When does the probability of evolutionary rescue increase with the strength of selection?

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Abstract

After an environmental change, populations may be rescued from extinction through adaptive evolution. Stronger environmental changes often cause a faster demographic decline but also more rapid adaptive evolution, with opposing effects on rescue. More generally, it is unclear if the probability of rescue increases with stronger selection, with implications for herbicide/drug resistance evolution. Here we show that, across many scenarios of rescue, stronger selection promotes rescue when: (1) the rate of evolution has a stronger response to selection and (2) the rate of population decline is more rapid. Condition (1) occurs when adaptive alleles are more dominant or the level of inbreeding is higher or, in quantitative genetic models, the genetic variance is larger and the environmental shift is more rapid. Intuitively, a stronger evolutionary response to selection increases the marginal benefit of increased selection, while a faster demographic decline lowers the marginal cost of a reduction in mean fitness.

Introduction

After an environmental change causing demographic decline, a population may avoid extinction through a process known as "evolutionary rescue" (Carlson et al., 2014; Bell, 2017).

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While rescue is desirable in conservation contexts, it is often undesirable in agriculture and medicine (Alexander et al., 2014). When there are no interactions among genotypes, the probability of rescue depends solely on the abundance and absolute fitness of genotypes with a positive growth rate (adaptive genotypes), and is completely independent of non-adaptive genotypes and therefore also independent of the selection strength (Orr and 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 balance between the pace of demographic decline and the selective advantage of adaptive genotypes.

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 and 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 fitness between aa and AA (whether the heterozygote is adaptive or not depends on dominance). 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 a heterozygote 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 more likely to be found in an adaptive 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 (Alexander et al., 2014).

Table 1 summarizes the three possible ways that the absolute fitness of the adaptive and

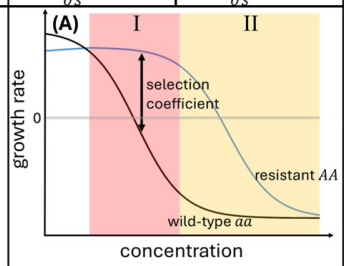
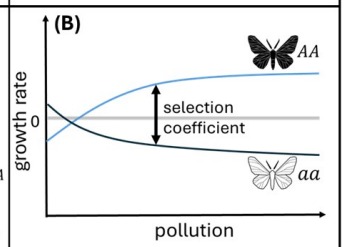
non-adaptive homozygotes can change with selection strength (the fitness of the heterozygote is determined by dominance). As selection gets stronger, the fitness of all genotypes can decline (scenario I), the fitness of all genotypes can increase (scenario II), or the fitness of the adaptive genotype can increase while the fitness of the non-adaptive genotype declines (Scenario III). As summarized in Table 1, the probability of rescue should increase with the strength of selection in scenario II. However, in scenarios I and III the consequences of stronger selection on the rescue probability are not clear due to opposing effects on demography and evolution. The opposing effects of selection on demographic changes and evolution also occur when rescue occurs via phenotypic selection on quantitative traits (Kopp and Matuszewski, 2014). Here stronger selection means a larger fitness change for a given change in phenotype, causing an environmental change to induce both more rapid evolution and faster demographic decline.

The aim of this paper is to identify the conditions under which the probability a population is rescued increases with the strength of 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 cases: 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 population size. In the quantitative genetic model, we also consider two scenarios, depending on whether the environmental change is abrupt or gradual.

Rescue via evolution at a single locus

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 $Fp_t + (1-F)p_t^2$, $2(1-F)p_tq_t$, 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, which may be generated by non-random mating (Caballero and Hill, 1992). We assume selection is weak

Table 1: The three possible ways that the absolute fitness of adaptive and non-adaptive genotypes can change with selection strength s, and the resulting effects on key factors that determine the rescue probability. Scenarios I and II can arise due to differences in drug-response curves. Scenario III may occur if the environmental change involves an increase in new resources that only the adaptive genotype can utilize, such as the evolution of the melanic-morph in the peppered moth under industrial melanism (Cook and Saccheri, 2013) and changes in food resources in the flour beetle (Agashe et al., 2011)

Genotype fitness	$\boldsymbol{m_{AA} = m_0 + (1-\phi)s,\ m_{Aa}=m_0 + (h-\phi)s,\ m_{aa}=m_0 - \phi s}$			**Rescue scenarios**
Scenarios	**(I) $\boldsymbol{\phi \geq 1}$** $\frac{\partial m_{AA}}{\partial s} \leq 0$, $\frac{\partial m_{aa}}{\partial s} < 0$	**(II) $\boldsymbol{\phi \leq 0}$** $\frac{\partial m_{AA}}{\partial s} \geq 0$, $\frac{\partial m_{aa}}{\partial s} > 0$	**(III) $\boldsymbol{0 < \phi < 1}$** $\frac{\partial m_{AA}}{\partial s} > 0$, $\frac{\partial m_{aa}}{\partial s} < 0$	
Illustrated example				
Establishment probability	↑	↑	Depends on dominance h, inbreeding level F, and ϕ	Rescue via the establishment of rare adaptive alleles from new mutations/standing variation
Number of new mutations/pre-existing alleles	↓	↑	↓	
Rate of evolution	↑	↑	↑	Rescue via the evolution of common adaptive alleles/ quantitative traits
Mean absolute fitness	↓	↑	↓	

so that F is mainly determined by mating system and is nearly constant during evolution. 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 absolute fitness changes with increased selection s, as summarized in Table 1. We assume $m_{AA} > 0$ and $m_{aa} < 0$, so that a population composed entirely of aa will initially decline but may avoid extinction if allele A reaches a sufficiently high frequency. This assumption requires $-s(1-\phi) < m_0 < \phi s$.

Rescue via the establishment of a rare allele

When allele A is initially rare, it may be lost by chance. Therefore, whether a population will be rescued or not mainly depends on whether allele A will establish (Orr and Unckless, 2008; Unckless and Orr, 2020). 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 variation). We assume that mutations from allele a to allele A occur at a rate u per generation, and we ignore backward mutations. For rescue via standing 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 (Orr and Unckless, 2008).

When allele A is rare, its marginal fitness is approximately $m_{Aa} = h_e s - r$, where $r = \phi s - m_0 > 0$ represents the declining rate of aa. 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 in a homozygote AA and a probability $1 - F$ that it is in a heterozygote Aa. For a haploid population, $h_e = 1$.

We assume allele A initially has a positive but low marginal fitness when it is rare ($0 < h_e s - r \ll 1$), so that the establishment probability of a single A allele is approximately $2\,(h_e s - r)$ from branching process theory (Unckless and Orr, 2020). The probability of

rescue by new mutations and standing genetic variation are then respectively (Glémin and Ronfort, 2013),

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

$$P_{res}^{old} \approx 1 - \left(1 + \frac{h_e s - r}{h_e' s'}\right)^{-4N_{0,e}u}, \tag{2}$$

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

For rescue from standing variation, when the selection and dominance coefficients before and after the environmental change are independent, Equation (2) shows that stronger selection after the environmental change will promote rescue. However, the strength of selection before and after the environmental change may often be correlated (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 assume that $s^{'}$ and $h^{'}$, are proportional to s and h, respectively.

Section I of the Supplementary Materials shows that, in addition to the bounds required for $m_{Aa} > h_e s - r > 0$ as well as $m_{aa} < 0$ and $m_{AA} > 0$, stronger selection s increases the probability of rescue (both P_{res}^{new} and P_{res}^{old}) when the baseline fitness is negative ($m_0 < 0$). All together, these conditions mean that stronger selection promotes rescue when

$$-s\left(h_e - \phi\right) < m_0 < \min\left\{\phi s, 0\right\}. \tag{3}$$

From this we see that stronger selection always reduces the rescue probability when the fitness of each genotype declines with s ($\phi > 1$; scenario I) and always promotes rescue when the fitness of each genotype increases with s ($\phi < 0$; scenario II).

When the fitness of AA increases with s but the fitness of aa decreases with s ($0 < \phi < 1$; scenario III), stronger selection promotes rescue when the baseline fitness m_0 is negative but inhibits rescue when m_0 is positive (Figure 1A).

For intuition, note that the rescue probability depends on the product of the establishment probability of each A allele and the total number of A alleles n_A that occur from new

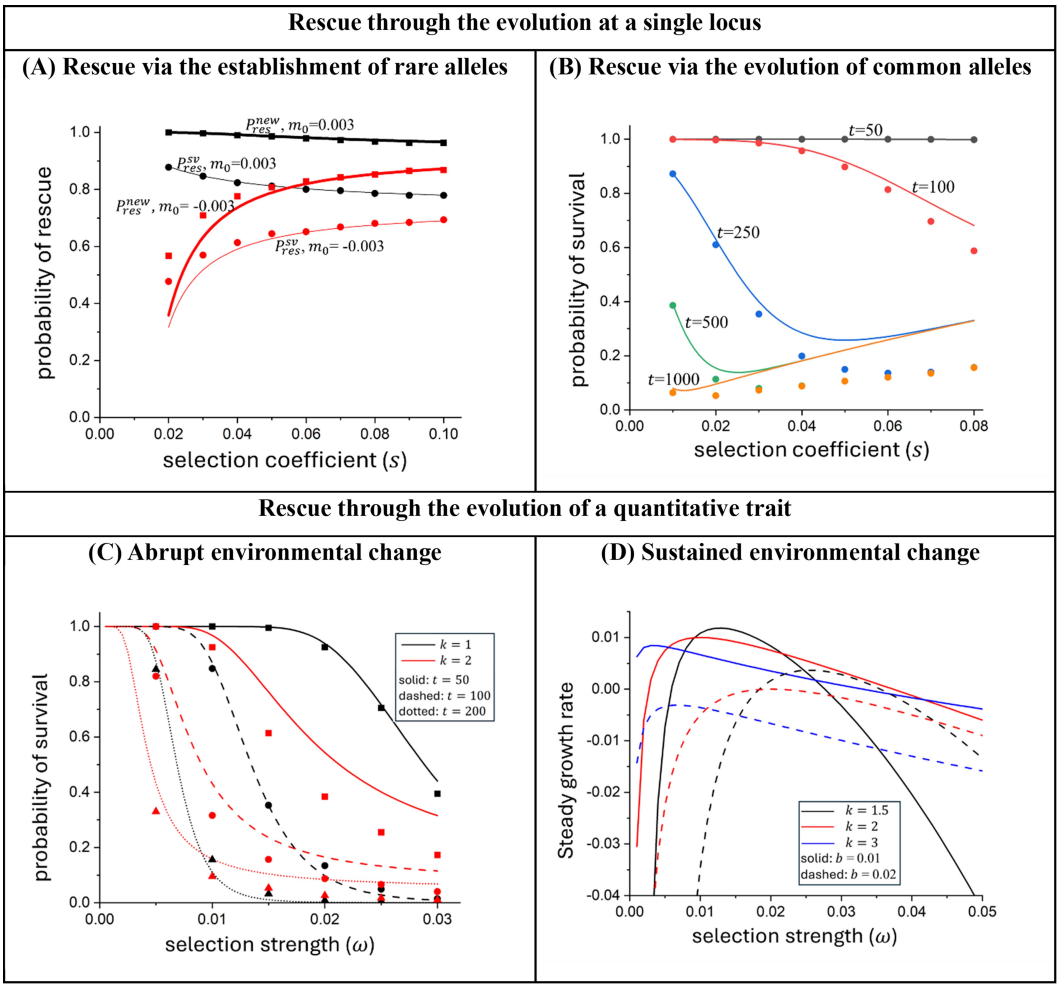


Figure 1: Effect of selection strength on population survival in four different rescue scenarios. In all panels, lines are model predictions and dots are from simulations (see Section V in the Supplementary Materials). **(A)** The probability of rescue via new mutations and rare standing variation (Equations (1) and (2)). Parameters: $h_e = 0.5$, $N_{0,e}u = 1$, $\phi = 0.3$, $s^{'} = s$, $h_e^{'} = h_e$. **(B)** The probability of survival until time t via the sweep of common alleles under demographic stochasticity (Equations (6) and (A2.1)). Parameters: $N_0/\sigma_d^2 = 500$, $p_0 = 0.01$, $h = 0.5$, $m_0 = 0$, $\phi = 0.5$, $F = 0$. **(C)** The probability of survival until time t via the evolution of a quantitative trait after an abrupt environmental change under demographic stochasticity (Equations (A2.1) and (A4.3)). Parameters: $\frac{N_0}{\sigma_d^2} = 1000$, $m_0 = 0.01$, $V_G = V_z = 2V_m = 1$, $\theta_0 = 5$. **(D)** The steady-state mean population fitness under a gradual environmental change (Equation (11)). Parameters:$m_0 = 0.02$, $V_G = V_z = 1$.

mutations or pre-exist in the population. The effects of s on this product are

$$\frac{1}{n_A\pi}\frac{\partial\left(n_A\pi\right)}{\partial s}=\frac{1}{n_A}\frac{\partial n_A}{\partial s}+\frac{1}{\pi}\frac{\partial\pi}{\partial s}=\begin{cases}-\frac{\phi}{r}+\frac{h_e-\phi}{h_e s-r}, & \text{new mutation}\\ -\frac{1}{s}+\frac{h_e-\phi}{h_e s-r}, & \text{standing variation}\end{cases} \tag{4}$$

The first term, which is always negative (as $r=\phi s-m_0>0$), represents the marginal cost of increased selection by reducing the number of A alleles that arise due to mutation exist in the standing variance. The second term is the marginal effect of increased selection 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 variation when $m_0<0$, matching our more formal analysis above (Equation (3)). A lower m_0 increases the marginal benefit from an increased establishment probability and also reduces the marginal cost of fewer new mutation inputs for rescue via the establishment of new mutations.

Rescue via the sweep of a common allele

When allele A is initially common, the change in its frequency is nearly deterministic (Hartfield and Glémin, 2016; Charlesworth, 2020). Since allele A is bound to fix, population extinction is caused by stochasticity in population size. Here we assume that population size is subject to either demographic or environmental stochasticity (Xu et al., 2023). The determinstic change in allele frequency is given by (Charlesworth, 2020)

$$\frac{dp_t}{dt}=sp_tq_t\left(h_e+(1-F)(1-2h)p_t\right). \tag{5}$$

The mean population fitness, $m_t=sp_t\left(2h_e-F+(1-F)(1-2h)p_t\right)-r$, can be obtained by solving Equation (5).

Under demographic and environmental stochasticity, the change of population size N_t

from time t to $t + dt$ is respectively,

$$dN_t = m_t N_t dt + \sigma_d \sqrt{N_t} dW_t \tag{6}$$

$$dN_t = m_t N_t dt + \sigma_e N_t dW_t. \tag{7}$$

Here W_t is the Wiener process and σ_d^2 and σ_e^2 are the strengths 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 II of the Supplementary Materials shows that if the cumulative absolute mean population fitness up to time t, $\int_0^t m_x dx$, is smaller, the survival probability at time t is lower. This is a sufficient but not necessary condition. For the special case when $h = 0.5$, Section III of the Supplementary Materials shows that

$$\frac{\partial \int_0^t m_x dx}{\partial s} = (p_t - \phi)\, t. \tag{8}$$

Therefore, stronger selection always increases the survival probability when the absolute fitness of all genotypes increases ($\phi \leq 0$; scenario II) and always reduces the survival probability when absolute fitness of all genotypes declines ($\phi \geq 1$; scenario I), indicating that faster evolution is not able to compensate for the cost of a quicker demographic decline.

When the absolute fitness of AA increases while the absolute fitness of aa decreases with increased selection ($0 < \phi < 1$; scenario III), stronger selection increases the cumulative absolute fitness when $p_t > \phi$. Therefore, when 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 (Figure 1A). Specifically, there exist selection strengths that give the highest and lowest survival probabilities at time t. The selection strength that minimizes survival becomes weaker over time (Figure 2). In contrast, the selection strength that maximizes the survival probability remains low soon

after the environmental change and then suddenly shifts to be high (at a time marked by arrows in Figure 2).

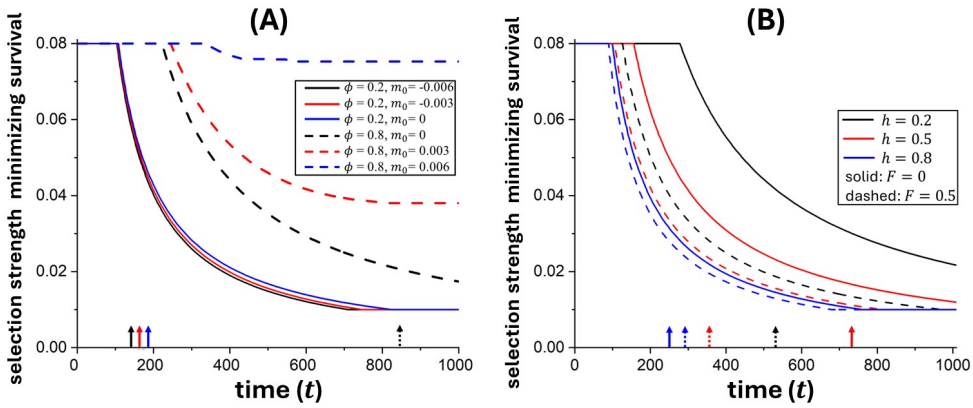


Figure 2: Selection strengths that minimize and maximize the survival probability at time t under demographic stochasticity when rescue is via the sweep of common alleles. The parameter range of s is constrained between 0.01 to 0.08. Lines denote s that minimizes the survival probability. The selection strength that maximizes the survival probability remains at $s = 0.01$ and suddenly shift to s=0.08 after the time point marked by the arrows. Other parameters used are $N_0/\sigma_d^2 = 500$, $p_0 = 0.01$, $h = 0.5$, $m_0 = 0$, $\phi = 0.5$, $F = 0$.

Stronger selection tends to promote survival when the baseline fitness m_0 is low (Figure 2A), i.e., the Malthusian fitness of aa is far below 0 and the fitness of AA is only slightly above 0. Intuitively, the marginal cost of increased selection on 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 increased selection on the rate of evolution. This result is qualitatively similar to our findings for rescue via the establishment of rare alleles, where increased selection increases the probability of rescue when $m_0 < 0$.

Stronger selection is also more likely to promote survival when the effective dominance of allele A, $h_e = F + (1 - F)h$, is higher (Figure 2B). 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 common since allele a is masked in heterozygotes. However, the former effect is more critical in determining survival, since once allele A is common the population already has a low risk of extinction.

Rescue via the evolution of a quantitative trait

For rescue via phenotypic selection on a quantitative trait, we consider a random-mating population with a normally distributed trait z under stabilizing selection. We denote the mean trait value at time t by $\overline{z}_t$ and set the initial value as $\overline{z}_{t=0} = 0$. We denote the genetic and phenotypic variance by V_G and V_z, respectively, and assume that they are constant. The absolute Malthusian fitness of phenotype z is $m(z) = m_0 - \frac{\omega}{k} \left|\theta_t - z\right|^k$. 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 ω and k. However, below we focus on the effects of ω on rescue given a fixed k, and we refer to ω as the selection strength.

By assuming weak selection ($\omega V_z \ll 1$) and a substantial environmental shift ($\theta_t - \overline{z}_t \gg 1$), Section IV of the Supplementary Materials shows that the mean phenotype $\overline{z}_t$ evolves at a rate (Lande, 1976)

$$\frac{d\overline{z}_t}{dt} \approx V_G \left.\frac{dm(z)}{dz}\right|_{z=\overline{z}_t} = \omega V_G \left|\theta_t - \overline{z}_t\right|^{k-1}. \tag{9}$$

We then calculate the mean absolute fitness over time based on Equation (9) and obtain the survival probability from Equation (A4.1).

Abrupt environmental change

Under an abrupt environmental change, we assume that the phenotypic optimum suddenly shifts from 0 to $\theta_t = \theta_0$, and population extinction is caused by stochasticity in demographic changes, as in the previous section. Analyses in Section IV of the Supplementary Materials show that the cumulative absolute fitness changes with selection strength ω as

$$\frac{\partial \int_0^t m_x dx}{\partial \omega} = \begin{cases} -\left(1 + \theta_0^2 e^{-2V_G\omega t}\right) t, & k = 2 \\ -\frac{1}{2}\left[\theta_0^{2-k} + (k-2)V_G\omega t\right]^{\frac{k}{2-k}} \left(\frac{\theta_0^{2-k}}{kV_G\omega} + t\right), & k \neq 2 \end{cases}. \tag{10}$$

Equation (10) shows that when $k \geq 2$, stronger selection always reduces the survival probability at any time (lines with $k = 2$ in Figure 1C). For $k < 2$, Equation (10) only applies for a

finite time $t < \frac{\theta_0^{2-k}}{(2-k)V_G\omega}$, and after that the mean phenotype will stay at the new phenotypic optimum ($\overline{z}_t = \theta_0$), but stronger selection still tends to reduce the survival probability (lines with $k = 1$ in Figure 1C). This is consistent with the deterministic analysis of Gomulkiewicz & Holt (1995).

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 $k > 1$ such that the system will converge to a steady state at which the mean phenotype $\overline{z}$ will lag behind the moving phenotypic optimum by a constant $\left(\frac{b}{V_G\omega}\right)^{\frac{1}{k-1}}$.

The mean fitness at the steady state is approximately (Section IV of the Supplementary Materials)

$$m_t \approx m_0 - \frac{\omega}{k}\left[\left(\frac{b}{V_G\omega}\right)^{\frac{k}{k-1}} + V_z\frac{k(k-1)}{2}\left(\frac{b}{V_G\omega}\right)^{\frac{k-2}{k-1}}\right]. \tag{11}$$

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

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

The first term in the square bracket represents the relative benefit of increased selection by 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 (Bürger and Lynch, 1995; Gomulkiewicz and Houle, 2009; Lande and

Shannon, 1996), as illustrated in Figure 1D. This fitness-maximizing selection strength is

$$\omega = \frac{b}{V_G}\left(\frac{2}{V_z(k-1)k}\right)^{\frac{k-1}{2}}. \tag{13}$$

Stronger selection increases the probability of survival whenever selection is weaker than this fitness-maximizing value. Stronger selection is therefore more likely to promote survival when the phenotypic optimum moves more quickly (compare $b = 0.01$ and $b = 0.02$ in Figure 1D) 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 (see Figure 1D).

Discussion

The severity of an environmental change will often determine both the initial rate of population decline and the strength of selection. These two factors affect several key aspects of rescue (summarized in Table 1), obscuring the consequences. For rescue via the establishment of rare alleles, the rescue probability depends on the number of adaptive alleles that arise and their establishment probability. For rescue via common alleles or a quantitative trait, the rescue probability is determined by the mean absolute fitness of a population and the rate of evolution. In either case, one determinant can increase with environmental severity while the other decreases. In population genetic terms, it is unclear when the probability of rescue will increase with the strength of selection. Here we have examined how the probability of rescue varies with the strength of selection across four different rescue scenarios (that span drug resistance and conservation applications, Alexander et al., 2014) in an attempt to reach a general consensus.

The probability of rescue tends to increase with stronger selection when stronger selection confers a higher marginal fitness benefit by 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 under a higher level of inbreeding. As an example, since most target-site herbicide resistance is conferred by dominant or semi-dominant alleles (Powles and Yu, 2010), our results suggest that too high a herbicide concentration (stronger selection) 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. In contrast, under sustained environmental shifts 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 a faster demographic decline 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 under sustained environmental shifts, the selection strength maximizing the steady-state mean fitness is higher when the shift is more rapid.

In practice, as concentrations of herbicides/antibiotics increase, selection strength 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 (scenario II in Table 1), higher concentrations should prevent resistance establishment. However, the absolute fitness of the resistant genotype may instead increase with higher concentrations (scenario III in Table 1), e.g., due to reduced competition from susceptible strains (Huijben et al., 2011; Day et al., 2015). In this scenario, higher concentrations may facilitate the establishment of resistance especially when the Malthusian fitness of the susceptible genotype is significantly below 0, although other factors, such as dominance and the mating systems, also matter. However, as the concentration continues to increase, selection weakens due to a decline in the absolute fitness of the resistant genotype (scenario I in Table 1), thus

preventing the establishment of resistance at sufficiently high concentrations.

Our study does not consider ecological interactions between strains, which can have significant influences on rescue (Osmond and De Mazancourt, 2013; Day and Read, 2016; Osmond et al., 2017). Apart from altering selection strengths, environmental changes may also affect these ecological interactions, e.g., as just mentioned, higher antibiotic concentrations may elevate the growth rate of resistant strains through competitive release. Evolution can also impact ecological interactions. For example, herbicides may induce resistance evolution in both weeds and crops and the species that evolves faster may become more competitive. Future studies integrating ecological interactions will provide a better understanding of the strength of selection affects the probability of evolutionary rescue.

Data availability

The simulation code is available at https://doi.org/10.5281/zenodo.13974037.

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Supplementary materials

I. Rescue via the establishment of a rare allele

When the growth rate of a rare adaptive allele, A, is positive (i.e., $h_e s - r > 0$), the probability of rescue from new mutations and standing variation are given by Equations (1) and (2), respectively. The effect of an increase in selection strength s on the probability of rescue is then

$$\frac{\partial P_{res}^{new}}{\partial s} \propto -\frac{h_e m_0}{(\phi s - m_0)^2} \tag{A1.1a}$$

$$\frac{\partial P_{res}^{sv}}{\partial s} \propto -\frac{m_0}{h_e' s^2}, \tag{A1.1b}$$

where we've assumed the selection and dominance coefficients of allele A before the environmental change are proportional to those after the environmental change (i.e., $s^{'} \propto s$ and $h^{'} \propto h$) for rescue from standing variation.

Stronger selection therefore increases the probability of rescue in either case when $m_0 < 0$. Given we also require $h_e s - r > 0$ and $(1-\phi)s < m_0 < \phi s$, the probability of rescue increases with selection strength when

$$-s\left(h_e - \phi\right) < m_0 < \min\left\{\phi s, 0\right\}, \tag{A1.2}$$

where the first inequity comes from the constraint $h_e s - r = \left(h_e - \phi\right) s + m_0 > 0$.

II. A sufficient condition for a lower population survival probability under demographic or environmental stochasticity

Here we prove a sufficient condition for a lower population survival probability when the population size change is subject to demographic or environmental stochasticity. Consider

two mean fitness trajectories over time $m_t^{'}$ and m_t. We define the survival probability at time t as the probability that the population has not become extinct at time t, and denote the survival probability under m_t and $m_t^{'}$ by $P_{surv}(t)$ and $P_{surv}^{'}(t)$, respectively. We show that if $m_t^{'}$ gives a higher cumulative growth rate than m_t up to time t, i.e., $\int_0^t m_x^{'} dx > \int_0^t m_x dx$, $\forall t$, then under either demographic and environmental stochasticity, $P_{surv}^{'}(t) > P_{surv}(t)$.

Under demographic stochasticity, we consider a population extinct when $N_t = 0$. The probability that a population is not extinct at time t is then (Anciaux et al. 2019)

$$P_{surv}(t) = 1 - \exp\left[-\frac{2N_0}{\sigma_d^2 \rho(t)}\right], \tag{A2.1}$$

where $\rho(t) = \int_0^t e^{-\int_0^\tau m(x)dx} d\tau$. Since $\int_0^t m_x^{'} dx > \int_0^t m_x dx$, $\forall t$, then $P_{surv}^{'}(t) > P_{surv}(t)$, $\forall t$.

Under environmental stochasticity, Equation (7) indicates that the population size at time t is

$$N_t = N_0 \exp\left(\int_0^t \left(m_x - \frac{\sigma_e^2}{2}\right) dx + \sigma_e W_t\right). \tag{A2.2}$$

Since N_t is always positive, we assume that the population becomes extinct when N_t is below a threshold N_c. Analytical solutions to the survival probability are not available when m_t changes over time. Instead, let the time that the population becomes extinct be $t^* = \inf\{t > 0 | N_t \leq N_c\}$, so that the survival probability is $P_{surv}(t) = 1 - P(t^* \leq t)$. Then, since $\int_0^t m_x^{'} dx > \int_0^t m_x dx$, $\forall t$, we have

$$\begin{aligned}
P(t^* \leq t) &= P(N_\tau \leq N_c, \tau \in [0,t]) \\
&= P\left(W_\tau \leq \frac{\ln\left(\frac{N_c}{N_0}\right) - \int_0^\tau \left(m_x - \frac{\sigma_e^2}{2}\right) dx}{\sigma_e}, \tau \in [0,t]\right) \\
&= P\left(t^{*'} \leq t\right) \\
&+ P\left(\frac{\ln\left(\frac{N_c}{N_0}\right) - \int_0^\tau \left(m_x^{'} - \frac{\sigma_e^2}{2}\right) dx}{\sigma_e} < W_\tau \leq \frac{\ln\left(\frac{N_c}{N_0}\right) - \int_0^\tau \left(m_x - \frac{\sigma_e^2}{2}\right) dx}{\sigma_e}, \tau \in [0,t]\right).
\end{aligned} \tag{A2.3}$$

Therefore, $P\left(t^{*'} \leq t\right) < P(t^* \leq t)$, so that $P_{surv}^{'}(t) > P_{surv}(t)$, $\forall t$. Intuitively, since the expected population size at time t is larger with a larger cumulative growth rate up to time

t, the probability of extinction is smaller.

III. Rescue via the sweep of a common allele

The change in frequency of a common rescue allele is given by Equation (5). For the special case when $h = 0.5$, an analytical solution is available to see how selection strength affects the cumulative growth rate $\int_0^t m_x dx$. From Equation (5), the allele frequency at time t is

$$p_t = \frac{p_0}{(1-p_0)^{-h_e st} + p_0}. \tag{A3.1}$$

Therefore, the cumulative growth rate is

$$\int_0^t m_x dx = \left(2 - \frac{F}{h_e}\right) \ln\left(1 + \left(e^{h_e st} - 1\right) p_0\right) - rt. \tag{A3.2}$$

The impact of s on the cumulative growth rate is then

$$\frac{\partial \int_0^t m_x dx}{\partial s} = \frac{(2h_e - F)\, p_0}{(1-p_0)^{-h_e st} + p_0} t - \phi t = (p_t - \phi)\, t, \tag{A3.3}$$

where the last expression uses the fact that $2h_e - F = 1$ when $h = 0.5$.

IV. Rescue via the evolution of a quantitative trait

Denote the genetic value of an individual with phenotype z by z_G. Based on the Price equation, the rate at which the mean phenotype evolves is

$$\begin{aligned}
\frac{d\overline{z}}{dt} &= \operatorname{cov}\left(z_G, m(z)\right) \\
&= \operatorname{cov}\left(z_G,\ m\left(\overline{z}\right) + \sum_{i=1} \frac{1}{i!} \left(z - \overline{z}\right)^i \left.\frac{\partial^i m(z)}{\partial z^i}\right|_{z=\overline{z}}\right) \\
&= \sum_{i=1} \mathbb{E}\left[\left(z_G - \overline{z}\right)^{2i}\right] \frac{1}{(2i-1)!} \left.\frac{\partial^{2i-1} m(z)}{\partial z^{2i-1}}\right|_{z=\overline{z}} \\
&= \sum_{i=1} \frac{1}{(2i-1)!} V_G^i \frac{2^i \Gamma\left(\frac{2i+1}{2}\right)}{\sqrt{\pi}} \left.\frac{\partial^{2i-1} m(z)}{\partial z^{2i-1}}\right|_{z=\overline{z}}.
\end{aligned} \tag{A4.1}$$

Since $m(z) = m_0 - \frac{\omega}{k}|\theta - z|^k$ we have $\frac{\partial^i m(z)}{\partial z^i}\Big|_{z=\overline{z}} = \frac{\omega}{k}\frac{k!}{(k-i)!}(\theta - \overline{z})^{k-i}$. Therefore, if the distribution of genetic values z_G in the population concentrates sharply around the mean phenotype $\overline{z}$ ($\omega V_G^i \ll 1, \forall i$) and the shift of the phenotypic optimum is large enough so that $\theta - \overline{z} \gg 1$, we can approximate the rate of change in the mean trait value with just the leading term,

$$\frac{d\overline{z}}{dt} \approx V_G \left.\frac{\partial m(z)}{\partial z}\right|_{z=\overline{z}} = \omega V_G \left(\theta - \overline{z}\right)^{k-1}. \tag{A4.2}$$

Equation (A4.2) is a continuous-time version of the approximate equation (A6) derived in Iwasa and Pomiankowski (1993).

Abrupt environmental change

Under an abrupt environmental change, we the population mean trait value $\overline{z}_{t=0} = 0$ is initially $\theta_t = \theta_0$ units from the optimum. The solution to Equation (A4.2) is then

$$\overline{z}_t = \begin{cases} \theta_0 \left(1 - e^{-V_G \omega t}\right), & k = 2 \\ \theta_0 - \left(\theta_0^{2-k} + V_G \omega (k-2) t\right)^{\frac{1}{2-k}}, & k \neq 2 \end{cases}. \tag{A4.3}$$

Time t can proceed towards infinity for $k \geq 2$, but the solution will be inaccurate since if $t \to \infty$ then $\overline{z}_t \to \theta_0$, which violates our assumption that $\theta_t - \overline{z}_t \gg 1$. When $k < 2$, the solution only applies to finite time, since $\overline{z}_t$ evolves to θ_0 in finite time $t = \frac{\theta^{2-k}}{(2-k)V_G\omega}$.

To see how the strength of selection affects the cumulative growth rate at time t, $\int_0^t m_x dx$, we need to calculate $\frac{\partial \int_0^t m_x dx}{\partial \omega} = \int_0^t \frac{\partial m_x}{\partial \omega} dx$. The mean population fitness can be expanded as

$$m_t = \mathbb{E}\left[m(z)\right] = m\left(\overline{z}_t\right) + \sum_{i=1} \frac{1}{2i!} \mathbb{E}\left[\left(z - \overline{z}_t\right)^{2i}\right] \left.\frac{\partial^{2i} m(z)}{\partial z^{2i}}\right|_{z=\overline{z}_t}. \tag{A4.4}$$

Since we assume weak selection ($\omega V_G \ll 1$), so that $\frac{b}{V_G \omega} \gg 1$, picking up the first two leading terms of m_t gives

$$m_t \approx m\left(\overline{z}_t\right) + \frac{1}{2}(k-1)\omega V_z \left(\theta_t - \overline{z}_t\right)^{k-2}. \tag{A4.5}$$

The first term depends on the mismatch between the mean phenotype and the phenotypic

optimum (lag load) and the second term is the fitness reduction due to phenotypic variation (variance load). Since we assume that the distribution of genetic and phenotypic values concentrates sharply around the mean phenotype $\overline{z}$ ($\omega V_z \ll 1$), the second term is ignored. Therefore, $\frac{\partial m_t}{\partial \omega} \approx \frac{\partial m(\overline{z}_t)}{\partial \overline{z}_t}\frac{\partial \overline{z}_t}{\partial \omega}$, which means that changes in selection strength ω affect population mean fitness at time t via the rate of decay of fitness around the optimum, $\frac{\partial m(\overline{z}_t)}{\partial \overline{z}_t}$, and the rate of evolution of the mean phenotype $\frac{\partial \overline{z}_t}{\partial \omega}$.

When z is normally distributed, $\frac{d\overline{z}}{dt} = V_G \frac{\partial m_t}{\partial \overline{z}_t}$ for any fitness function $m(z)$ (Lande 1976). Therefore, $\frac{\partial m_t}{\partial \overline{z}_t} = \frac{1}{V_G}\frac{d\overline{z}}{dt} \approx \left.\frac{\partial m(z)}{\partial z}\right|_{z=\overline{z}}$, where the approximation is based on Equation (A4.2). The change in mean fittnes with selection is then

$$\frac{\partial m_t}{\partial \omega} \approx \frac{\partial m(\overline{z}_t)}{\partial \overline{z}_t}\frac{\partial \overline{z}_t}{\partial \omega} \approx \left(\left.\frac{\partial m(z)}{\partial z}\right|_{z=\overline{z}_t}\right)\frac{\partial \overline{z}_t}{\partial \omega} = \omega\left(\theta - \overline{z}_t\right)^{k-1}\frac{\partial \overline{z}_t}{\partial \omega}, \tag{A4.6}$$

where

$$\frac{\partial \overline{z}_t}{\partial \omega} = \begin{cases} V_G \theta^{-V_G \omega t} t, & k = 2 \\ V_G t\left(\theta^{2-k} + (k-2)V_G \omega t\right)^{\frac{1}{2-k}-1}, & k \neq 2 \end{cases}. \tag{A4.7}$$

Equation (10) is obtained by substituting the above equations into $\int_0^t \frac{\partial m_x}{\partial \omega} dx$.

Gradual environmental change

To model a gradual environmental change we assume the phenotypic optimum changes over time as $\theta_t = \theta_0 + bt$. Based on equation (A4.2), at steady-state the mean phenotype lags behind the phenotypic optimum by an amount $\left(\frac{b}{V_G \omega}\right)^{\frac{1}{k-1}}$. Evaluating mean fitness (Equation (A4.5)) at this steady-state lag gives Equation (11).

V. Simulation

Rescue via evolution at a single locus

For simulation of rescue via evolution at a single locus, we census the genotype frequency immediately after reproduction. We assume the offspring number of each individual is Poisson distributed with mean equal to their absolute fitness. Instead of determining the offspring number of each individual, following the simulation procedure in Roze (2015), we

speed up the simulation by obtaining the total offspring number first. Specifically, since Poisson distributions are additive, we first determine the population size N_{t+1} by drawing from a Poisson distribution with the mean being the expected total offspring number $N_t\overline{W}_t$, where $\overline{W}_t = \sum_i^{N_t} W_i/N_t$ is the mean absolute fitness. We then calculate the expected genotype frequencies after viability selection, reproduction and mutation, from which the number of each genotype in the next generation is sampled for N_{t+1} offspring. For rescue from standing variation, we assume the population size is constant before the environmental change, and we run the system for $6N_0$ generations to reach mutation-selection-drift balance. After the environmental change, population size is allowed to change, and the simulation procedure is the same as that described above. The simulation stops either when the population goes extinct ($N_t = 0$) or when the population is considered established, ($N_t \geq N_0$ and $\overline{W}_t > 1$).

Rescue via the evolution of a quantitative trait

For simulation of rescue through the evolution of a quantitative trait, we use the infinitesimal model (Barton et al. 2017) and assume mating is random. Briefly, the model assumes that the genetic value of an offspring is

$$z_{g,o} = \frac{z_{g,f} + z_{g,m}}{2} + \zeta_{\text{seg}}, \tag{A5.1}$$

The first term is the expectation, which is the average of the genetic value of its mother and father. The term ζ_{seg} is the noise due to genetic processes including segregation and recombination, which is assumed to be normally distributed with mean 0 and variance V_{seg}. The phenotypic value of the offspring is $z_o = z_{g,o} + \zeta_e$, where ζ_e is the environmental noise drawn from a normal distribution with mean 0 and variance V_e. As in the one-locus case, we assume the offspring number of each individual is Poisson distributed with mean equal to its absolute fitness. To generate the next generation, we first determine the population size in the next generation by drawing from a Poisson distribution with mean $N_t\overline{W}_t$, where the mean absolute fitness $\overline{W}_t$ is calculated by averaging over the absolute fitness of each

individual W_i based on its phenotypic value z_i. For each offspring, we sample its mother and father from the parental population with probability proportional to their individuals fitnesses.

When there is no selection, the equilibrium genetic variance is $2V_{seg}$. Therefore, to compare the results from simulation with model predictions, we set $V_{seg} = V_G/2$, where V_G is the genetic variance parameter used in the model. However, in the model, the genetic variance is a parameter and assumed to be constant over time. In contrast, in the simulation, the genetic variance is determined by the input every generation by the segregation variance V_{seg} and the depletion due to selection and sexual reproduction. Therefore, the genetic variance will change over time and tend to be lower as selection strength increases. Moreover, under an abrupt environmental change, our predictions ignore the fitness reduction caused by phenotypic variation, and thus tend to give a higher survival probability compared to simulation results.

It should be emphasized that when population extinction is due to demographic stochasticity, the strength of demographic stochasticity in our model and that in the simulation slightly differs. Specifically, in the model, we assume the variance of population size in the next generation relative to the population size in the current generation is $\mathrm{var}\left(N_{t+1}\right)/N_t = \sigma_d^2$, with constant σ_d^2. In contrast, in the simulation the variance of population size is $\mathrm{var}\left(N_{t+1}\right)/N_t = \overline{W}_t$, which will therefore change over time. In Figure 1, we use $\sigma_d^2 = 1$ for results from model predictions. Since we assume weak selection, the strength of demographic stochasticity in the simulation, $\overline{W}_t$, remains close to 1. Therefore, the strength of demographic stochasticity in the model and in the simulation are very similar.

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