Phenotypic plasticity can facilitate evolutionary rescue

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Abstract

Environmental variation is commonplace, but unpredictable. Populations that encounter a deleterious environment can sometimes avoid extinction by rapid evolutionary adaptation. Phenotypic plasticity, whereby a single genotype can express multiple different phenotypes, might play an important role in rescuing such populations from extinction. This type of evolutionary bet-hedging need not confer a direct benefit to a single individual, but it may increase the chance of long-term survival of a lineage. Here we develop a population-genetic model to explore how partly heritable phenotypic variability influences the probability of evolutionary rescue and the mean duration of population persistence, in changing environments. We find that the probability of population persistence depends non-monotonically on the degree of phenotypic heritability between generations: some heritability can help avert extinction, but too much heritability removes any benefit of phenotypic plasticity. We discuss the implications of these results in the context of therapies designed to eradicate populations of pathogens or aberrant cellular lineages.

Keywords:

evolutionary rescue; time to extinction; bacterial persistence; stochastic switching; evolutionary bet-hedging; fluctuating environments; adaptation to environmental change

Introduction

The very first study in experimental evolution, led by W. D. Dallinger in the 1880s, attempted to demonstrate that populations can rapidly adapt to environmental change and that evolutionary rescue of a population from extinction depends on the rate of change (Dallinger, 1887). Evolutionary rescue is the process by

which a population is able to recover from abrupt environmental changes that would otherwise lead to a demographic decline and eventual extinction (Bell and Andrew, 2009; Alexander et al., 2014; Gonzalez et al., 2013; Lindsey et al., 2013; Carlson et al., 2014). Evolutionary responses that allow populations to adapt to change on a sufficiently fast time scale to prevent extinction have been the focus of considerable experimental and theoretical interest, across diverse biological systems. In the field of conservation biology, questions of rescue are framed around ensuring the survival of species in deteriorating global habitats (Palumbi, 2001; Gonzalez et al., 2013; Davis et al., 2005). In contrast, in clinical contexts, the goal is eradication of pathogens or harmful populations of cells (Gonzalez et al., 2013; Alexander et al., 2014). These two bodies of work share a common thread (as Maynard Smith (1989) emphasized, adaptation in threatened populations is not like ordinary adaptation, it is a race against extinction), yet each present unique difficulties.

Here we focus on the questions of population eradication that arise in medically-relevant settings, where populations are often surprisingly resilient or recalcitrant to treatment due to evolutionary adaptation. In particular, we ask: how does heritable phenotypic variability alter the probability of evolutionary rescue? We study the evolutionary advantage of heritable phenotypic variability in populations of non-constant size. We determine the probability of rescue and the mean time to extinction in changing environments, through both analytical approximation and Monte Carlo simulations of population genetic models.

We are motivated in asking this question by well-documented examples of phenotypic heterogeneity used as evolutionary bet-hedging strategy in volatile environments. Classic examples include the bifurcation of a genotypically monomorphic population into two phenotypically distinct bistable subpopulations (Dubnau and Losick, 2006); bacterial persistence (Lewis, 2010; Cohen et al., 2013; Kussell et al., 2005; Sharma et al., 2015), whereby a genetically identical bacterial population survives periods of antibiotic stress by producing phenotypically heterogeneous sub-populations, some of which are drug-insensitive (Lewis, 2007); or quiescent phenotypes in cancer cell populations (Aguirre-Ghiso, 2007; Sharma et al., 2010; Smith et al., 2016), which are transient phenotypic (epi)states protected from the action of drugs. These dormant phenotypic states confer the population with some degree of phenotypic heterogeneity, helping it withstand periods of environmental stress. Phenotypes may be partially heritable upon cellular division, so that the offspring cell can sometimes "remember" and express the phenotypic state of its parent, or sometimes switch between phenotypic states at rates that greatly exceed those of genetic mutations (Balaban et al., 2004; Van den Bergh et al., 2016). Partial phenotypic inheritance through epigenetic mechanisms can lead to faster rates of adaptation and environmental tracking than genetic mutations alone. Even though persisters in such populations rely on a non-genetic form of inheritance, the rate of 'phenotypic mutation' is itself likely under genetic control (Levin

and Rozen, 2006).

Epigenetic bet-hedging strategies that use dynamic regulation of phenotypic variability can allow a population to persist and escape extinction, until more permanent genetic strategies arise. Many studies have addressed questions of genetic responses in evolutionary rescue (Lindsey et al., 2013; Uecker and Hermisson, 2015; Wilson et al., 2016; Uecker et al., 2014; Orr and Unckless, 2008, 2014; Alexander et al., 2014). Less attention has been given to the potential impact of phenotypic plasticity on evolutionary rescue (Ashander et al., 2016; Chevin et al., 2013). A recent study integrated stochastic demography with quantitative genetic theory in a model with evolving plasticity to explore the probability of rescue from a single, abrupt change in the environmental conditions (Ashander et al., 2016). Evolving plasticity was shown to facilitate evolutionary rescue unless the new environment is unpredictable.

Epigenetic plasticity as studied in Ashander et al. (2016) can cause phenotypes to differ widely within a lineage, whereas purely genetically encoded phenotypes only allow offspring phenotypically similar to the parents. The type phenotypic variability we explore here can produce phenotypic heterogeneity with familial correlations intermediate to these two extremes – for example, as observed in the contributions of DNA methylation variation to the heritability of phenotypes in Arabidopsis thaliana (Johannes et al., 2009) (Carja et al., 2014; Carja and Plotkin, 2016). This type of partly heritable phenotype is commonplace in medical settings, and its role in evolutionary rescue is yet to be understood.

We explore the evolutionary fate of a population that experiences either one sudden shift in the environmental regime, or many periodic changes in the environment. In the case of one abrupt environmental change, we study the probability of rescue when one mutant allele permits the expression of multiple phenotypic states. We imagine these phenotypic states as partially heritable, so that the phenotype expressed by an individual will be inherited by the offspring with some probability, p. We call this probability p the phenotypic memory. We are especially interested in the longterm fate of the population as a function of the variance in expressible phenotypes that the mutant allele confers, and also as a function of the amount of phenotypic memory between generations.

Our paper starts by specifying a mathematical model, based on birth-death processes, for populations subject to environmental change and to the introduction of a mutant allele that permits a range of expressible, partly heritable phenotypes. We pose our research question in terms of analyzing the long-term probability of extinction of such a population. We show that after one abrupt environmental change, the probability of evolutionary rescue is significantly increased when the population is phenotypically heterogeneous, and this increase critically depends on the phenotypic memory of individuals expressing the variable allele.

When the population experiences multiple environmental changes, the mean time to population extinction also increases for phenotypically heterogeneous populations (i.e. population persistence increases) and this increase depends non-monotonically on the phenotypic memory of the mutant allele, p. We provide a simple intuition for the complex dependence of evolutionary rescue on the degree of phenotypic memory, and we discuss the implications of our results for the eradication of evolving populations in medical contexts.

Model

We use a continuous-time Moran-type model to describe changes in allele numbers in a finite population of changing size N, with carrying capacity K. Each individual's genotype is defined by a single biallelic locus A/a, which controls its phenotype. The A allele encodes a fixed phenotypic value, whereas individuals with the a allele may express a wider range of phenotypes, drawn from a fixed distribution.

We study two versions of the model. In the first version, the population, assumed to be initially fixed for the wild-type non-plastic allele A, experiences a single abrupt change in the environmental regime. This environmental shift is expected to lead to a demographic decline in the population, meaning that death rates exceed birth rates for allele A. We ask what is the probability of evolutionary rescue if, at time $t = 0$, a new mutant phenotypically-plastic allele a appears in the population? The phenotype of this one initial mutant is assumed to be sampled randomly from the phenotypic distribution available to a. This phenotypic distribution is chosen such that both alleles A and a have the same expected fitness, so that the only difference between them is the possibility of (partly heritable) phenotypic variability. We analyze the probability of rescue as a function of the phenotypic variance and the phenotypic memory associated with the a allele.

In the second version of the model, we assume the same demographic setup (a population otherwise fixed on the non-plastic A allele with one phenotypically-variable a mutant appearing at time $t = 0$); but here we assume multiple epochs of environmental changes, occurring periodically. The question of persistence is framed in terms of the mean time to extinction of the population, as a function of the environmental period, the phenotypic variance and the phenotypic memory available to the a allele. In this case, the mapping from phenotype to fitness depends on the environmental regime, and it is chosen so that both alleles have the same expected fitness across environments.

Single environmental change

The constant-environment model studies how a novel allele that can express multiple phenotypes might alter the probability of evolutionary rescue of a population otherwise headed towards extinction. We describe the population using a continuous time birth-death model. Individuals of the wild type A and mutant type a each give birth and die according to the following per-capita rates:

Genotype	A	a
Phenotype	Φ_A	Φ_a
Birth rate	$\Phi_A(1-\frac{N}{K})$	$\Phi_a(1-\frac{N}{K})$
Death rate	1	1,

where Φ_A and Φ_a are random variables, N is the current population size, and K is the carrying capacity. The death rates of the two alleles are both assumed to be equal to 1. The random variable Φ_A is assumed deterministic with variance zero – that is, an individual with the A allele can express only one phenotype. By contrast, Φ_a is not deterministic and it can be either a discrete or continuous random variable with positive variance. Φ_A and Φ_a are chosen so that the two alleles have the same mean fitness: $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a)$. We choose fitness functions with equal means so we can focus our analysis on the effect of variance in phenotypes expressed by allele a, $\mathrm{Var}(\Phi_a)$, and not on any mean-fitness effect. An illustration of this model is presented in **Figure 1A**. In our analysis of this model we initiate the population at half its carrying capacity, $N = K/2$, in a regime where the wild-type allele has a higher per-capita death rate than its maximum possible birth rate, so that a wild-type population is expected to go extinct fairly quickly. We analyze the conditions under which the mutant allele a will rescue the populations from extinction, and we compare this analysis with Monte Carlo simulations in which we record the proportion of replicate simulations in which rescue occurs (defined as the population reaching carrying capacity $N = K$).

Periodic environmental changes

In our analysis of periodic environmental changes we assume that the population experiences two different types of environments, E_1 and E_2, which alternate deterministically every n generations, so that both environments are experienced every $2n$ generations. We assume that one environment is more favorable to one allele, and the other environment to the other allele. We study a scenario where the plastic allele a has lower expected fitness than the wild-type allele in one of the environmental regimes; and higher expected fitness than the wild-type in the other regime. In the case of persister phenotypes in bacteria, for example,

the environment that is detrimental to the allele a corresponds to the "no antibiotic" regime; whereas the persister a has a higher expected fitness than wild-type in the presence of antibiotic pressure.

We choose phenotypic ranges and fitness functions so that the mean fitness expressed by each of the two genotypes are equal, averaging over the two environmental regimes. This setup allows us to focus on the evolutionary advantage of phenotypic variance of a, $\mathrm{Var}(\Phi_a)$, and to study its consequences for population persistence without conflating its effect with any mean-fitness advantage of the a allele over the A allele.

Individuals of the wild type A and mutant type a each give birth and die according to the following per-capita rates:

Genotype	A	a
Phenotype	Φ_A	Φ_a
Birth rate in environment E_1	$f^1(\Phi_A)(1-\frac{N}{K})$	$f^1(\Phi_a)(1-\frac{N}{K})$
Birth rate in environment E_2	$f^2(\Phi_A)(1-\frac{N}{K})$	$f^2(\Phi_a)(1-\frac{N}{K})$,
Death rate in environment E_1	1	1
Death rate in environment E_2	1	1

where Φ_A and Φ_a denote random variables, although Φ_A is in fact deterministic with zero variance. The functions $f^i : \mathbb{R} \to \mathbb{R}$ $(i \in \{1,2\})$ map phenotype to fitness in each of the two environments, and f^1 is taken to be the identity function. We assume that both alleles have the same mean fitness in their preferred environment, and the same mean fitness in their unpreferred environment: $\mathbb{E}(f^1(\Phi_A)) = \mathbb{E}(f^2(\Phi_a))$ and $\mathbb{E}(f^2(\Phi_A)) = \mathbb{E}(f^1(\Phi_a))$. This condition also ensures that the average of two alleles' mean fitnesses, which we denote $M = \frac{\mathbb{E}(f^1(\Phi_A))+\mathbb{E}(f^1(\Phi_a))}{2} = \frac{\mathbb{E}(f^2(\Phi_A))+\mathbb{E}(f^2(\Phi_a))}{2}$, is the same in both environments. The function f^2 is defined as a reflection of f^1 around M: $f^2(x) = 2M - f^1(x)$. As a result, the variance in fitness of allele a with randomly drawn phenotype is the same in both environments: $\mathrm{Var}(f^1(\Phi_a))$=$\mathrm{Var}(f^2(\Phi_a))$ =$\mathrm{Var}(\Phi_a)$. These fitness functions describe a model in which each genotype has a preferred environment, but allele a can express a range of phenotypes whereas allele A expresses only a single phenotype (see illustration in **Figure 1B**). The symmetry conditions we have imposed on phenotypic means allow us to focus our analysis on the effects of phenotypic variation alone.

We study the possible long-term advantage of heritable phenotypic variability by analyzing how the introduction of the a allele into an otherwise non-variable population (A) changes the population's probability of rescue or mean times to extinction. We quantify how the probability of rescue or the time to extinction depends on environmental factors, such as the environmental period $2n$, on demographic factors, such as the carrying capacity N, and on molecular factors, such as the variance in phenotypes that can be expressed by

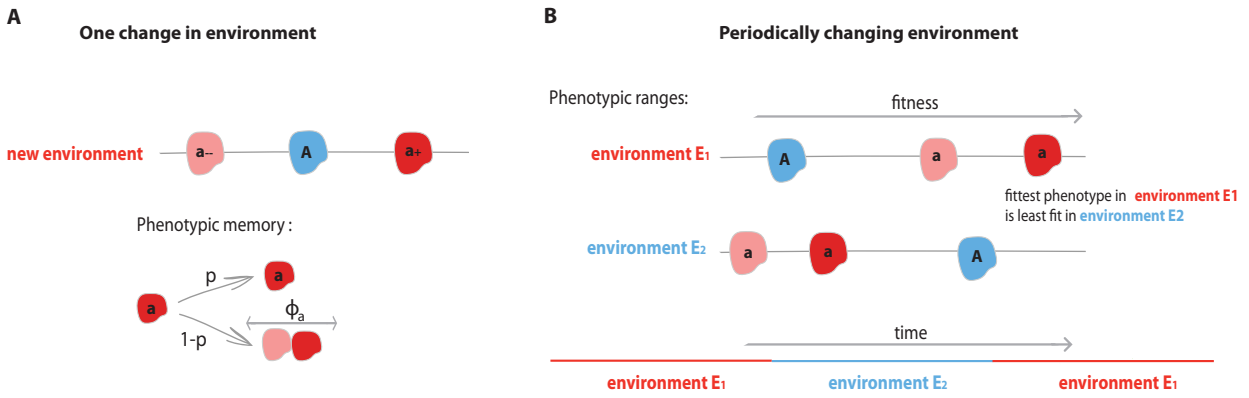

Figure 1: **Illustration of the two versions of the model.**

allele a, $\mathrm{Var}(\Phi_a)$, and the degree of phenotypic memory, p. We derive analytic approximations in the case of one environmental change, and we determine the mean times to extinction in changing environments by Monte Carlo simulations (Gillespie, 1976), using an ensemble of at least 10,000 replicate populations. All simulations are initiated at half carrying capacity, $N = K/2$, with the wild-type population in decline. In particular, we initiate all populations with $N = \frac{K}{2} - 1$ wild-type alleles A and with one copy of the a allele. In the case of a single environmental shock, we simulate until the population either goes extinct or achieves evolutionary rescue (defined as the population reaching carrying capacity $N = K$). In the case of multiple periodic environments, we simulate the process until extinction of the population.

We simulate the birth-death process in continuous time as follows. We sample the waiting time for an event from an exponential distribution with rate parameter equal to the sum of all possible rates beginning at time zero; we then randomly assign a specific event according to the relative probabilities of occurrence of each event type (birth or death events) and update the population status, time, and all event rates. If the event implemented is a birth we then determine the phenotypic state of the offspring as follows. If the individual chosen to reproduce has genotype A, then the phenotypic state of the offspring always equals its parent's (fixed) phenotypic value. For a reproducing individual with the a allele, however, there exists a probability of phenotypic memory, denoted by the parameter p, between parent and offspring: with probability p the offspring retains the phenotypic state of its parent, and with probability $1-p$ the offspring's phenotype is drawn independently from the random variable Φ_a. Thus, individuals of type a can express a range of phenotypic values, and their phenotype is partly heritable between generations (provided $p > 0$). In the case of periodic environments, we implement environmental changes (and re-calculate event rates) at

deterministic times: n, $2n$, $3n$, etc. Time is measured in units of an individual's expected lifetime – that is, the death rate is set to unity for all individuals in all simulations.

Results

Evolutionary rescue from a single environmental change

After a single, abrupt environmental change, the probability of evolutionary rescue is significantly increased when the population has access to phenotypic variability. To study a simple version of this problem within the context of our model we assume that the a allele has access to two different phenotypic states: $\Phi_{a,-}$ and $\Phi_{a,+}$, such that $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a)$. (In other words, we assume the random variable Φ_a consists of two point masses.) The probability of rescue depends critically on whether the plastic mutant a is initially introduced with its beneficial or its deleterious phenotype – that is, whether its birth rate is initially larger or smaller than its death rate.

When the a allele is introduced with a beneficial phenotype $\Phi_{a,+}$, its birth rate exceeds its death rate, and there is some chance that the population will be rescued from extinction. The population will be rescued, by definition, if the a lineage manages to become established (Uecker and Hermisson, 2011). As shown in **Figure 2A**, the chance of evolutionary rescue increases monotonically with the strength of phenotypic memory, p. This result makes intuitive sense: high-fitness variants of the a allele are preferentially transmitted to the next generation, and greater phenotypic memory p increases their propensity to maintain the high-fitness phenotype and become established in the population. Moreover, the probability of rescue is uniformly greater when the a allele can express a greater diversity of phenotypes, i.e. for $\mathrm{Var}(\Phi_a)$ large (**Figure 2A**), because the larger variance is associated with a greater fitness for the $\Phi_{a,+}$ phenotype. In summary, when the plastic allele is introduced with a beneficial phenotype, rescue is facilitated by increased phenotypic memory and by increased phenotypic variance of the plastic allele.

When the a allele is introduced with a deleterious phenotype $\Phi_{a,-}$, whose birth rate is smaller than its death rate, there is still the possibility of evolutionary rescue, because the phenotype of type-a individuals may change between generations. In this case, **Figure 2B** shows that the probability of evolutionary rescue depends non-monotonically on the strength of phenotypic memory p. There is simple intuition for this result as well, and it is informed by our mathematical analysis below. Intuitively, the probability of rescue in this case is the product of the probability that some a-type individual produces an offspring with the beneficial phenotype, $\Phi_{a,+}$, before the a-lineage is lost, times the probability of rescue associated with such

an individual with phenotype $\Phi_{a,+}$. Therefore, rescue is facilitated as the strength of phenotypic memory increases above zero (this effect is driven by the increase in the probability of rescue once an individual of phenotype $\Phi_{a,+}$ arises); but as the phenotypic memory increases further, towards one, the probability of rescue is reduced, because the entire a lineage will likely go extinct before producing any individual with a beneficial phenotype.

To provide a clear analysis of the intuitions described above, we first derive the probability of rescue, $\mathbb{P}_r(a_+)$, when the a mutation is introduced with the beneficial phenotype $\Phi_{a,+}$. To do so, we compute an effective selection coefficient of the entire, phenotypically variable a lineage, by assuming that the two phenotypes within the a lineage quickly reach mutation-selection balance. Given "mutation" rate $\mu = \frac{1-p}{2}$ between the two phenotypes, at equilibrium, the frequency of phenotype $\Phi_{a,+}$ within the a-lineage is given by $f_{a,+}$:

$$f_{a,+} = \frac{\Phi_{a,+} - \Phi_{a,-} - \mu\Phi_{a,-} - \mu\Phi_{a,+}}{2(\Phi_{a,+} - \Phi_{a,-})} + \frac{\sqrt{4\Phi_{a,-}\mu(\Phi_{a,+} - \Phi_{a,-}) + (\Phi_{a,-} - \Phi_{a,+} + \mu\Phi_{a,+} + \mu\Phi_{a,-})^2}}{2(\Phi_{a,+} - \Phi_{a,-})} \tag{1}$$

We then compute the effective birth rate of the a lineage

$$s_a = \Phi_{a,-}(1 - f_{a,+}) + \Phi_{a,+}f_{a,+}. \tag{2}$$

If the effective birth rate s_a is lower than the death rate, then there is zero probability of rescue, as all individuals of either wild or mutant type are expected to leave fewer than one offspring per lifetime. But when the effective birth rate s_a of the a lineage exceeds its death rate (unity), then the probability of rescue can be approximated by $\mathbb{P}_r(a_+) = \frac{s_a - 1}{s_a}$. This analytic approximation is shown in **Figure 2**, alongside the results of an ensemble of Monte Carlo simulations. In the case of perfect phenotypic memory ($p = 1$), we recover the results from (Wilson et al., 2016; Orr and Unckless, 2008): the probability of rescue from standard genetic variation (the presence of one mutant a at the time of the environmental change) can be approximated by the probability of establishment (Uecker and Hermisson, 2011) of this new mutation in the population, which increases monotonically with time and, as $t \to \infty$, asymptotes to

$$p_\infty = \frac{\Phi_{a,+} - 1}{\Phi_{a,+}}, \tag{3}$$

according to equation (3) in Wilson et al. (2016) (setting $d_m = 1$ and $b_m = \Phi_{a,+}$). This result differs from

equation (2) in Orr and Unckless (2014) by a factor of two, because the variance in offspring number in our Moran-type model is twice that of the Wright-Fisher model.

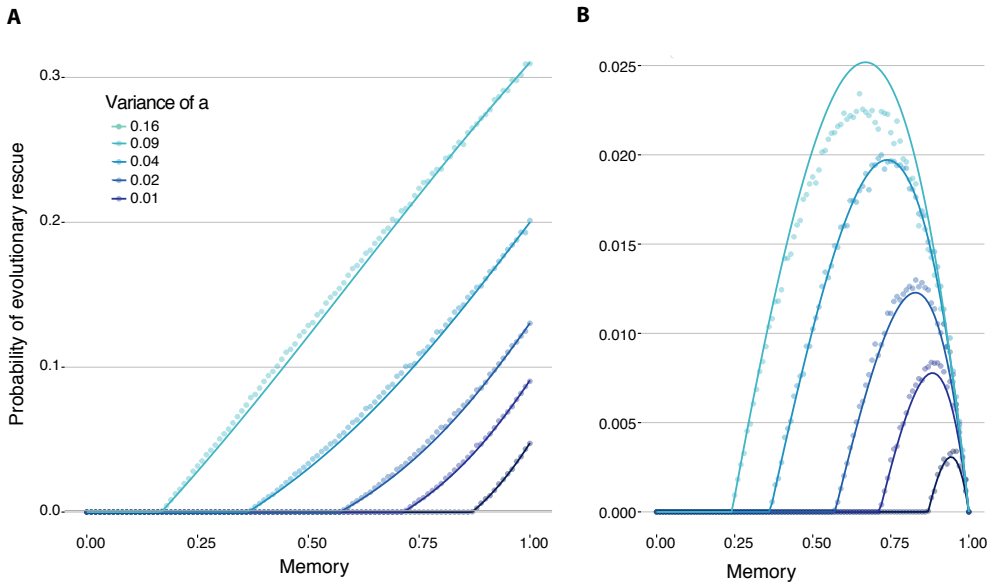

Figure 2: **Probability of evolutionary rescue.** The dots represent the ensemble average across 10,000 replicate Monte Carlo simulations, whereas the curves show our analytical approximations. **Panel A**: Probability of rescue starting with one copy of allele a with phenotype $\Phi_{a,+}$, in an otherwise wild-type A population. **Panel B**: Probability of rescue starting with one copy of allele a with phenotype $\Phi_{a,-}$, in an otherwise wild-type population. All populations are initiated at half carrying capacity, $N = K/2 = 2,500$, and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$.

Conversely, when the a mutation is introduced with its deleterious phenotypic state, $\Phi_{a,-}$, we derive an approximation for the probability of rescue $\mathbb{P}_r(a_-)$ as the probability of at least one phenotypic mutation to $\Phi_{a,+}$ before the loss of the a allele, multiplied by $\mathbb{P}_r(a_+)$. In other words, if we let η denote the event that there is at least one phenotypic mutation within the a-lineage before its loss, then we will approximate the probability of rescue

$$\mathbb{P}_r(a_-) = \mathbb{P}(\eta)\mathbb{P}_r(a_+). \tag{4}$$

We need only derive an expression for $\mathbb{P}(\eta)$. Note that frequency of a deleterious allele with selection coefficient $-s$, introduced in one copy, is expected to decay e^{-st}, and so the probability that no mutation occurs before its loss is $\mathrm{e}^{(-\int_0^\infty \mu \mathrm{e}^{-st} dt)}$, according to mutation viewed as a time-inhomogeneous Poisson process with intensity function $\mu \mathrm{e}^{-st}(1 - \frac{K}{N}) = \frac{\mu \mathrm{e}^{-st}}{2}$ (recall that our populations are initiated size $N = \frac{K}{2}$).

As a result we obtain

$$\mathbb{P}(\eta) = 1 - \mathrm{e}^{(-\int_0^\infty \mu \mathrm{e}^{-st} dt)} = 1 - \mathrm{e}^{-\frac{\mu}{s}}. \tag{5}$$

where $s = \Phi_A - \Phi_{a,-}$.

Finally, the probability of rescue when the a allele is introduced with random phenotype can be approximated as:

$$\mathbb{P}_r(a) = \frac{1}{2}\mathbb{P}_r(a_+) + \frac{1}{2}\mathbb{P}_r(a_-) = \frac{1}{2}\mathbb{P}_r(a_+) + \frac{1}{2}\mathbb{P}(\eta)\mathbb{P}_r(a_+). \tag{6}$$

Population persistence in periodically changing environments

Phenotypic variability and phenotypic memory also influence population persistence in periodically changing environments, in addition to the case of a single environmental change that has been the subject of most work on evolutionary rescue. With a periodically changing environment, the question of persistence is conveniently framed in terms of the mean time before population extinction. Even in this more complicated setting we once again observe a non-monotonic effect of phenotypic memory, p, on population persistence: populations go extinct quickly for either small p or large p, whereas intermediate amounts of phenotypic memory can promote persistence for long periods of time.

Figure 3A shows the mean time to extinction as a function of the phenotypic memory, for a range of environmental periods n. In all these cases, a population comprised of only the non-plastic wild-type allele A goes extinct quickly (cf. **Supplementary Figure S1**). But populations initiated with a single copy of the plastic allele a have the potential to persist for very long times, especially for intermediate values of the phenotypic memory parameter, p.

In our model of periodic environments, faster environmental changes are correlated with longer population persistence, even in the case of a phenotypically invariant wild-type population (**Supplementary Figure S1**). This occurs because long stretches of the environmental regime deleterious to the A allele lead to population declines that the beneficial periods cannot replenish. It is particularly in faster-changing environments that phenotypic memory in a plastic allele a provides the largest advantage for population persistence – because it helps the high-fitness realizations of a allele remain high-fitness, which is essential for population persistence through environmental epochs deleterious to the wild-type A allele. The non-monotonic dependence of persistence time on phenotypic memory also makes intuitive sense. On the one hand, it is beneficial for the a allele to have some phenotypic memory within each environment (E_1 or E_2), as this helps the high-fitness realizations of the allele with little effect on its low-fitness realizations. On

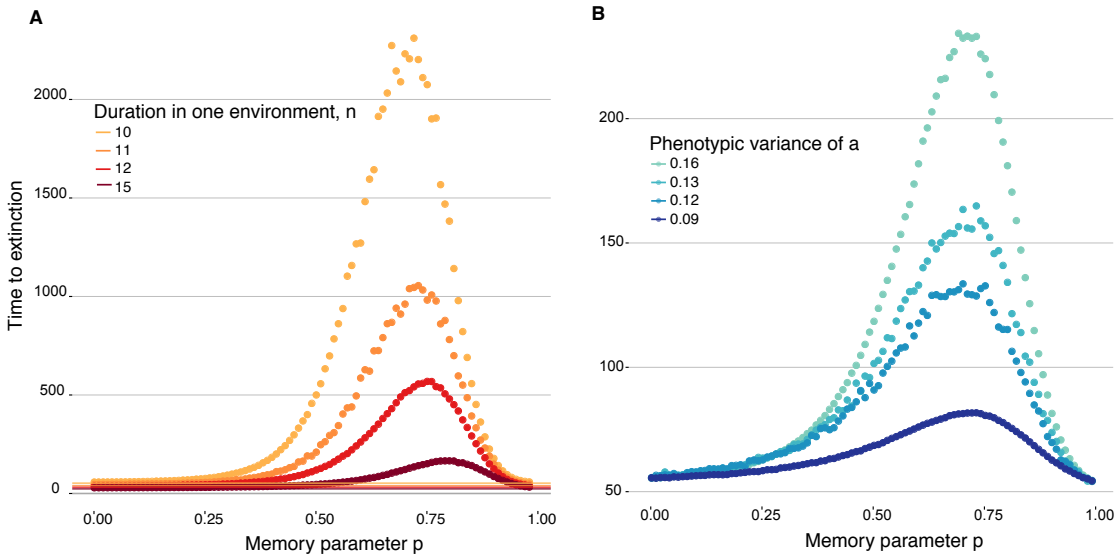

Figure 3: **Population persistence in periodically changing environments.** The dots represent the mean time before population extinction across 10,000 replicate simulations. All populations are initiated at half carrying capacity, $N = K/2 = 500$, with a single mutant genotype a drawn with a random phenotype introduced into a random one of the two different environments. The two environments then cycle deterministically with each environmental epoch lasting n time units, where time is measured in units of the expected lifespan of an individual. **Panel A**: Mean time until population extinction for a range of different environmental periods, with $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$ and $\mathrm{Var}(\Phi_a) = 0.25$. The lines, each corresponding to a different value of n, show the mean time to extinction of a population comprised of only wild-type A alleles. **Panel B**: Mean time until population extinction for different amounts of phenotypic plasticity, $\mathrm{Var}(\Phi_a)$, with a fixed environmental duration of $n = 10$ units, $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$.

the other hand, too much phenotypic memory is detrimental in the long-run, because once the environment shifts, the a lineage will be "stuck" with a deleterious phenotype. Moreover, regardless of the phenotypic memory, the duration of persistence always increases with the variance in phenotypes that a can express, $\mathrm{Var}(\Phi_a)$ (**Figure 3B**) – that is, the population can persist longer when the plastic allele has access to a larger phenotypic range.

Discussion

Evolutionary adaptation occurring on the same timescale as demographic dynamics can have profound effects on the persistence of a population. The theory of evolutionary rescue provides a conceptual framework that links demography and evolution in finite populations of variable size (Lindsey et al., 2013; Uecker and Hermisson, 2015; Wilson et al., 2016; Uecker et al., 2014; Orr and Unckless, 2008, 2014; Alexander et al., 2014; Bertram et al., 2016). Populations experiencing a sudden change in section pressures or, frequent

and unpredictable environmental variation, may either genetically adapt or be unable to recover. These populations have a limited window of opportunity for individuals with phenotypic solutions advantageous in the novel environment to appear and establish. Genetic adaptation after abrupt environmental changes can prevent extinction under several different demographic scenarios, but such a mechanism of rescue is inherently limited by the genomic mutation rate.

Transient and variable phenotypes, which can be mediated by rapid transitions in the epigenome, may provide an additional, selectable layer of traits that enable populations to persist until the appearance of more permanent strategies, such as genetic resistance. In systems ranging from bacterial infections, to latency in viral populations, or cellular neoplastic development, this form of epigenetic, partly heritable phenotypic heterogeneity has been shown to facilitate adaptation and population persistence under changing selection pressures (Seger and Brockman, 1987; Acar et al., 2008; Veening et al., 2008). These responses via partially heritable phenotypic variability can occur on faster time scales than genetic responses, and they may play a critical role in the path towards long-term resistance eventually reinforced by genetic changes.

The goal of this study has been to develop a population-genetic model to quantify the probability of evolutionary rescue and mean times to extinction for populations that harbor heritable variation in expressed phenotype. Although our simple model neglects the myriad of mechanisms that give rise to phenotypic variability, it makes some general qualitative and quantitive predictions that should hold broadly and can inform the design of therapies in clinical contexts where population eradication is desired. Indeed, many clinical examples of therapy failure are now known to be caused by phenotypic heterogeneity, persistence or quiescent cellular states (Cohen et al., 2013; Deris et al., 2013).

By exploring the interplay between phenotypic memory and treatment period, our results suggest that two very different types of intervention will be effective. Both options stem from the fact that, unlike genetic changes, epigenetic or phenotypic changes are reversible. The existence of an intermediate phenotypic memory that maximizes the time to extinction suggests that effective interventions are treatments that disrupt the molecular memory to either extreme ($p = 0$ or $p = 1$). This would facilitate eradication by decreasing the chance of a phenotypically resistant type establishing before the population goes extinct. Of course, further detailed predictive models, specialized to particular populations and drug actions, are needed to formulate optimal therapies across the plethora of diseases where transient phenotypic variability drives treatment failure. But we expect the lessons learned from simple models, concerning the complex effect of phenotypic memory on persistence, to hold generally.

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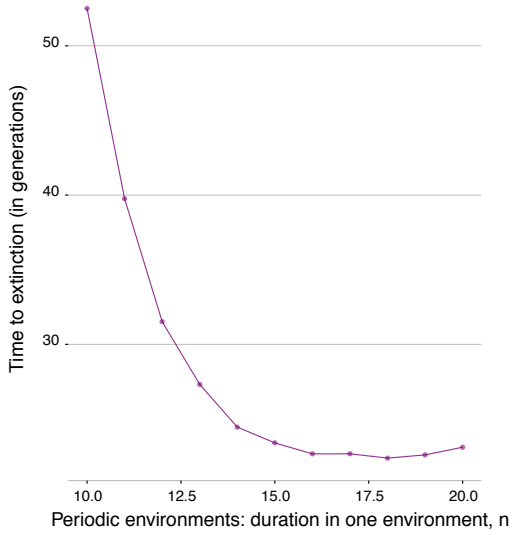
List of Figures

Figure 1. **Illustration of the two versions of the model.**

Figure 2. **Probability of evolutionary rescue.** The dots represent the ensemble average across 10,000 replicate Monte Carlo simulations, whereas the curves show our analytical approximations. **Panel A**: Probability of rescue starting with one copy of allele a with phenotype $\Phi_{a,+}$, in an otherwise wild-type A population. **Panel B**: Probability of rescue starting with one copy of allele a with phenotype $\Phi_{a,-}$, in an otherwise wild-type population. All populations are initiated at half carrying capacity, $N = K/2 = 2,500$, and $\mathbb{E}(\Phi_A) = \mathbb{E}(\Phi_a) = 0.95$.

Figure 3. **Population persistence in periodically changing environments.** The dots represent the mean time before population extinction across 10,000 replicate simulations. All populations are initiated at half carrying capacity, $N = K/2 = 500$, with a single mutant genotype a drawn with a random phenotype introduced into a random one of the two different environments. The two environments then cycle deterministically with each environmental epoch lasting n time units, where time is measured in units of the expected lifespan of an individual. **Panel A**: Mean time until population extinction for a range of different environmental periods, with $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$ and $\mathrm{Var}(\Phi_a) = 0.25$. The lines, each corresponding to a different value of n, show the mean time to extinction of a population comprised of only wild-type A alleles. **Panel B**: Mean time until population extinction for different amounts of phenotypic plasticity, $\mathrm{Var}(\Phi_a)$, with a fixed environmental duration of $n = 10$ units, $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$.

Figure S1. **Mean time to population extinction for populations fixed on the wild-type A.** Here $f^1(\Phi_A) = 0.5$, $f^2(\Phi_A) = 1.5$ and the carrying capacity is $K = 1,000$.



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