x) \sim e^{-x^2} \), diverging in finite time; in dashed green, a Gaussian distribution \( Q(x) \sim e^{-x^2} \); and in dotted blue the jump distribution \( Q(x) = \frac{1}{2} (\delta(x + \Delta) + \delta(x - \Delta)) \). The variances of \( Q(x) \) are equal in all three cases, and we have chosen \( r_0 = 1, r_1 = 1 \) and \( \mu_0 = 1 \). The initial population is monomorphic. (Online version in colour.)
For an uncorrelated, the so-called rugged landscape, we can obtain a more general extension where the only unexpected, additional term in change of mean population fitness to the population variance, where the constant $\mu(x)$, $\mu_0$, $\alpha = 1$, $\nu = 0.1$. (Online version in colour.)

2.2.1. Fundamental theorem on an epistatic landscape

For a non-epistatic landscape, we found that a simple extension of Fisher's fundamental theorem related the rate of change of mean population fitness to the population variance, where the only unexpected, additional term in equation (2.9) represents the net excess of deleterious over beneficial mutations. We can obtain a more general extension of the theorem by multiplying equation (2.1) by the fitness of class $x$, $r(x)$, and then integrating over all fitness classes:

$$\frac{dF}{dt} = V(t) + \int \frac{dy \Delta(y) \mu(y) \langle n(y,t) \rangle}{\int dy \langle n(y,t) \rangle},$$

(2.14)

where

$$\Delta(y) = \int dx (r(x) - r(y)) Q(y,x),$$

(2.15)

is the expected jump in fitness arising from a single mutation occurring in an individual in fitness class $y$. In words, equation (2.14) combines the effect of selection acting on standing variation with the effect of mutations on individual fitnesses, where we have quantitatively characterized the latter in terms of the NFD.

Let us again assume constant mutation rate, $\mu(x) = \mu_0$, and consider some special cases. For a non-epistatic landscape, we have that $\Delta(y)$ is a constant, and we reproduce equation (2.9). For an uncorrelated, the so-called rugged landscape, $Q(y,x) = Q(x)$, independent of the fitness of the parent. For any such landscape, we immediately have

$$\frac{dF}{dt} = V(t) + \mu_0 (c - F(t)),$$

(2.16)

where the constant $c = \int e^x Q(x)$. Finally, let us suppose for more general landscapes that $\Delta(y)$ can be expanded in powers of $y$:

$$\Delta(y) = c_0 + c_1 y + c_2 y^2 + \cdots$$

(2.17)

and make our usual parametrization for the fitness of class $x$:

$$r(x) = r_0 + r_1 x.$$

Then

$$\frac{dF}{dt} = V(t) + \mu_0 \left(c_0 + \frac{c_1}{r_1} (F(t) - r_0) + \frac{c_2}{r_1^2} (V(t) + F^2(t)) + \cdots \right).$$

(2.18)

We emphasize that we are looking at only one of an infinite set of equations for the moments $F(t)$, $V(t)$, etc., and while the expectation value $\langle n(x,t) \rangle$ underlies this set of equations, we do not know its general solution, as we do in equation (2.5) for non-epistatic landscapes. Nevertheless, we do have a direct relationship between the time-evolution of the moments $F(t)$, $V(t)$, etc., and the mean jump in fitness arising from a single mutation, $\Delta(y)$. Given that the signature of epistasis is that this mean jump changes with fitness class of the parent, we have a direct, albeit more complicated connection between the expected properties of a population through time, and the fitness landscape underlying its dynamics.

2.2.2. An example of negative epistasis

We now present an example where we can solve explicitly for $\langle n(x,t) \rangle$: an initial monomorphic population of fitness $x_0$, where all single mutations give rise to an offspring of higher fitness $x_1$, and all subsequent mutations produce no further change in fitness, providing a canonical example of strong negative epistasis. The neighbourhood fitness distribution takes the form $Q(y,x) = \delta(x - x_1)$ so that

$$\frac{\partial}{\partial t} \langle n(x,t) \rangle = \mu_0 \int dy (\delta(x - x_1) - \delta(x - y)) \langle n(y,t) \rangle$$

$$+ (r_0 + r_1) \langle n(x,t) \rangle.$$  

(2.19)

With initial population $\langle n(x,0) \rangle = n_0 \delta(x - x_0)$, the solution for $\langle n(x,t) \rangle$ is

$$\langle n(x,t) \rangle = n_0 e^{(l_0 + \mu_0 \langle n \rangle) t} \delta(x - x_0) + \frac{\mu_0 n_0}{r_1 (y_1 - y_0) + \mu_0} \times (e^{(l_0 + \mu_0 \langle n \rangle) t} - e^{(l_0 + \mu_0 \langle n \rangle) x_1}) \delta(x - x_1).$$

(2.20)

so that the population shifts from being dominated by individuals in fitness class $x_1$ at early times to the vast majority of individuals being in fitness class $x_1$ at late times. In figure 3, we plot mean fitness and within-population variance for this population. Finally, we note that at late times, the population is dominated by the higher fitness class, and the dynamics of this fitness class are governed by a stochastic birth–death process, effectively with no mutation.
fitness landscape, where one or multiple mutations provide the same increase in fitness, regardless of the number of mutations; solid line indicates fitness and dashed line indicates within-population variance. We have chosen $f_0 = 0$, initial fitness class $x_0 = 0$, mutant fitness class $x_1 = 1$ and units where $R_0 = 1$ and $\mu_0 = 0.01$. (Online version in colour.)

**Figure 3.** The mean fitness and variance through time for a strongly epistatic fitness landscape, where one or multiple mutations provide the same increase in fitness, regardless of the number of mutations; solid line indicates fitness and dashed line indicates within-population variance. We have chosen $f_0 = 0$, initial fitness class $x_0 = 0$, mutant fitness class $x_1 = 1$ and units where $R_0 = 1$ and $\mu_0 = 0.01$. (Online version in colour.)

### 3. Conclusions

This manuscript explores two overlapping questions: what is the range of possible dynamics of an unregulated adapting population? And are there direct connections between the fitness landscape and readily accessible empirical data? In order to tackle these questions, we have made a series of assumptions about selection and mutation. First, our description of the landscape is statistical, and assumes that each genotype of fitness class $x$ has the same distribution of possible changes in fitness from a single mutation [17]. Then we have divided our results into two cases, non-epistatic and epistatic, with the majority of our results presented for the former, where each fitness class $x$ has the same distribution of fitness effects as every other fitness class $y$. For a non-epistatic landscape with constant mutation rate, we obtained a direct connection between the mean fitness of the unregulated population through time, $F(t)$, and the Fourier transform of the distribution of mutational effects, the NFD $Q(x-y)$. There are undoubtedly alternative ways to describe population fitness, but the explicit connection we obtain between $F(t)$ and the landscape provides a potential basis to empirically map out landscapes satisfying our assumptions above, one of the central questions in evolutionary dynamics. We also derive a generalization of Fisher’s theorem, which in turn can be thought of as an explicit version of the Price equation [31,33] for a stochastic, unregulated population.

For the more general problem of an adapting, unregulated population on an epistatic landscape, we were unable to find a similarly simple relationship between mean population fitness and the shape of the landscape; it may be that further progress will rest on case-by-case, or class-by-class analysis of different kinds of NFDs. However, we obtained an intuitive extension of Fisher’s fundamental theorem, generalizing our non-epistatic analysis, and we were further able to derive a solution for a specific case of negative epistasis.

Various conceptual issues are raised by this work. First, for non-epistatic landscapes over a wide range of parameters, we found that population fitnesses and variances increased without bound through time. The reason for this apparently pathological behaviour is the combination of a lack of population regulation, the lack of epistasis and the implicit assumption of infinite sites open to mutations. One or more of these assumptions is likely to break down in realistic populations, and the lack of population regulation will always have a limited range of applicability. On the other hand, the more common assumption of fixed population size is also an approximation which may break down in some real populations—for example, the serial transfer often employed in experimental evolution leads to successive phases of exponential growth, followed by dilution, rather than a truly constant population size. Developing a multiplicity of qualitatively different models to describe related problems will potentially offer deeper insight into the factors driving adaptation.

There are three clear future directions, each building on the three objectives in this paper. First, we plan to extend this work to further explore the impact and experimental relevance of fluctuations. Second, can we use the tools of non-equilibrium field theory [34,35] to introduce weak population regulation perturbatively, and compute corrections to our results in perturbation theory? While it is unlikely that a perturbative approach will capture the strongly interacting case of fixed-population size, weak interactions may provide some insight into the nature of deviations from the unregulated case. Finally, we plan to treat more general cases of unregulated population dynamics on epistatic landscapes. This will be essential to relate our framework to more general fitness landscapes, which are often expected to exhibit negative epistasis [28,29]. We have begun to explore epistasis, but more general NFDs and the possible inclusion of multiple traits affecting fitness in different ways will lead to a more complete picture.

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### Appendix A

#### A.1. The master equation

We begin our analysis with a master equation [26] describing the stochastic evolution of an unregulated population adapting on a discrete fitness landscape. On this landscape, we initially take fitness to be a discrete quantity, with fitness classes labelled by indices $i$. The population is then described by the probability $P(n_1, n_2, \ldots, t)$ that the system has $n_i$ individuals at each of the fitness classes, $i$. In our model of an unregulated population, this probability satisfies the following master equation:

$$\frac{\partial P}{\partial t} = \sum_{j=0}^{\infty} d_j (n_j + 1) P(\ldots, n_j + 1, \ldots, t)$$

$$- \sum_{j=0}^{\infty} d_j n_j P(\ldots, n_j, \ldots, t)$$

$$+ \sum_{j=0}^{\infty} b_j (n_j - 1) P(\ldots, n_j - 1, \ldots, t)$$

$$- \sum_{j=0}^{\infty} b_j n_j P(\ldots, n_j, \ldots, t)$$

$$+ \sum_{j=0}^{\infty} \sum_{j=0}^{\infty} \mu_j (n_j - \delta_j) Q_{ij}$$

$$\times P(\ldots, n_j - \delta_j, \ldots, n_j - 1, \ldots, t)$$

$$- \sum_{j=0}^{\infty} \sum_{j=0}^{\infty} \mu_j n_j P(\ldots, n_j, \ldots, t).$$

(A1)
Death of individuals occurs with per capita rate \(d_o\), and birth of new individuals with no mutation occurs at per capita rate \(d_b\). Mutation events occur with a per capita rate \(d_m\), so that the total number of birth events per unit time for an individual in class \(i\) is \(d_i = d_b + d_m\). The outcome of a mutation event is the production of a new individual with fitness \(j\), occurring with probability \(Q_{ij}\). \(Q_{ij}\) therefore describes the distribution of single-mutant fitness classes \(j\) for a genotype in fitness class \(i\): the neighbourhood fitness distribution.

**A.2. Continuum limit and moment equations**

When fitness increments are relatively small compared with the overall range of possible fitnesses, we can take the continuum limit of this equation, so that discrete fitness classes \(i\) are replaced by continuous fitness classes, \(x\). To take this continuum limit, we first re-express equation (A 1) in terms of a multivariate generating function:

\[
Z(\ldots, h_1, \ldots, t) = \sum_{[u]} P(\ldots, u_1, \ldots, t) e^{\sum_i u_i h_i}, \tag{A 2}
\]

so that derivatives of \(Z(\ldots, h_1, \ldots, t)\) (with \(h_i\) then set equal to zero) are equal to the moments of \(P(\ldots, u_1, \ldots, t)\). Rewriting equation (A 1) in terms of this generating function, we have

\[
\frac{\partial Z}{\partial t} = \sum_{i=0}^\infty d_i \frac{\partial Z}{\partial h_i} (e^{-h_i} - 1) + \sum_{i=0}^\infty b_i \frac{\partial Z}{\partial h_i} (e^{h_i} - 1) + \sum_{i=0}^\infty \sum_{j=0}^\infty \mu_{ij} \frac{\partial Z}{\partial h_i} (e^{h_i} - 1). \tag{A 3}
\]

In the continuum limit, this becomes a generating functional, \(Z[H(x), t]\), and using standard methods [34] this functional satisfies the following functional differential equation:

\[
\frac{\partial Z[H(x), t]}{\partial t} = \int_{-\infty}^{\infty} dx \left( H(x) - 1 \right) \left[ \int_{-\infty}^{\infty} dy \mu(y) Q(y, x) \frac{\partial Z[H(y)]}{\partial H(y)} + b(x) - d(x) e^{-H(x)} \right]. \tag{A 4}
\]

This equation therefore captures the behaviour of the moments of our original distribution \(P(r_1, n_2, \ldots, t)\) in the limit of a continuous fitness spectrum, and we will primarily focus on the two lowest moments of this distribution: the expectation value of the distribution of fitness classes in a population, \(\langle n(x, t) \rangle\), and the two point correlation function \(\langle n(x_1, t) \rangle \langle n(x_2, t) \rangle - \langle n(x_1, t) \rangle \langle n(x_2, t) \rangle - \langle n(x_1, t) \rangle \langle n(x_2, t) \rangle\).

The expectation value \(\langle n(x, t) \rangle\) is equal to a single functional derivative of our generating functional, with \(H(x)\) then set to zero:

\[
\frac{\partial Z[H(x), t]}{\partial H(x)} \bigg|_{H=0} = \left\langle n(x, t) \right\rangle e^{\int dx H(x)} \left| \right. _{H=0} = \left\langle n(x, t) \right\rangle. \tag{A 5}
\]

We find that

\[
\frac{\partial}{\partial t} \left\langle n(x, t) \right\rangle = \int dy (Q(y, x) - \delta(x - y)) \mu(y) \left\langle n(y, t) \right\rangle + r(x) \left\langle n(x, t) \right\rangle, \tag{A 6}
\]

where we have defined \(r(x) = b(x) + \mu(x) - d(x)\), the total net number of individuals produced per capita per unit time by individuals in fitness class \(x\).

The two-point function is given by two functional derivatives of \(\log Z[H, t]\) with respect to \(H(x_1), H(x_2)\), with \(H\) then set to zero:

\[
\frac{\delta \log Z[H, t]}{\delta H(x_1)} \bigg|_{H=0} = \left\langle n(x_1, t) \right\rangle e^{\int dx H(x)} \left| \right. _{H=0} - \left\langle n(x, t) \right\rangle e^{\int dx H(x)} \left| \right. _{H=0}^2 \right. = \left( n(x_1, t) \langle n(x_2, t) \rangle - \langle n(x_1, t) \rangle \langle n(x_2, t) \rangle \right). \tag{A 7}
\]

Applying this identity, we find that \(c(x_1, x_2, t)\) satisfies equation (A 27):

\[
\frac{\partial}{\partial t} c(x_1, x_2, t) = \int dy (Q(y, x_1) - \delta(y - x_1)) c(y, x_2, t) + (Q(y, x_2) - \delta(y - x_2)) c(x_1, y, t) + r(x_1) + r(x_2) c(x_1, x_2, t) + \delta(x_1 - x_2) \int dy Q(y, x_1) \langle n(y, t) \rangle + (b(x_1) + d(x_1)) \langle n(x_1, t) \rangle. \tag{A 8}
\]

**A.3. Fitness through time for constant mutation rate**

We first give a precise definition of the mean fitness of the population, \(F(t)\):

\[
F(t) = \frac{\int dx (n_0 + r_1) \langle n(x, t) \rangle}{\int dx n(x, t)}. \tag{A 9}
\]

We note that this is one of a number of possible generalizations of the corresponding expression for fixed population size, \(N\):

\[
\frac{\int dx (n_0 + r_1) \langle n(x, t) \rangle}{\int dx n(x, t)}, \tag{A 10}
\]

and may seem less natural than

\[
\frac{\int dx (n_0 + r_1) \langle n(x, t) \rangle}{\int dx n(x, t)} \tag{A 11}
\]

On the other hand, without population regulation, it is possible for the population to go extinct, and so this expression is not well-defined.

Applying the following identity satisfied by the Fourier transform (2.3), we then have

\[
\int dx (n_0 + r_1) \langle n(x, t) \rangle \int dx n(x, t) = r_0 - r_1 \frac{\partial}{\partial k} \log \tilde{n}(k) \bigg|_{k=0}. \tag{A 12}
\]

Putting these definitions together, and applying them to our solution (2.5) for \((\tilde{n}(k, t))\) with \(\tilde{n}(k, 0) = N_0\) we have:

\[
F(t) = r_0 - \mu_0 + \mu_0 \langle n(x, t) \rangle. \tag{A 13}
\]

**A.4. Fitness through time for scaling mutation rate**

For populations where mutation rate is proportional to reproductive rate, and where reproductive rate is in turn increasing with fitness class, then it is realistic to assume that \(\mu(x) = \mu_0 + \mu_x x\). In this case, our defining equation for \(\langle n(x, t) \rangle\) has an additional term relative to the case of constant mutation rate:

\[
\frac{\partial}{\partial t} \langle n(x, t) \rangle = \int dy (Q(y, x) - \delta(x - y)) \times (\mu_0 + \mu_x) \langle n(y, t) \rangle + (r_0 + r_1) \langle n(x, t) \rangle. \tag{A 14}
\]
where
$$F(g) = \log g - (Q(0) - 1)g,$$
and
$$g^{-1}(g) = k.$$
A.5. Two-point function and between population variation for constant mutation rate

Our results so far have focused on the expectation value for the distribution \( n(x, t) \) of fitness classes \( x \) at time \( t \) for an unregulated population, and its consequences for mean population fitness and within-population variation in fitness. For constant mutation rate, \( \mu_0 \), we now consider fluctuations around this expectation value, characterized by the equal-time two-point correlation function:

\[
c(x_1, x_2, t) = \langle n(x_1,t)n(x_2,t) \rangle - \langle n(x_1,t) \rangle \langle n(x_2,t) \rangle. \tag{A25}
\]

Applying the following identity:

\[
\frac{\partial \log Z[H,t]}{\partial \mu(x_1)} = \left( \langle n(x_1,t)n(x_2,t) \rangle e^{\Delta S[H]|n(x_2,t)} \right)_{|H=0} \bigg( \left( \langle n(x_1,t) \rangle e^{\Delta S[H]|n(x_1,t)} \right)_{|H=0} \bigg)^2 \\
= \langle n(x_1,t)n(x_2,t) \rangle - \langle n(x_1,t) \rangle \langle n(x_2,t) \rangle. \tag{A26}
\]

we find that \( c(x_1, x_2, t) \) satisfies:

\[
\frac{\partial}{\partial t}(c(x_1, x_2, t)) = \int d\mu(y) \left[ (Q(y, x_1) - \delta(y - x_1))c(y, x_2, t) + (Q(x_2, y) - \delta(y - x_2))c(x_1, y, t) \right] \\
+ \left[ r(x_1) + r(x_2) \right] c(x_1, x_2, t) \\
+ \delta(x_1 - x_2) \left[ \int d\mu(y) \frac{\partial}{\partial \mu(y)}(Q(y, x_1) \langle n(x_1,t) \rangle) \right]. \tag{A27}
\]

Making the assumption that \( Q(x, y) = Q(x - y) \), and that mutation rate \( \mu_0 \) is constant, equation (A27) can be written in terms of the Fourier transformed \( \tilde{c}(k_1, k_2, t) \) as:

\[
\frac{\partial \tilde{c}}{\partial t} = \mu_0 \langle Q(k_1) + Q(k_2) - 2\tilde{c}(k_1, k_2, t) \rangle \\
+ \left[ 2r_0 - ir_1 \frac{\partial}{\partial k_1} - ir_1 \frac{\partial}{\partial k_2} \right] \tilde{c}(k_1, k_2, t) \\
+ \mu_0 \langle Q(k_1 + k_2) + b \left( -i \frac{\partial}{\partial k_1} \right) \rangle \\
+ d \left( -i \frac{\partial}{\partial k_1} \right) \langle n(k_1 + k_2, t) \rangle. \tag{A28}
\]

We can obtain a solution by method of characteristics, and with initial condition \( \tilde{c}(k_1, k_2, 0) = 0 \) we have:

\[
\tilde{c}(k_1, k_2, t) = \mu_0\langle Q(k_1 + k_2) + 2ir_1(s-t), s \rangle n(k_1 + k_2 + 2ir_1(s-t), s) \\
/ n(k_1 + ir_1(s-t), s) n(k_2 + ir_1(s-t), s). \tag{A29}
\]

This result is so far completely general. To get an intuitive sense of how large this variation is, we consider the special case of mutation rate zero. It is then straightforward to derive that at early times the \( \langle n(1, t) \rangle / \langle n(1) \rangle \) as for unregulated growth without mutation. At later times, this variance becomes much larger very quickly. In concrete terms, in order to estimate mean population abundance, fitness or variance from an experimental system with a given precision, the necessary number of replicates will increase rapidly. This is partly due to the assumption of no epistasis: because fitness can increase without bound, the distribution of these quantities around the mean values we have derived can become very broad.

References
