When does stronger selection increase the probability of evolutionary rescue?

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Author Contributions

K.X. conceived the project, conducted the analyses and wrote the initial draft. Both K.X. and M.O. contributed to all the analyses and the revision of the manuscript.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Abstract

After an environmental change, populations may be rescued from extinction through adaptive evolution. Stronger environmental changes often cause a more rapid decline of non-adapted genotypes and, meanwhile, increase the selective advantage of adaptive genotypes, which can have opposing effects on the probability of rescue. More generally, it is unclear if the probability of rescue increases or decreases with stronger selection, with important implications for herbicide/drug resistance evolution. By investigating various scenarios of rescue, we show that, in general, rescue becomes more likely with stronger selection when: 1) the rate of evolution has a stronger response to selection and 2) the rate of population decline is more rapid. A stronger evolutionary response to selection occurs when adaptive alleles are more dominant or the level of inbreeding is higher, or the genetic variance is larger and the environmental shift is more rapid for rescue via the evolution of quantitative traits. The intuition is that a stronger evolutionary response to selection increases the marginal benefit of increased selection, while a more rapid decline of the population lowers the marginal cost of a reduction in mean absolute fitness.

Introduction

After an environmental change, a population may avoid extinction through a process known as "evolutionary rescue" (Carlson el. 2014, Bell 2017). While rescue is desirable in conservation contexts, it is often undesirable in agriculture (herbicide/pesticide resistance) and medicine (drug resistance). When there are no interactions among genotypes, the probability of rescue depends solely on the abundance and absolute fitness of genotypes that have a positive growth rate (adaptive genotypes), completely independent of non-adaptive genotypes and therefore also independent of the selection strength (Orr & Unckless 2008, Day et al. 2015). However, interactions between adaptive and non-adaptive genotypes are ubiquitous, occurring, for example, via mutations, segregation, and recombination. In this case, the rescue probability can depend on the selective advantage of adaptive genotypes over the non-adaptive genotypes and the pace of demographic decline in the non-adapted population.

Both the selective advantage and the demographic decline rate often vary with the environment, obscuring the consequences of an environmental change on the probability of rescue. For example, higher concentrations of herbicides or antibiotics tend to reduce the absolute fitness of both non-resistant and resistant genotypes by different extents, thus altering the fitness difference between them (Busi et al. 2011, Gullberg et al. 2011, Gould et al. 2018; illustrated in Table 1). It therefore remains controversial whether higher concentrations of herbicides or antibiotics should lead to a lower likelihood of resistance evolution (Andersson & Hughes 2012, Bell 2017).

To illustrate the problem more concretely, consider a locus with alleles A and a within a diploid population. Assume genotype AA is adaptive and aa is non-adaptive, with Aa having an intermediate growth rate between aa and AA. If a faster decline rate of the non-adaptive genotype aa is accompanied with stronger selection, conflicting effects emerge on the rescue probability. When allele A is rare, its fitness is dragged down by allele a, since allele A is mainly found in heterozygotes Aa. Stronger selection accelerates evolution and thus makes the marginal fitness of allele A increase faster, by more rapidly eliminating allele a so that allele A is likely to be found in homozygote AA. However, stronger selection also lowers the initial population mean fitness and therefore causes a faster initial population decline. It is unclear how faster evolution and faster population decline combine to affect the rescue probability.

Table 1 summarizes three ways in which the absolute fitness of the adaptive and non-adaptive genotypes can change with the strength of selection (whether the heterozygote is adaptive or not will depend on dominance, see results below). In scenario I, the absolute fitness of all genotypes declines with stronger selection, but the fitness of the non-adaptive genotype declines faster than the fitness of the adaptive genotype. In scenario II, the absolute fitness of all genotypes increases with stronger selection.

The two scenarios may often occur as herbicide/antibiotic concentration increases, as illustrated by figure (A) in Table 1. In scenario III, stronger selection increases the fitness of the adaptive genotype but reduces fitness of the non-adaptive genotype. This scenario may occur if the environmental change involves an increase in new resources that the adaptive genotype can utilize, such as the evolution of the melanic-morph in the peppered moth under industrial melanism (see figure (B) in Table 1; Cook & Saccheri 2013) and changes in food resources in the flour beetle (Agashe et al. 2011). As summarized in Table 1, in scenario II stronger selection should always enhance the probability of rescue via various factors, while in scenarios I and III the consequences of stronger selection on the rescue probability are not clear due to opposing effects.

The opposing effects of selection on population survival also occur when rescue occurs via phenotypic selection on quantitative traits (Kopp & Matuszewski 2014). Here stronger selection means larger fitness changes with the phenotypic value, causing an environmental change to induce both faster evolution and a larger decline in population mean fitness.

The aim of this paper is to identify the conditions under which the rescue probability of a population increases with stronger selection. We investigate rescue scenarios involving selection on two alleles at a single locus and phenotypic selection on a quantitative trait. For evolution at a single locus, we examine two scenarios: 1) the adaptive genotype is initially rare and may get lost by chance and 2) the adaptive genotype is initially at a relatively high frequency and bound to fix, so that extinction risk is mainly due to stochasticity in demographic growth. In the quantitative genetic model, we also consider two scenarios, depending on whether the environmental change is abrupt or gradual.

Rescue via the establishment of rare alleles

We first consider a diploid population experiencing an abrupt environmental change and a locus with two alleles A and a. The frequencies of genotypes AA, Aa, and aa are expressed as $Fp_t + (1-F)p_t^2$, $2(1-F)p_t q_t$, and $Fq_t + (1-F)q_t^2$, respectively. Here p_t and $q_t = 1 - p_t$ are the frequencies of alleles A and a at time t, respectively. The inbreeding coefficient, F, quantifies the departure of homozygosity from Hardy-Weinberg equilibrium, with possible values ranging from $1 - \frac{2}{1+|2p_t-1|}$ to 1. An excess of homozygosity may occur due to genetic drift in small populations and non-random mating (Caballero & Hill 1992). An excess of heterozygosity may occur when there is asexual reproduction (Stoeckel et al. 2006, Haag & Roze 2017) or negative assortative mating (Workman 1964). By setting $F = 1$, the model also applies to a haploid population.

We define selection strength $s > 0$ and dominance $0 \leq h \leq 1$ such that the differences in absolute Malthusian fitness between genotypes are $m_{AA} - m_{aa} = s$ and $m_{Aa} - m_{aa} = hs$. The absolute fitness of genotypes AA, Aa and aa are $m_{AA} = m_0 + (1-\phi)s$, $m_{Aa} = m_0 + (h-\phi)s$, and $m_{aa} = m_0 - \phi s$, respectively. The parameter ϕ determines how the absolute fitness of genotypes changes with increased selection s and different parameter ranges of ϕ correspond to the three scenarios in Table 1. We assume $m_{AA} > 0$ and $m_{aa} < 0$, so that a population composed primarily of aa genotypes initially suffers demographic decline but may avoid extinction if allele A reaches a sufficiently high frequency. This assumption requires $-s(1-\phi) < m_0 < \phi s$.

When allele A is initially rare, it may be lost by chance (Charlesworth 2020). Therefore, whether a population will be rescued or not mainly depends on whether allele A will establish (Orr & Unckless 2008). We investigate the probability of rescue either via the establishment of mutations that occur after the environmental change (de novo mutations) or via the establishment of pre-existing A alleles before the environmental change (standing genetic variation). We assume that mutations from allele a to allele A occur at a rate u per generation, and we ignore back-mutation. For rescue via standing genetic variation, we assume that allele A is selected against before the environmental change, with selection and dominance coefficients s' and h', and is maintained under mutation-selection-drift balance.

To be consistent with previous studies (Orr & Unckless 2008), we use the alternative notation $m_{AA} = s - r$, $m_{Aa} = hs - r$, and $m_{aa} = -r$, where $r = \phi s - m_0 > 0$ represents the declining rate of aa. When allele A is rare, its marginal fitness is approximately $h_e s - r$. Here $h_e = F + (1-F)h$ is referred to as the effective dominance coefficient, since when allele A is rare, there is a probability F that it is found in a homozygote AA and a probability $1-F$ that it is found in a heterozygote Aa. When the population is haploid or completely selfing, $h_e = 1$.

We assume that allele A initially has a positive but low marginal fitness when it is rare, i.e., $0 < h_e s - r \ll 1$, so that the establishment probability of a single A allele is approximately $2(h_e s - r)$ (Orr & Unckless 2008). The probability of rescue by new mutations and standing genetic variation is then respectively (Glémin & Ronfort 2013),

$$P_{res}^{new} \approx 1 - \exp\left[-4N_{0,e}u\frac{h_e s - r}{r}\right], \tag{1a}$$

$$P_{res}^{sv} \approx 1 - \left(1 + \frac{h_e s - r}{h_e' s'}\right)^{-4N_{0,e}u}, \tag{1b}$$

where $N_{0,e}$ is the initial effective population size.

For rescue from standing variation, if the selection and dominance coefficient before and after the environmental change are independent, it is conceptually clear that stronger selection before the environmental change will reduce the rescue probability, while stronger selection after the environmental changes will promote rescue. Nevertheless, the strength of selection before and after the environmental change may often be positively correlated (e.g., antibiotic resistance alleles, Melnyk et al. 2015), and a related question is whether rescue from standing variation is more likely via large-effect or small-effect alleles. Therefore, below we present results assuming that the selection and dominance coefficient before the environmental change, s' and h', are proportional to s and h, respectively.

Section I of the Supplementary Materials shows that, in addition to the bounds required for $h_e s - r > 0$ as well as $m_{aa} < 0$ and $m_{AA} > 0$ (i.e., $-s(h_e - \phi) < m_0 < \phi s$), increased selection strength s raises both P_{res}^{new} and P_{res}^{sv}, despite their different forms (eqn 1) when the baseline fitness is negative ($m_0 < 0$). All together, these conditions mean that stronger selection promotes rescue when

$$-s(h_e - \phi) < m_0 < \min\{\phi s, 0\}. \tag{2}$$

From this we see that stronger selection always increases the rescue probability when the fitness of all genotypes increases with s ($\phi < 0$), and always reduces the rescue probability when the fitness of all genotypes decreases with s ($\phi > 1$).

When the fitness of AA increases with s but the fitness of aa decreases with s ($0 < \phi < 1$), stronger selection promotes rescue when the baseline fitness m_0 is negative, but inhibits rescue when m_0 is positive, as illustrated in Figs. 1(a) and 1(b). To see the reason, note that the rescue probability depends on the product of the establishment probability of each A allele, $\pi = 2\frac{N_e}{N}(h_e s - r)$, and the total number of A alleles n_A that occur from new mutations ($n_A = \frac{2N_0 u}{r}$) or pre-exist in the population ($n_A = \frac{2N_0 u}{h_e' s'}$). The effects of s on this product are

$$\frac{1}{n_A \pi}\frac{\partial(n_A \pi)}{\partial s} = \frac{1}{n_A}\frac{\partial n_A}{\partial s} + \frac{1}{\pi}\frac{\partial \pi}{\partial s} = \begin{cases} -\dfrac{\phi}{r} + \dfrac{h_e - \phi}{h_e s - r}, \text{new mutations} \\ -\dfrac{1}{s} + \dfrac{h_e - \phi}{h_e s - r}, \text{standing variation} \end{cases}. \tag{3}$$

The first term, which is always negative (since $r = \phi s - m_0 > 0$), represents the marginal cost of increased selection by reducing the number of A alleles. The second term is the marginal effect on the establishment probability, which is a benefit when $h_e - \phi > 0$. When $h_e - \phi < 0$, increased selection instead causes a marginal cost by reducing the establishment probability, thus always lowering the rescue probability. Stronger selection promotes rescue when the marginal benefit outweighs the cost. This occurs

for rescue by new mutations or from standing genetic variance when $m_0 < 0$, matching our more formal analysis above (eqn 2). A lower m_0 increases the marginal benefit from an increased establishment probability and also reduces the cost of fewer new mutation inputs for rescue via the establishment of new mutations. The above results also qualitatively hold when allele A initially has a negative marginal fitness, i.e., $h_e s - r < 0$ (Section II of the Supplementary Materials).

Rescue via deterministic evolution of common alleles

When allele A is initially common, changes of its frequency will be nearly deterministic unless the population size declines to be very small (Hartfield & Glémin 2016, Charlesworth 2020). Since in this case allele A is bound to fix, population extinction is mainly caused by stochasticity in population size. We assume that the population size change is subject to either demographic or environmental stochasticity (Xu et al. 2023), while the rate of allele frequency change is deterministic, given by (Charlesworth 2020)

$$\frac{dp_t}{dt} = sp_t q_t (h_e + (1-F)(1-2h)p_t). \tag{4}$$

Note that the rate of evolution only depends on the relative fitness differences and therefore does not depend on the parameter ϕ. By solving for the allele frequency, the mean fitness of the population at time t is $m_t = sp_t(2h_e - F + (1-F)(1-2h)p_t) - r$.

Under demographic and environmental stochasticity, the change of population size N_t during time t to $t + dt$ is respectively,

$$dN_t = m_t N_t dt + \sigma_d \sqrt{N_t} dW_t, \tag{5a}$$

$$dN_t = m_t N_t dt + \sigma_e N_t dW_t. \tag{5b}$$

Here W_t is the Wiener process and σ_d^2 and σ_e^2 represent the strength of demographic and environmental stochasticity, respectively.

We define the survival probability at time t as the probability that the population has not gone extinct by time t. Changes in selection strength impact the survival probability by affecting the allele frequency and thus the mean fitness m_t over time. Section III of the Supplementary Materials shows that if the cumulative growth rate up to time t, $\int_0^t m(x)dx$, is smaller, the survival probability at time t is lower, which is a sufficient but not necessary condition. In contrast, a larger cumulative growth rate up tom time t is a necessary but not sufficient condition for a higher survival probability.

For the special case when $h = 0.5$, Section III of the Supplementary Materials shows that

$$\frac{\partial \int_0^t m_x dx}{\partial s} = (p_t - \phi)t. \quad (6)$$

Therefore, stronger selection always increases the survival probability when the absolute fitness of all genotypes increases ($\phi \leq 0$, Table 1). Stronger selection always reduces the survival probability when absolute fitness of all genotypes declines ($\phi \geq 1$), which indicates that faster evolution is not able to compensate for the cost of quicker demographic decline.

When the absolute fitness of AA increases while the absolute fitness of aa decreases with increased selection ($0 < \phi < 1$), stronger selection increases the cumulative growth rate when $p_t > \phi$. Therefore, given the initial allele frequency is small enough ($p_0 < \phi$), stronger selection reduces the survival probability immediately after the environmental change but potentially increases it later (see Fig. 2(a)). Specifically, there exist selection strengths that cause the highest and lowest survival probabilities at time t (see Fig. 2(a)). The selection strength that minimizes the survival probability gradually declines over time (see lines in Figs. 2(b)-(c)). In contrast, the selection strength maximizing the survival probability remains low soon after the environmental change, and suddenly shifts to be high after some time (marked by arrows in Figs. 2(b)-(c)).

Stronger selection is more likely to increase the survival probability when the effective dominance of allele A, $h_e = F + (1 - F)h$, is higher (Fig. 2(b)), as in the previous section. Intuitively, higher effective dominance accelerates evolution when allele A is rare ($\frac{dp_t}{dt} \approx sh_e p_t$ when $p_t \ll 1$), but slows down evolution when allele A becomes predominant since allele a is masked in heterozygotes. However, the former effect is more critical in determining population survival, since once allele A is common the population already has a low risk of extinction.

Stronger selection tends to promote survival when the baseline fitness m_0 is lower (Fig. 2(c)), so that the growth rate of aa is far below 0 and the growth rate of AA is only slightly above 0 (Fig. 2(d)). This impact of m_0 is particularly prominent when ϕ is high (compare dashed vs solid lines in Fig. 2(c)), so that both Aa and aa tend to have high growth rates (Fig. 2(d)). Intuitively, the marginal cost of increased selection on reducing the initial absolute fitness is weaker with a lower baseline fitness m_0, while changes in m_0 do not affect the marginal benefit of an increased rate of evolution. This result is qualitatively similar to the finding in the previous section when rescue is via the establishment of rare alleles, where increased selection increases the rescue probability when $m_0 < 0$.

Rescue via the evolution of a quantitative trait

For rescue via phenotypic selection on a quantitative trait, we consider a random-mating diploid population with a trait z under stabilizing selection. We assume that the phenotype follows a normal distribution, with the mean value at time t being $\overline{z}_t$ and the genetic and phenotypic variance being V_G and V_z, respectively. Without loss of generality, we assume that the mean trait value is initially zero, $\overline{z}_{t=0} = 0$. The absolute Malthusian fitness of phenotype z is $m(z) = m_0 - \frac{\omega}{k}|\theta_t - z|^k$. Fitness reaches the highest value, m_0, at the phenotypic optimum, θ_t, which may change over time. The strength of selection depends on both the parameters ω and k. However, below we focus on the effects of parameter ω on rescue given a fixed k, and we refer ω as the selection strength.

We assume that selection strength is weak relative to the amount of phenotypic variation ($\omega V_z \ll 1$), so that the phenotype distribution remains nearly normal and the genetic and phenotypic variances remain nearly constant over time. Assuming a substantial shift in the phenotypic optimum ($\theta_t - \overline{z}_t \gg 1$), Section IV of the Supplementary Materials shows that the rate at which the mean phenotype $\overline{z}_t$ evolves is approximately

$$\frac{d\overline{z}_t}{dt} \approx V_G \frac{dm(z)}{dz}|_{z=\overline{z}_t} = \omega V_G |\theta_t - \overline{z}_t|^{k-1}. \tag{7}$$

By solving for the mean phenotype over time, we can calculate the mean absolute fitness and thus obtain the survival probability (eqn (A3.1)).

Abrupt environmental change

Under an abrupt environmental change, we assume that the phenotypic optimum suddenly shifts from 0 to $\theta_t = \theta_0$. Since we assume the fitness change is deterministic, extinction is caused by demographic or environmental stochasticity during demographic growth, as in the previous section.

For stronger selection to promote survival, a necessary but not sufficient condition is when increased selection increases the cumulative growth rate (Section III of the Supplementary Materials). Analyses in Section IV of the Supplementary Materials show that the cumulative growth rate changes with selection strength ω as

$$\frac{\partial \int_0^t m_x dx}{\partial \omega} = \begin{cases} -(1 + \theta_0^2 e^{-2V_G\omega t})t, & k = 2 \\ -\frac{1}{2}\left[\theta_0^{2-k} + (k-2)V_G\omega t\right]^{\frac{k}{2-k}}\left(\frac{\theta_0^{2-k}}{kV_G\omega} + t\right), & k \neq 2 \end{cases}. \tag{8}$$

For $k < 2$, equation (8) only applies for a finite time $t < \frac{\theta_0^{2-k}}{(2-k)V_G\omega}$, and the mean phenotype will arrive at the new phenotypic optimum ($\overline{z}_t = \theta_0$) after that. Equation (8) shows that when $k \geq 2$, stronger selection

always reduces the survival probability at any time (see $k = 2, 3$ in Fig. 3(a)). When $k < 2$, increased selection strength increases the cumulative growth rate when the benefit from faster evolution surpasses the initial fitness cost, which requires that selection is strong enough,

$$\omega > \omega^* = \frac{\theta_0^{2-k}}{(2-k)V_G t}. \tag{9}$$

By equation (9), stronger selection can promote survival in a larger parameter space (lower ω^*) when the genetic variance V_G is larger (enhanced response to selection) and the shift of the phenotypic optimum θ_0 is smaller (smaller fitness cost due to phenotypic displacement from the optimum). Similar to the deterministic population genetic model (Fig. 2(a)), there is a certain selection strength that gives the lowest survival probability at time t, which declines over time ($k = 1$ in Fig. 3(a), Fig. 3(b)). This survival-minimizing selection strength is smaller when the baseline growth rate m_0 is lower (Fig. 3(b)), since the marginal cost of increased selection on the survival rate due to phenotypic displacement becomes weaker, which is also seen in the population genetic model (Fig. 2(c)).

Gradual environmental change

Under gradual environmental change, we assume that the phenotypic optimum moves linearly over time as $\theta_t = bt$, where b is the moving rate. We assume $k > 1$, so that the mean phenotype $\bar{z}$ will lag behind the moving phenotypic optimum by a constant $\left(\frac{b}{V_G\omega}\right)^{\frac{1}{k-1}}$ at the steady state.

At the steady state, the mean fitness is approximately (Section IV of the Supplementary Materials)

$$m_t \approx m_0 - \frac{\omega}{k}\left[\left(\frac{b}{V_G\omega}\right)^{\frac{k}{k-1}} + V_z\frac{k(k-1)}{2}\left(\frac{b}{V_G\omega}\right)^{\frac{k-2}{k-1}}\right]. \tag{10}$$

The first term in the square bracket represents the fitness reduction directly due to the lag of the mean phenotype behind the phenotypic optimum. The second term is the fitness reduction due to phenotypic variation V_z (variance load), which also depends on the lag of the mean phenotype behind the phenotypic optimum when $k \neq 2$. The impact of selection strength ω on the mean fitness is then

$$\frac{\partial m_t}{\partial \omega} = \left(\frac{b}{V_G\omega}\right)^{\frac{k}{k-1}}\left[\frac{1}{k(k-1)} - \frac{1}{2}V_z\left(\frac{V_G\omega}{b}\right)^{\frac{2}{k-1}}\right]. \tag{11}$$

The first term in the square bracket represents the relative benefit of increased selection reducing the lag of the mean phenotype behind the phenotypic optimum. The second term represents the relative cost of

stronger selection increasing the variance load. Fitness is maximized at an intermediate selection strength that strikes a balance between the cost and benefit (Lande & Arnold 1996, Gomulkiewicz & Houle 2009), as illustrated in Fig. 3(b). This fitness-maximizing selection strength is given by

$$\omega = \frac{b}{V_G}\left(\frac{2}{V_z(k-1)k}\right)^{\frac{k-1}{2}}. \tag{12}$$

Increasing selection increases the probability of survival whenever selection is less than this fitness-maximizing value. Increasing selection is therefore more likely to increase the probability of survival when the phenotypic optimum moves more quickly (larger b) and the genetic and phenotypic variances are smaller, as these all increase the lag that can then be reduced by selection. The relationship with k is a little more subtle, but generally increasing selection is more likely to increase survival when k is large.

Discussion

The severity of an environmental change often impacts both the strength of selection and mean absolute fitness of the population. These two factors affect several key determinants of the rescue probability (summarized in Table 1), making the consequences of environmental severity on the probability of rescue unclear. For rescue via the establishment of rare alleles, the rescue probability primarily depends on the establishment probability and number of adaptive alleles, either from mutation or in the standing genetic variation. For rescue accomplished via common alleles or a quantitative trait, the rescue probability is determined by the rate of evolution and the mean absolute fitness of the population. In either case, one determinant can increase while the other decreases.

In general, the rescue probability tends to increase with stronger selection when increasing selection confers a higher marginal fitness benefit from enhancing the rate of evolution or the establishment probability. When rescue is via the evolution of major adaptive alleles, there is a larger marginal benefit when adaptive alleles are more dominant or the level of inbreeding is higher. As an example, since most target-site herbicide resistance is conferred by dominant or semi-dominant alleles (Powles & Yu 2010), our results suggest that too high a herbicide concentration may promote herbicide resistance, especially if weeds are highly selfing. Similarly, for rescue after an abrupt change via the evolution of quantitative traits, the marginal benefit increases with genetic variance if the environmental shift is abrupt. When the environmental shift is gradual, the marginal benefit declines with larger genetic variance, because we examine the system at equilibrium where a larger variance leads to a smaller lag behind the optimum, leaving less room for improvement.

Moreover, rescue becomes more probable with stronger selection when the absolute fitness of non-adaptive genotypes is lower. This is because when the non-adaptive genotypes already decline rapidly, the marginal cost of increased selection reducing absolute fitness is weaker. Specifically, when rescue occurs via the evolution of adaptive alleles, stronger selection increases the rescue probability when the growth rate of non-adaptive genotypes is far below 0. Similarly, for rescue via the evolution of quantitative traits, when the environmental shift is abrupt, stronger selection promotes survival in a larger parameter space when the baseline growth rate is lower.

In practice, as concentrations of herbicide or antibiotics increase, selection often initially rises due to a rapid decline in the fitness of the susceptible genotype. Generally, our results suggest that if the absolute fitness of the resistant genotype also decreases (case (II) in Table 1), higher concentrations should prevent resistance establishment. However, the absolute fitness of the resistant genotype may instead increase with higher concentrations (case (III) in Table 1), e.g., if the resistant strain can utilize herbicides/antibiotics for growth. In this scenario, higher concentrations may facilitate the establishment of resistance if the growth rate of the susceptible genotype is significantly below 0, although other factors, such as dominance and the mating system, also matter. However, as the concentration continues to increase, selection weakens due to a decline in the absolute fitness of the resistant genotype (case (I) in Table 1), thus preventing the establishment of resistance at sufficiently high concentrations.

Our study does not consider ecological interactions between conspecific strains or species, which can have significant influences on the rescue probability of a focal population (Osmond & Mazancourt 2013, Day & Read 2016, Osmond et al. 2017). Apart from altering selection strengths, environmental changes may also affect ecological interactions. For example, higher concentrations of antibiotics may elevate the absolute fitness of the resistant strain due to relaxed competition from the susceptible strain (competitive release; De Roode et al. 2004, Huijben et al. 2011, Day et al. 2015). Additionally, evolution can also influence ecological interactions. For example, herbicides may induce the evolution of herbicide resistance in both weeds and crops, and the species with more rapid adaptation may have higher competitiveness than the other species in the new environment. Future studies that integrate (co)evolution in multiple populations and their ecological interactions are necessary to gain a better understanding of the effects of selection on the rescue probability in nature.

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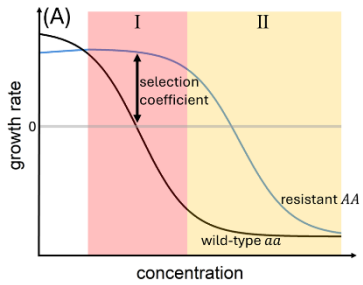
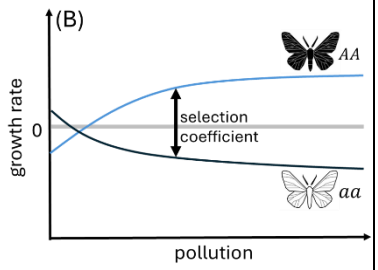
Tables and Figures

Table 1. Three scenarios for how the absolute fitness of non-adaptive and adaptive genotypes may change with increased selection strength, and the resulting effects on key factors that determine the rescue probability. For simplicity, the dominance of allele A is assumed to be constant, so that the fitness of Aa is not shown in the figures.

	(I) $m'_{AA}(s) \leq 0$, $m'_{aa}(s) < 0$	**(II)** $m'_{AA}(s) \geq 0$, $m'_{aa}(s) > 0$	**(III)** $m'_{AA}(s) > 0$, $m'_{aa}(s) < 0$	**Rescue scenario**
				
Establishment probability	↑	↑	Depends on dominance h, inbreeding level F, and ϕ	Rescue via the establishment of adaptive alleles from new mutations/standing variation
Number of new mutations/pre-existing alleles	↓	↑	↓	
Rate of evolution	↑	↑	↑	Rescue via deterministic evolution of adaptive alleles/ quantitative traits
Mean absolute fitness	↓	↑	↓	
Parameter range of ϕ	$\phi \geq 1$	$\phi \leq 0$	$0 < \phi < 1$	

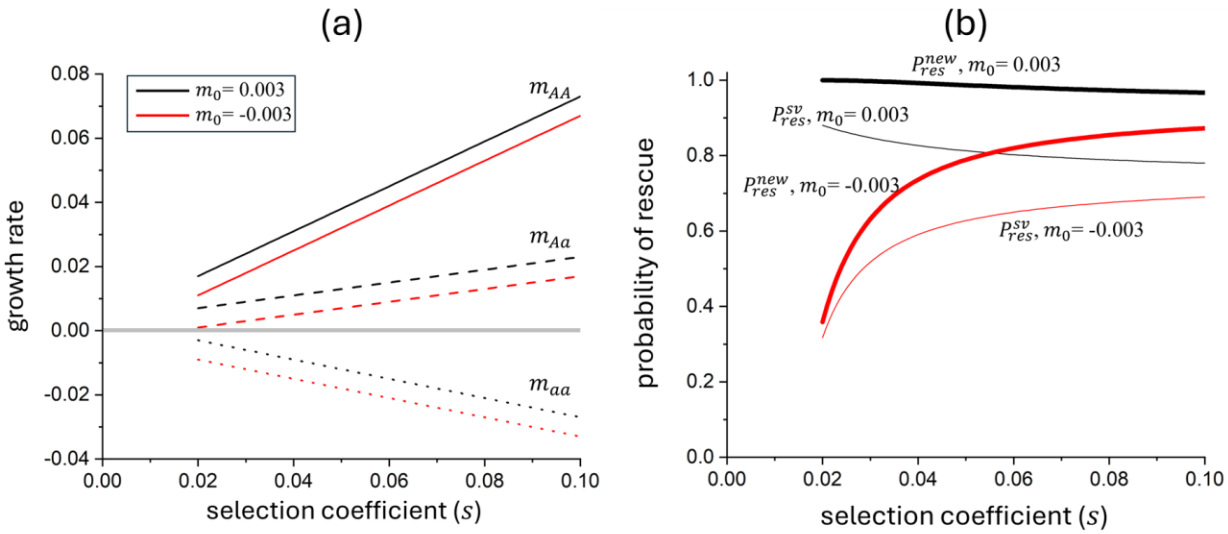


Figure 1. Effects of selection strength on the growth rate of each genotype (panel (A)) and the probability of rescue from new mutations and standing variation (panel (B)) when the baseline fitness $m_0 > 0$ and $m_0 < 0$. Rescue probabilities are obtained from equations (1a) and (1b). Other parameters are $h_e = 0.5$, $N_{0,e}u = 1$, $\phi = 0.3$, $s' = s$, $h_e' = h_e$.

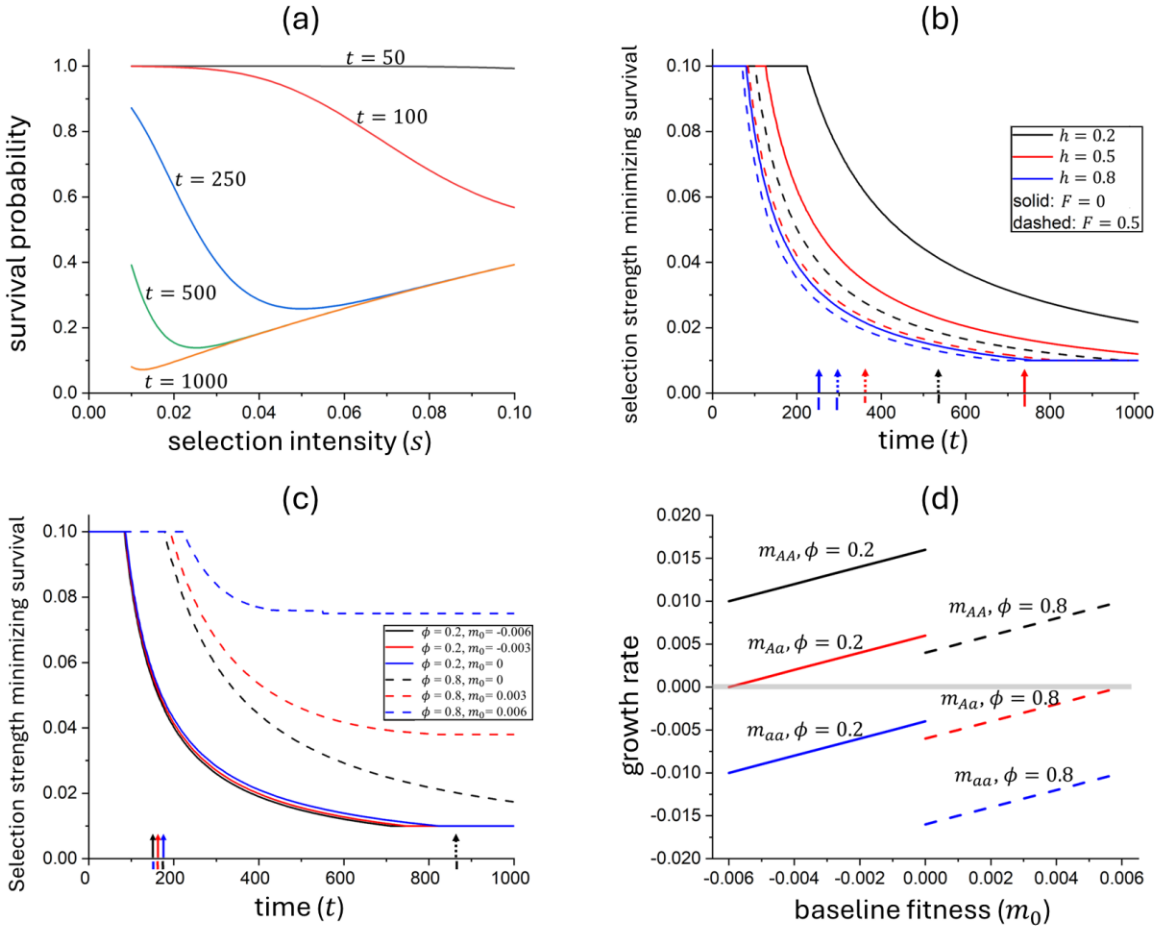


Figure 2. Effects of selection strength on the population survival probability at time t under deterministic genetic changes. (A): survival probabilities at different time points under demographic stochasticity, calculated from equation (A3.1). (B)-(C): Changes of the selection strengths that minimize and maximize the population survival probability under demographic stochasticity over time, where the parameter range of s is constrained between 0.01 to 0.1. Lines denote survival-minimizing s and arrows denote the time when the selection strength that maximizes the survival probability shifts from 0.01 to 0.1. (D): Effects of m_0 on the absolute fitness of each genotype, with $s = 0.02$. Unless otherwise specified, $p_0 = 0.01$, $h = 0.5$, $m_0 = 0$, $\phi = 0.5$, $F = 0$.

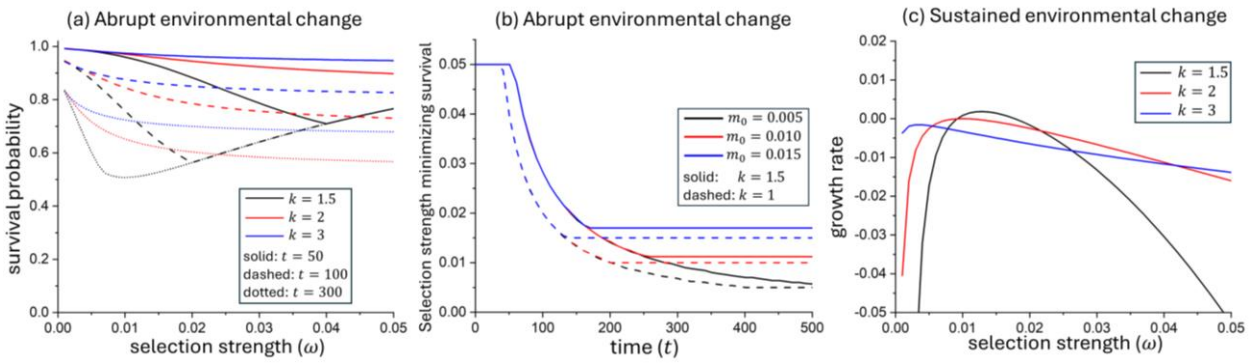


Figure 3. Effects of selection strength ω on the probability of survival via the evolution of a quantitative trait after an abrupt environmental change (panels (a), (b)) and the steady-state growth rate under gradual environmental changes (panel (c)). Results in panels (a) and (b) are obtained from equations (A3.1) and (A4.4). Results in panel (c) are obtained from equation (10). Parameters used are $N_0/\sigma_d^2 = 100$, $m_0 = 0.01$, $V_G = V_z = 1$, $\theta_0 = 2$, $b = 0.01$.