



Evolutionary rescue in randomly mating, selfing, and clonal populations

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Severe environmental change can drive a population extinct unless the population adapts in time to the new conditions (“evolutionary rescue”). How does biparental sexual reproduction influence the chances of population persistence compared to clonal reproduction or selfing? In this article, we set up a one-locus two-allele model for adaptation in diploid species, where rescue is contingent on the establishment of the mutant homozygote. Reproduction can occur by random mating, selfing, or clonally. Random mating generates and destroys the rescue mutant; selfing is efficient at generating it but at the same time depletes the heterozygote, which can lead to a low mutant frequency in the standing genetic variation. Due to these (and other) antagonistic effects, we find a nontrivial dependence of population survival on the rate of sex/selfing, which is strongly influenced by the dominance coefficient of the mutation before and after the environmental change. Importantly, since mating with the wild-type breaks the mutant homozygote up, a slow decay of the wild-type population size can impede rescue in randomly mating populations.

KEY WORDS: Dominance, environmental change, rapid adaptation, rate of sex, rate of selfing.

Harsh environmental change can cause a population to decline in size and ultimately go extinct. However, if adaptation is rapid enough, the population can recover and survive the change (“evolutionary rescue”). Understanding which genetic and environmental factors influence the outcome is of great importance in conservation biology and in the management of drug and pesticide resistance. Over the past few years, several theoretical studies investigated the effect of genetic linkage on the probability of evolutionary rescue. Using a multilocus model to describe adaptation to climate change, Schiffers et al. (2013) and Bourne et al. (2014) observe that linkage slows down adaptation. In contrast, using a generic two-locus model, Uecker and Hermisson (2016) show that genetic linkage plays a more complicated role that is determined by the sign of epistasis before and after the environmental change and by stochastic effects. They find that the probability of rescue may increase or decrease with higher recombination or may have a local maximum or minimum at intermediate values of recombination. While recombination is an important component of sexual reproduction, the role of sex and the role of recombination in evolutionary rescue are distinct. For example, sexual reproduction alone allows for the mixing of chromosomes through segregation, and

recombination occurs during other modes of reproduction as well (cf. viruses or homologous recombination in bacteria). Moreover, sexual reproduction can be biparental through outcrossing or uniparental through self-fertilization. Thus, in addition to recombination, the mode of reproduction is an important factor for the survival chance of a population subjected to environmental change.

Evolution has brought about an astonishing variety of reproductive strategies, both sexual and asexual. Some hermaphrodites are able to self-fertilize while other hermaphroditic species have evolved refined self-incompatibility systems. A huge body of research has been devoted to disentangling the costs and benefits of the various forms of reproduction, focusing on the rate of adaptation (traditionally in populations of constant size), the colonization of new habitats, the accumulation of deleterious mutations, and the maintenance of standing genetic variation (for review articles see e.g., Stebbins 1957; Barton and Charlesworth 1998; Otto 2009; Hartfield and Keightley 2012; Barrett 2013). Biparental sexual reproduction is often said to be beneficial for adaptation since it generates the genetic variation, on which natural selection acts. However, sexual reproduction does not always increase variation, and the generation of variation is not necessarily beneficial

(Otto 2009). In general, sexual reproduction plays a double-edged role in adaptation. Segregation and recombination can efficiently create favorable gene combinations accessible only through sequential mutation events in clonal populations. But, the very same processes can also break up well-adapted gene complexes.

Despite the significance of the topic, little work has explicitly addressed the question of how the mode of reproduction affects the capability of populations to cope with severe environmental change. In their review of evolutionary rescue research, Carlson et al. (2014) list only one experimental study on the role of sexual reproduction. This study by Lachapelle and Bell (2012) finds that sexual reproduction increases chances that the algae *Chlamydomonas reinhardtii* can survive increasing salt concentrations. Likewise, Morran et al. (2009) show that outcrossing populations of *Caenorhabditis elegans* adapt more easily to harsh environmental change than do selfing populations. Similarly, little theoretical work on the role of sexual reproduction in rescue exists. In one study, Glémin and Ronfort (2013) analyze a diploid one-locus model for evolutionary rescue in partially selfing populations. However, Glémin and Ronfort (2013) exclusively focus on scenarios in which the heterozygotes have a fitness considerably larger than one. In this case, establishment of the heterozygote is sufficient for rescue, meaning that the generation and destruction of the mutant homozygote in a randomly mating population has a negligible effect on the rescue probability.

A better understanding of the link between the reproductive strategy and extinction risk helps to explain the variety and distribution of reproductive modes we observe and to predict the impact of current anthropogenic change on species' diversity. It is of equal importance for developing strategies to prevent the emergence of resistance in pathogens, insects, and weeds, which vary greatly in their mode of reproduction. For example, *Anopheles* and the grass weed *Lolium rigidum* undergo biparental sexual reproduction, while the wheat rust fungus *Puccinia triticina* and *Salmonella* provide examples of clonal reproduction in diploids and haploids, respectively. Horseweed reproduces by selfing, and other species use combinations of these three modes (e.g., pea aphids, *C. elegans*, *Candida albicans*, *Plasmodium*). Knowing how the mode of reproduction affects the emergence of resistance is crucial for choosing the best treatment plan. For example, different management strategies might be required for weeds that are primarily selfing versus weeds that are primarily outcrossing.

In this article, we compare rescue in randomly mating, selfing, and clonal populations, and we consider how the rate of sex and the rate of selfing affect evolutionary rescue. We focus on the generation and establishment of homozygote mutants as it is the simplest mechanistic aspect of adaptation in which the three modes of reproduction differ. As in Glémin and Ronfort (2013), there is a discrete change in the environment, and adaptation to the novel environment depends on one locus. For the most part, we

assume that only the mutant homozygote has fitness greater than 1 in the new environment. For clonal populations, in addition to two-step mutation, we include the possibility of mitotic recombination as an alternative pathway to rescue. Adaptation to the novel environment can happen from standing genetic variation or de novo mutations. Thus, the mode of reproduction influences the probability of population survival by shaping the genetic composition of the population both before and after the environmental change.

After introducing the model, we briefly discuss the advantages and disadvantages of the three modes of reproduction. Subsequently, we provide a more detailed analysis of the effects of both the rate of sex and the rate of selfing on rescue. We derive analytical approximations for the probability of evolutionary rescue and complement these with computer simulations to develop an intuitive understanding of the main forces underlying rescue in randomly mating, selfing, and clonal populations. In the main text, we stick to simple intuitive approximations. A more careful analysis can be found in the supporting information.

The model

We consider a panmictic population of diploid individuals with nonoverlapping generations that is exposed to a sudden and severe change in its environment. As a consequence, the population size $N = N(t)$ declines over time, and the population risks going extinct. Adaptation to the new conditions relies on an allelic change at a single locus. Focusing on this locus, we distinguish three genotypes: the wild-type aa , the mutant heterozygote Aa , and the mutant homozygote AA . The numbers of the three possible genotypes are denoted by n_{aa} , n_{Aa} , and n_{AA} , respectively, and $N = n_{aa} + n_{Aa} + n_{AA}$. Prior to the environmental change, the population is well-adapted and maintains constant size N_0 . The mutant allele is deleterious under these conditions, and the three genotypes have relative fitnesses 1, $1 + \delta_{Aa}$, and $1 + \delta_{AA}$ with $\delta_{Aa} < 0$ and $\delta_{AA} < 0$. After the environmental change, the absolute fitness of the wild-type drops to $1 + s_{aa} < 1$ such that the wild-type population size declines exponentially. The mutant heterozygote and homozygote have absolute fitnesses $1 + s_{Aa}$ and $1 + s_{AA}$, and type AA is the most fit type in the population. We mainly focus on $s_{Aa} < 0$ and $s_{AA} > 0$ such that only the mutant homozygote grows in the new environment. The heterozygote can be more fit than the wild-type ($s_{Aa} > s_{aa}$) or less fit ($s_{Aa} \leq s_{aa}$), in which case the population must cross a fitness valley. We assume a hard carrying capacity N_0 . If $N > N_0$, $N - N_0$ randomly chosen individuals are removed from the population. If $N \leq N_0$, fitness is density independent. During reproduction, mutations happen with probability u in both directions.

We compare three modes of reproduction: clonal reproduction, selfing, and random mating, and we also consider partially

clonal and partially selfing populations. For partially clonal populations, individuals produce offspring sexually (modeled as random mating without a cost of sex) with probability σ_{sex} and clonally with probability $1 - \sigma_{\text{sex}}$. For partially selfing populations, individuals produce offspring through selfing with probability σ_{self} and through outcrossing (again modeled as random mating) with probability $1 - \sigma_{\text{self}}$. We assume that σ_{sex} and σ_{self} are independent of population density. We furthermore assume that sexually reproducing individuals produce so many gametes that fertilization is guaranteed; selection acts via viability not via fertility.

A formal description of the model and the life cycle can be found in section S1 of the supplement. In the simulations, we let the population evolve for a large number of generations before the environment changes (increasing the number of generations did not affect the results). We subsequently follow the population until either extinction occurs or the rescue genotype *AA* reaches 20% of the carrying capacity N_0 . The simulation code written in the C programming language makes use of the *Gnu Scientific Library* (Galassi et al. 2009).

Analysis and Results

The probability of rescue is determined by the composition of the standing genetic variation, the efficiency with which the rescue type is generated de-novo, and the probability that it establishes. This can be roughly summarized as

$$P_{\text{rescue}} \approx 1 - e^{-\left(n_{AA}(0) \times p_{\text{est}}^{(AA)}(n_{aa}(0), n_{AA}(0)) + \sum_{t=0}^{\infty} f(n_{aa}(t), n_{AA}(t)) \times p_{\text{est}}^{(AA)}(n_{aa}(t+1), n_{AA}(t+1)) \right)}, \tag{1}$$

where $n_{AA}(0)$ is the number of mutant homozygotes at the time of environmental change, the function f captures the generation of mutant homozygotes in the new environment, and $p_{\text{est}}^{(AA)}$ is the establishment probability of the generated type *AA* individual. The approximation is the Poisson probability for having at least one rescue event and is based on the assumption that rescue mutants reproduce independently of each other when they are rare. Unless reproduction is purely clonal or purely selfing, both f and $p_{\text{est}}^{(AA)}$ depend on the genotypic composition of the population. We ignore the dependence of f and $p_{\text{est}}^{(AA)}$ on n_{AA} , since we focus on scenarios in which the rescue type *AA* is rare during the time when the fate of the population is decided. We apply branching process theory to estimate the establishment probability $p_{\text{est}}^{(AA)}$. To account for variation in $n_{AA}(0)$, we average equation (1) over the frequency distribution of mutant homozygotes in the standing genetic variation. To do so, we derive an approximation for the corresponding probability generating function in the supplementary material. With this approach, we analyse a set

of limiting cases that we discuss in detail below. The complete mathematical analysis is found in the supplementary material.

THE ADVANTAGES AND DISADVANTAGES OF THE THREE MODES OF REPRODUCTION

Table 1 summarizes how each mode of reproduction affects the genotypic composition of the standing genetic variation, the rate of de novo generation of the mutant genotypes, and the establishment of the rescue type.

For all three modes of reproduction, mutant heterozygotes are generated from wild-type homozygotes by mutation at rate $\sim 2un_{aa}$. The formation of mutant homozygotes differs. In clonal populations, the rescue type *AA* is generated by a second mutation at a very low rate $\sim un_{AA}$ (for mitotic recombination, see below). In fully selfing populations, one quarter of the offspring of a mutant heterozygote are mutant homozygotes. The latter hence arise at rate $\frac{1}{4}n_{AA}$. In randomly mating populations, mutant homozygotes are generated by the random union of mutant gametes. Unlike in selfing populations, the rate depends on the genotypic composition of the population ($\frac{1}{4}\frac{n_{aa}^2}{N}$). The efficient generation of the rescue type in selfing populations goes hand in hand with the depletion of heterozygotes. The number of heterozygotes is hence much lower in selfing than in randomly mating or clonal populations. Finally, the rescue type does not only have to be generated, it also needs to increase in frequency. In clonal and selfing populations, this only depends on the fitness of type *AA*. In randomly mating populations, mating between the two homozygote types breaks the rescue type up. Its “effective selection coefficient” is reduced from δ_{AA} and s_{AA} to roughly $\delta_{AA} - \frac{n_{aa}}{N_0} \approx \delta_{AA} - 1$ and $s_{AA} - \frac{n_{aa}(t)}{N(t)}$, respectively. This has two consequences. In clonal and selfing populations, the frequency of the mutant homozygote *AA* prior to the environmental change strongly depends on its fitness, while in randomly mating populations, the rescue type remains at a low frequency, (nearly) independent of its selection coefficient, before the environmental change. Second, establishment of the rescue type after the environmental change is hampered unless the wild-type is depleted fast enough.

THE RATE OF SEX

The role of segregation in a diploid one-locus model, in which individuals reproduce sexually with probability σ_{sex} , is very similar to the role of recombination in a haploid two-locus model (see SI Section S3 and Otto (2003)). We can therefore transfer methods and results obtained for the role of recombination in Uecker and Hermisson (2016) to the current problem (compare also Figs. 1 and 2 in the present article to Figs. 3 and 4 in Uecker and Hermisson (2016)). As in Uecker and Hermisson (2016), we focus on large populations in which we can describe the number of wild-type homozygotes and heterozygotes deterministically both before and after the environmental change. The mutant

Table 1. The three determinants of rescue. The table summarizes how clonal, selfing, and randomly mating populations differ in the composition of the standing genetic variation, the de novo generation of the rescue genotype, and in its establishment probability (see text for details). For the approximations of the expected number of heterozygotes and homozygotes in the standing genetic variation, \bar{n}_{Aa} and \bar{n}_{AA} , see SI Section S3, (S5.3) and (S5.7), (S6.2), and (S6.4).

Clonal	Selfing	Random mating
<p>Standing genetic variation</p> <ul style="list-style-type: none"> many heterozygotes $\bar{n}_{Aa} \approx -\frac{2uN_0}{\delta_{Aa}}$ homozygotes: fitness-dependent $\bar{n}_{AA} \approx \frac{2u^2N_0}{\delta_{Aa}\delta_{AA}}$ 	<p>Standing genetic variation</p> <ul style="list-style-type: none"> few heterozygotes $\bar{n}_{Aa} \approx 4uN_0$ homozygotes: fitness-dependent $\bar{n}_{AA} \approx -\frac{uN_0}{\delta_{AA}}$ 	<p>Standing genetic variation</p> <ul style="list-style-type: none"> many heterozygotes $\bar{n}_{Aa} \approx -\frac{2uN_0}{\delta_{Aa}}$ few homozygotes (\approx independent of fitness) $\bar{n}_{AA} \approx \frac{u^2N_0}{\delta_{Aa}^2}$
<p>De novo generation</p> <ul style="list-style-type: none"> heterozygotes $2un_{aa}(t)$ homozygotes: inefficient $un_{AA}(t)$ 	<p>De novo generation</p> <ul style="list-style-type: none"> heterozygotes $2un_{aa}(t)$ homozygotes: very efficient (but loss of heterozygotes) $\frac{1}{4}n_{AA}(t)$ 	<p>De novo generation</p> <ul style="list-style-type: none"> heterozygotes $2un_{aa}(t)$ homozygotes: depends on the genotypic composition $\frac{1}{4} \frac{n_{AA}(t)^2}{N(t)}$
<p>Establishment</p> <ul style="list-style-type: none"> fitness-dependent $\approx 2s_{AA}$ 	<p>Establishment</p> <ul style="list-style-type: none"> fitness-dependent $\approx 2s_{AA}$ 	<p>Establishment</p> <ul style="list-style-type: none"> fitness-dependent depends on genotypic composition $p_{\text{est}}^{(AA)}(n_{aa}(t), n_{AA}(t))$

homozygote, however, will initially be rare, requiring a stochastic treatment of its dynamics. To assess the stochasticity in the number of mutant homozygotes, we apply branching process theory. For details on the analysis, we refer to SI Sections S2 and S3 and to Uecker and Hermisson (2016).

The role of the dominance coefficient

As known from classical population genetics, whether segregation in sexual reproduction speeds up or slows down adaptation strongly depends on the relative fitness of each genotype. For continuous-time models, the critical factor is the dominance coefficient on an additive scale. For discrete-time models (as considered in this article), dominance on a multiplicative scale is more relevant (Chasnov 2000; Otto 2003). Sexual reproduction speeds up adaptation if the fitness across the alleles at one locus is submultiplicative and slows down adaptation if supermultiplicative (Chasnov 2000; Otto 2003). (A multiplicative fitness scheme corresponds to a dominance coefficient $h_c < \frac{1}{2}$ on an additive scale.) In models of evolutionary rescue, the population faces two different environments and the dominance coefficient may potentially shift between environments (Gerstein et al. 2014). To quantify deviations from multiplicativity in both phases, we define

$$\iota_1 := 1 \cdot (1 + \delta_{AA}) - (1 + \delta_{Aa})^2 \tag{2}$$

for the old environment and

$$\iota_2 := (1 + s_{aa})(1 + s_{AA}) - (1 + s_{Aa})^2 \tag{3}$$

for the new environment. Comparing to a haploid two-locus model, the measure ι corresponds to epistasis and plays an analogous role (see SI Section S3 and Otto (2003)). Just as epistasis generates linkage disequilibrium, nonzero ι leads to an under- or overrepresentation of homozygotes as measured by the inbreeding coefficient

$$F = \frac{p_{AA}p_{aa} - \frac{1}{4}p_{Aa}^2}{p_A p_a}, \tag{4}$$

where p_{aa} , p_{Aa} , and p_{AA} denote the relative frequencies of the three genotypes and p_a and p_A the relative frequencies of the two alleles. This deviation from Hardy–Weinberg equilibrium is diminished by segregation (cf. recombination counteracting linkage disequilibrium). For $\iota < 0$, segregation increases the number of homozygotes (speeding up adaptation), whereas for $\iota > 0$, it decreases them (slowing down adaptation).

Depending on the sign of ι_1 and ι_2 , the fitness-related effect of segregation can stay the same or change when the environment changes. Figure 1 considers an example of each possibility. For negative ι across environments, the probability of rescue increases with the rate of sex (Panel A). For a switch in the sign of ι from

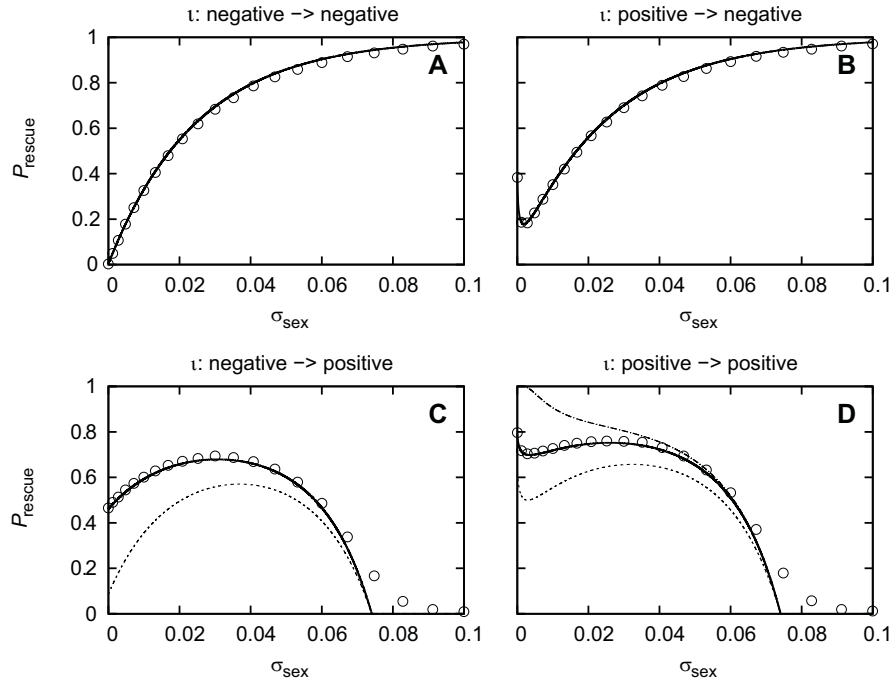


Figure 1. Probability of evolutionary rescue as a function of the probability of sex for different fitness schemes before and after the environmental change. The parameter ι measures dominance at a multiplicative scale. For $\iota < 0$, sexual reproduction speeds up adaptation; for $\iota > 0$, it slows down adaptation. As the environment shifts, ι might change sign, reversing the effect of sex. As examples for $\iota < 0$ and $\iota > 0$ in the new environment, we consider the special scenarios $s_{aa} = -1$ (lethal wild-type) and $s_{aa} = s_{Aa}$ (recessive mutant allele). Solid line: total probability of rescue; dashed line: probability of rescue from the standing genetic variation (i.e., without new mutations after the environmental change). In Panels A and B, both lines coincide. Dashed-dotted line in Panel D: probability of evolutionary rescue, ignoring stochastic variation in the number of AA mutants before the environmental change. For the analytical predictions, see SI Section S3 and Uecker and Hermisson (2016). Parameter values: $N_0 = 10^8$, $u = 2 \cdot 10^{-6}$, $\delta_{Aa} = -0.01$; first row (A+B): $s_{Aa} = -0.5$, $s_{aa} = -1$, $s_{AA} = 0.002$, and $\delta_{AA} = -0.1$ (i.e., $\iota_2 \approx -0.08$, Panel A), $\delta_{AA} = -0.0001$ (i.e., $\iota_1 \approx 0.02$, Panel B); second row (C+D): $s_{aa} = s_{Aa} = -0.03$, $s_{AA} = 0.08$, and $\delta_{AA} = -0.1$ (i.e., $\iota_1 \approx -0.08$, Panel C), $\delta_{AA} = -0.0001$ (i.e., $\iota_1 \approx 0.02$, Panel D). Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

positive to negative, we find a minimum in $P_{\text{rescue}}(\sigma_{\text{sex}})$, and for a switch from negative to positive, we find a maximum (Panels B and C). For $\iota_1 > 0$ and $\iota_2 > 0$, based on the fitness scheme, we expect a monotonic decrease of the rescue probability with σ_{sex} . Surprisingly, however, the decrease is not monotonic in Figure 1D. This cannot be explained by the classical deterministic theory and is rather due to stochastic effects that we discuss below.

Before moving on, we briefly outline the analysis underlying the predictions shown in Figure 1 that directly demonstrates the two effects of segregation (generating and breaking up type AA individuals). We start by considering the contribution of the rescue mutants from the standing genetic variation. In the original environment, mutant homozygotes are generated at approximately constant rate $u\bar{n}_{Aa} + \frac{\sigma_{\text{sex}}}{4} \frac{\bar{n}_{Aa}^2}{N_0}$, where $\bar{n}_{Aa} \approx \frac{2uN_0}{-\delta_{Aa}}$ is the expected number of heterozygotes in the standing genetic variation. By mating with the wild-type homozygote, they are broken up at rate $\sim \sigma_{\text{sex}}$, leading to a reduced “effective fitness” $\delta_{AA} - \sigma_{\text{sex}}$. Using this, we derive the distribution of mutant homozygotes with the

help of a branching process with immigration (here, immigration corresponds to the generation of mutant homozygotes through mutation and segregation). The mean number of AA mutants in the standing genetic variation can be approximated by $\bar{n}_{AA} \approx \frac{u^2 N_0}{\delta_{Aa}^2} \left(1 + \frac{\iota_1}{\sigma_{\text{sex}} - 2\delta_{Aa} - \iota_1}\right)$ (the approximation assumes weak selection and $\delta_{AA} \approx 2\delta_{Aa} + \iota_1$; see SI Section S3). If the number of mutant homozygotes is large enough to ignore variation around its mean, the probability of rescue from mutant homozygotes in the standing genetic variation can be approximated by

$$P_{\text{rescue}}^{\text{SGV}} \approx 1 - e^{-\bar{n}_{AA} p_{\text{est}}^{(AA)}} \approx 1 - e^{-\frac{u^2 N_0}{\delta_{Aa}^2} \left(1 + \frac{\iota_1}{\sigma_{\text{sex}} - 2\delta_{Aa} - \iota_1}\right) p_{\text{est}}^{(AA)}} \quad (5)$$

(see the first term in the exponent of eq. (1)). If the wild-type is lethal in the new environment, $p_{\text{est}}^{(AA)} \approx 2s_{AA}$, independent of the rate of sex. We see from equation (5) that the probability of rescue from AA mutants in the standing genetic variation increases with the rate of sex if $\iota_1 < 0$ and decreases with the rate of sex if $\iota_1 > 0$ as expected from the classical theory outlined above.

Note also how the importance of ι_1 diminishes as the level of sex increases.

We now turn to the postchange dynamics (the second term in eq. (1)) and analyze one example each for $\iota_2 < 0$ and $\iota_2 > 0$. As an (extreme) example for $\iota_2 < 0$, we choose the wild-type to be lethal under the new environmental conditions ($s_{aa} = -1$). In that case, the population dynamics after the environmental shift is—at least initially—determined by the heterozygotes, $N(t) \approx n_{Aa}(t)$. Since one half of all matings between heterozygotes leads to a homozygote offspring, the number of heterozygotes decays at rate $|s_{Aa} - \frac{\sigma_{sex}}{2} - 2u|$ and $n_{Aa}(t) \approx \bar{n}_{Aa}(1 + s_{Aa} - 2u - \frac{\sigma_{sex}}{2})^t$. Mutant homozygotes arise at rate $f(n_{Aa}(t)) = (u + \frac{\sigma_{sex}}{4})n_{Aa}(t)$. Since the wild-type is lethal, the mutant homozygotes cannot be broken up anymore in the new environment; once generated, they establish with probability $p_{est}^{(AA)} \approx 2s_{AA}$. Until extinction, the total number of newly generated “successful” mutant homozygotes is hence given by $\sum_{t=0}^{\infty} f(n_{Aa}(t))p_{est}^{(AA)} = \sum_{t=0}^{\infty} (u + \frac{\sigma_{sex}}{4})n_{Aa}(t) \cdot 2s_{AA} = 2s_{AA}(\frac{\sigma_{sex} + u}{\frac{\sigma_{sex}}{2} + 2u - s_{Aa}}) \bar{n}_{Aa}$. Following equation (1) and using $\bar{n}_{Aa} \approx \frac{2uN_0}{-\delta_{Aa}}$ (which assumes that the number of heterozygotes in the standing genetic variation is not affected by the rate of sex), we obtain the probability for rescue from de novo generated rescue individuals

$$P_{rescue}^{de\ novo} \approx e^{-2s_{AA} \frac{\sigma_{sex} + u}{\frac{\sigma_{sex}}{2} + 2u - s_{Aa}} \cdot \frac{2uN_0}{-\delta_{Aa}}} \tag{6}$$

For $\iota_2 > 0$, we focus on a recessive or underdominant mutant allele, that is the wild-type is as least as fit as the heterozygotes ($s_{aa} \geq s_{Aa}$) and the population stays dominated by the wild-type until rescue occurs (if it occurs) and the mutant homozygote takes over. The proportion of heterozygotes changes over time such that the rate at which the rescue type gets generated, $f(n_{aa}(t), n_{Aa}(t))$, does not take such a simple form as in the first scenario (but the problem remains analytically tractable). Virtually all matings of the mutant homozygote occur with the wild-type homozygote, breaking it up and reducing its “effective” fitness to $s_{AA}^{eff} \approx s_{AA} - \sigma_{sex}$. We can then approximate the establishment probability of the rescue genotype by $p_{est}^{(AA)} \approx 2 \max [s_{AA} - \sigma_{sex}, 0]$.

The role of stochasticity

Predicting the role of segregation on the basis of dominance (as done in the qualitative discussion of Fig. 1 in the previous section) ignores all effects of stochasticity. Given stochastic fluctuations in the genotype frequencies, how does segregation alter the probability of rescue? For simplicity, we first consider rescue from the type AA individuals in the standing genetic variation (the first term in the exponent of eq. (1)). The number of rescue type individuals present in the population at the time of the environmental change is a stochastic variable. For any population with

a given n_{AA} at the time of environmental change, the probability of rescue from the standing genetic variation is given by

$$P_{rescue}^{sgv}(n_{AA}) \approx 1 - e^{-n_{AA} p_{est}^{(AA)}} \tag{7}$$

This is a concave function in n_{AA} because a single successful mutant that establishes a permanent lineage is sufficient for population rescue; a second successful mutant does not help (the population would simply be “rescued twice”). In contrast, the population goes extinct if no mutant is successful. This implies that deviations of n_{AA} below the mean \bar{n}_{AA} reduce the survival chances of a population more than deviations above the mean increase it. Averaging over the distribution of n_{AA} , stochastic variation in the number of mutant homozygotes therefore diminishes the probability of evolutionary rescue. By counteracting any deviations from Hardy–Weinberg equilibrium, segregation reduces variation in the number of mutant homozygotes and hence mitigates this negative effect of stochasticity. The dotted line in Figure 1 shows the probability of evolutionary rescue for the parameters of Panel D if we ignore stochastic variation in n_{AA} prior to the environmental change (hence applying eq. (5)). For low levels of sex, stochastic variation reduces P_{rescue} significantly; with increasing rate of sex, the difference between the curves with and without stochasticity diminishes. A similar reasoning holds for de novo generated mutant homozygotes. The effect is particularly pronounced when the population size has declined to small numbers and stochastic fluctuations in all genotypes are strong. In particular, right before the wild-type goes extinct and cannot break the mutant homozygote up anymore, presence of the rescue type in sexually reproducing species increases the probability of rescue considerably. Sexually reproducing populations can therefore have an advantage despite of ι_2 being significantly larger than 0.

The population dynamics

Having established the principles behind the role of sexual reproduction in rescue, we next discuss a surprising consequence of segregation.

It is natural to think that a mild environmental change with a slow decline of the wild-type population would lead to an increased probability of population survival. This common belief is based on the reasoning that a slow population decline increases the time for adaptive mutations to appear and has been confirmed in early models of rescue (e.g., Orr and Unckless 2008). As mainly discussed in the context of emerging resistance to drug treatment, this simple picture changes when competition for resources is strong. In that case, fast elimination of the wild-type strain increases the establishment probability of the rescue type. Then, the probability of rescue can be higher for a quickly rather than slowly declining wild-type population (Gatenby 2009; Gatenby et al. 2009; Read et al. 2011; Peña-Miller et al. 2013; Uecker et al. 2014;

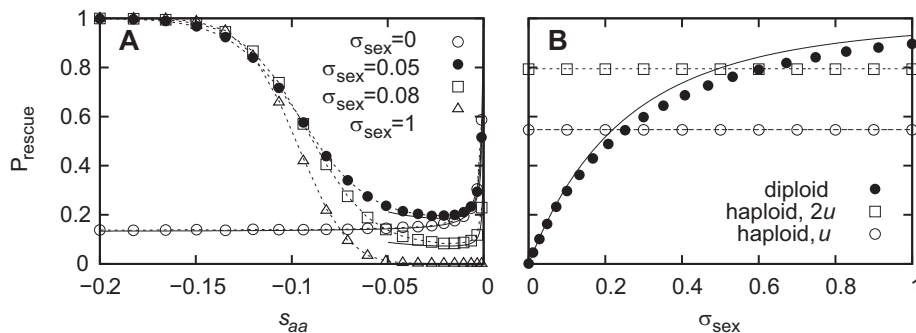


Figure 2. Probability of evolutionary rescue. (Panel A) Probability of evolutionary rescue as a function of wild-type fitness for various values of σ_{sex} . Solid curves constitute analytical predictions (see eq. (S5.9) with $r = 0$ for $\sigma_{\text{sex}} = 0$ and SI Section S3 for $\sigma_{\text{sex}} > 0$). Dotted lines interpolate between simulation points and are included to guide the eye. Note that sexual reproduction turns beneficial for a value of s_{aa} that corresponds to a supermultiplicative fitness scheme. This is due to stochastic effects as discussed in the main text. Parameter values: $\delta_{Aa} = -0.01$, $\delta_{AA} = -0.0199$, $s_{Aa} = -0.05$, $u = 10^{-5}$, $N_0 = 10^6$, $s_{AA} = 0.1$. (Panel B) Probability of evolutionary rescue in a diploid sexually reproducing population and in a haploid clonally reproducing population. The solid line shows rescue in a population of diploid individuals with mutation probability u ; the dashed line shows rescue in a haploid population with mutation probability u ; the dotted lines shows rescue in a haploid population with mutation probability $2u$. For the analytical predictions, see SI Section S3 (for diploid populations) and equation (S2.2) (for haploid populations). Parameter values: $u = 2 \cdot 10^{-6}$, $N_0 = 10^7$, $\delta_{Aa} = -0.01$, $\delta_{AA} = -0.1$, $s_{aa} = -1$, $s_{Aa} = -0.5$, $s_{AA} = 0.002$. Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

Day and Read 2016). As seen in Figure 2A, when rescue relies on the establishment of the mutant homozygote, the simple picture breaks down in sexually reproducing species, even in the absence of competition. This is because the wild-type again plays a double role in the process. On the one hand, wild-type individuals can have mutant offspring, providing the raw material for rescue. On the other hand, mutant homozygotes are broken up if they mate with wild-type individuals. Presence of the wild-type after the environmental change has hence antagonistic effects on rescue, which can lead to a decrease of P_{rescue} with increasing wild-type fitness. Note also that due to the deleterious effect of segregation, a randomly mating population can still go extinct even though the initial frequency of the rescue type is very high (not shown).

In the last two parts of this section, we briefly consider asexual populations that can generate the mutant homozygote more efficiently through mitotic recombination and haploid populations that only require one mutational step for rescue. We show that despite this advantage, they are not necessarily more successful than sexually reproducing species.

Clonal population with mitotic recombination

Until now, we assumed that in diploid clonal populations, the rescue type could only be created by two-step mutation, which is rather inefficient. However, mitotic recombination provides organisms with an alternative way to reach homozygosity. This holds true both for unicellular organisms and for multicellular organisms when mitotic recombination happens in the germline. Mitotic recombination has been shown to speed up adaptation

tremendously in populations of constant size (Mandegar and Otto 2007; Gerstein et al. 2014). We denote by r the probability at which heterozygous mother cells produce homozygous daughter cells through mitotic recombination. Half of these daughter cells are mutant homozygotes, so the rescue genotype is generated with rate $\sim un_{Aa} + \frac{r}{2}n_{Aa}$. Mathematically (but not biologically), this is similar to a clonal population with a little bit of selfing. To give an example, Mandegar and Otto (2007) estimate the average rate of mitotic recombination in *Saccharomyces cerevisiae* to be approximately 0.8×10^{-4} per cell per generation.

Figure 3 shows that mitotic recombination significantly enhances rescue in clonal populations. However, it only gets more likely than in sexual populations for high rates of recombination (relative to estimates in *S. cerevisiae*). Note that the advantage of sexual over clonal populations in Figure 3 is due to weaker stochastic fluctuations in genotype frequencies (as discussed above) and not from the fitness scheme.

Comparing to a clonal haploid population

How does adaptation in a haploid clonal population compare to adaptation in a diploid sexual population? If in the haploid population, only one mutational step is required for adaptation to the new conditions (assuming that the single mutant has the same fitness as the mutant homozygote), rescue seems a priori easier. However, as Figure 2 demonstrates, rescue may be more likely to occur in sexual populations. Figure 2B considers a scenario with $s_{aa} = -1$ (cf. eq. (5) and eq. (6)). In the clonal population, adaptation relies entirely on the rescue mutants from the standing

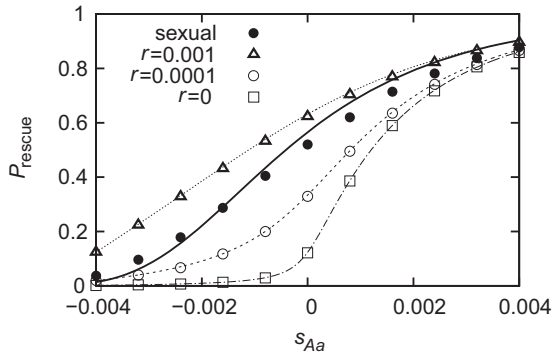


Figure 3. Probability of evolutionary rescue in the presence of mitotic recombination. The figure compares rescue in a sexually reproducing population with rescue in clonal populations with different degrees of mitotic recombination. The figure shows by how much mitotic recombination increases the chance of rescue for various values of s_{Aa} . The analytical predictions are based on equation (S5.9) and equation (S6.26). The expression for P_{rescue} in equation (S6.26) got evaluated for a discrete set of points that were connected to give a continuous line in the figure. Parameter values: $\delta_{AA} = -0.01$, $\delta_{Aa} = -0.005$, $s_{aa} = -0.01$, $s_{AA} = 2s_{Aa} - s_{aa}$, $u = 5 \cdot 10^{-6}$, $N_0 = 10^5$. Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

genetic variation, which are present at absolute frequency $\sim \frac{uN_0}{-\delta_{AA}}$. In (partially) sexual populations, mutant homozygotes can still be generated after the environmental change via mutation or mating of mutant heterozygotes. At the same time, due to the lethality of type aa , sexual reproduction has no negative effect on the establishment of the mutant homozygote. Figure 2B shows that, overall, P_{rescue} can be higher in sexual populations than in a haploid clonal population as mutant heterozygotes buffer the environmental change. In fact, even the standing genetic variation can contain more mutant homozygotes than rescue mutants in a haploid population (not shown). Even if we double the mutation

rate in the haploid population to compensate for the smaller mutational target size of haploids, rescue remains slightly more likely in sexual populations (see the dotted line in Fig. 2B).

THE RATE OF SELFING

In the second part of the article, we explore how selfing affects rescue. For this, we consider a population in which individuals reproduce by selfing with probability σ_{self} and by outcrossing with probability $1 - \sigma_{\text{self}}$. The mathematical analysis is again based on branching process theory and can be found in SI Section S6.

The composition of the standing genetic variation and the role of the population dynamics

To demonstrate how differences in the standing genetic variation affect rescue, we focus on the limiting cases of fully selfing and fully outcrossing populations (cf. also Table 1).

In a fully selfing population, only half the offspring of a heterozygous individual are again heterozygous, reducing the “effective selection coefficient” of heterozygotes to $\delta_{Aa}^{\text{eff}} = -\frac{1}{2} + \frac{\delta_{Aa}}{2}$. As a consequence, the mean number of heterozygotes in the standing genetic variation, $\bar{n}_{Aa} \approx \frac{2uN_0}{\frac{1}{2} - \frac{\delta_{Aa}}{2}} \approx 4uN_0$, is low compared to that of an outcrossing population, where $\bar{n}_{Aa} \approx \frac{2uN_0}{-\delta_{Aa}}$. Heterozygotes have offspring of type AA with probability $\frac{1}{4}$ and homozygotes cannot be broken up by segregation, hence $\bar{n}_{AA} = \frac{\frac{1}{4}\bar{n}_{Aa}}{-\delta_{AA}}$ prior to the environmental change. If the mutant homozygote is only weakly deleterious, it accumulates in the selfing population, whereas in outcrossing populations, segregation impedes the accumulation. If the mutant homozygote is strongly deleterious, however, both heterozygotes and homozygotes are rare in a selfing population.

Figure 4A compares P_{rescue} as a function of δ_{AA} for a fully selfing and a fully outcrossing population if rescue occurs only from the standing genetic variation ($s_{aa} = -1$). Since type aa is lethal in the new environment, the establishment probability

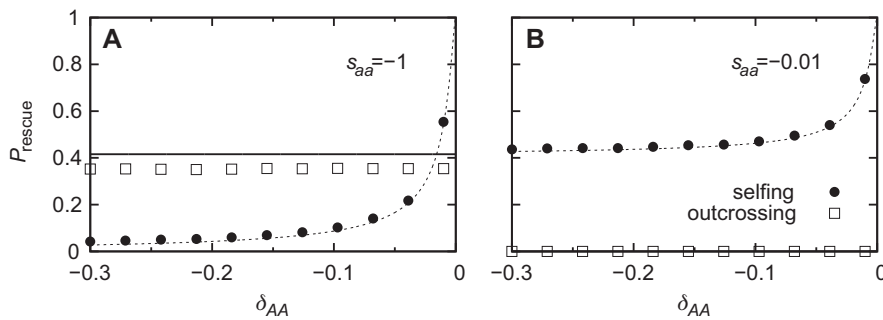


Figure 4. The probability of evolutionary rescue as a function of δ_{AA} if the wild-type is lethal (Panel A) and if it disappears slowly (Panel B). For selfing populations, the number of AA individuals in the standing genetic variation and hence the probability of evolutionary rescue are sensitive to the fitness of type AA . In contrast, in randomly mating populations, where type AA is continuously broken up, the fitness of type AA in the old environment has little influence on rescue. For analytical results, see equation (S6.6) and SI Section S3. Parameters: $\delta_{Aa} = -0.01$, $s_{Aa} = -0.3$, $s_{AA} = 0.005$, $u = 10^{-6}$, $N_0 = 10^6$. Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

of the rescue type is $p_{\text{est}}^{(AA)} \approx 2s_{AA}$ for both populations. In the outcrossing population, type AA is rare in the standing genetic variation, independent of its selection coefficient, and rescue happens primarily through rescue individuals generated by the mating of heterozygotes after the environmental change. Hence, rescue is effectively independent of δ_{AA} . By contrast, in selfing populations, rescue relies on the mutant homozygotes in the standing genetic variation and is strongly affected by δ_{AA} .

In Figure 4B, we allow for new mutations after the environmental change ($s_{aa} = -0.01$). A slow decay of the wild-type after the environmental switch enhances rescue in a fully selfing population (comparison of Panels A and B). Again, we find that rescue is completely impeded in the fully outcrossing population (note that $\nu_2 > 0$ for the choice of parameters in Fig. 4B).

A stochastic treatment of rescue in fully selfing populations can be found in SI Section S6.1.

For the last part, we focus on partially selfing populations. For the analysis, it proves useful to track the number of copies of the mutant allele rather than the numbers of the three genotypes. This is equivalent since establishment of the A allele implies establishment of the rescue genotype and vice versa. Following the same rationale as in equation (1), the probability of evolutionary rescue can be approximated by

$$P_{\text{rescue}} \approx 1 - e^{\left(-n_A(0)p_{\text{est}}^{(A)}(0) - \sum_{t=0}^{\infty} f(n_A(t))p_{\text{est}}^{(A)}(t+1)\right)}. \quad (8)$$

$n_A(0)$ is the number of A -alleles at the time of environmental change. This is again a stochastic variable, and equation (8) needs to be averaged over the respective distribution. $p_{\text{est}}^{(A)}(t)$ denotes the establishment probability of the A -allele, and $f(n_A(t))$ describes the generation of A alleles and can be approximated by $f(n_A(t)) \approx 2un_{aa}(t) \approx 2uN_0(1 + s_{aa})^t$.

In the following, we first discuss the effect of the rate of selfing on the establishment probability after the environmental change, $p_{\text{est}}^{(A)}(t)$, with a focus on dominance and the fitness effect of the beneficial allele. We subsequently consider a situation in which selfing affects the two factors $n_A(0)$ and $p_{\text{est}}^{(A)}(t)$ antagonistically.

As outlined above, dominance on a multiplicative scale critically affects how the rate of sex alters the rescue probability. It is hard to come up with an equally universal criterion to predict the dependency of rescue on the rate of selfing. Dominance is still an important factor but it proves more useful to consider dominance on an additive scale as does previous literature on selection in selfing populations (see e.g., Glémin 2007; Glémin and Ronfort 2013). Instead of ν_1 and ν_2 , we use the parameters h' and h that satisfy the relations $\delta_{Aa} = h'\delta_{AA}$ and $s_{Aa} = s_{aa} + h(s_{AA} - s_{aa})$. Since we assume $\delta_{Aa} < 0$, it holds

that $h' > 0$, and since we assume that the mutant homozygote is the most fit type in the new environment, it holds that $h < 1$.

The establishment probability of the mutant allele in partially selfing populations

In a selfing population, the mutant allele is very likely to occur in a homozygous individual, which affects the strength of selection it experiences; after the environmental change, it experiences stronger selection in selfing than in outcrossing (or clonal) populations. However, for the probability of establishment of the mutant allele, not only does the expected rate of increase matter but also the strength of stochasticity that it experiences. In SI Section S6.3.1, we argue—assuming weak selection and equilibrium—that the variance in the number of descendants of an A -allele is given by $1 + F$, with F approximated by its value in the absence of selection and at equilibrium, $F = \frac{\sigma_{\text{self}}}{2 - \sigma_{\text{self}}}$. In line with this, the approximation for $p_{\text{est}}^{(A)}$ derived by Glémin and Ronfort (2013) is given by

$$p_{\text{est}}^{(A)} = \frac{2(h_{\text{eff}}(s_{AA} - s_{aa}) + s_{aa})}{1 + F} \quad (9)$$

with $h_{\text{eff}} = h + F - hF$. Within this approximation, the establishment probability is higher in selfing than in outcrossing populations if $h < h_c = \frac{1}{2} + \frac{s_{aa}}{2(s_{aa} - s_{AA})}$ and lower otherwise (cf. eq. (24) with $\alpha = 1$ in Glémin and Ronfort 2013). However, the approximation requires that $\frac{N_0}{1+F}(h_{\text{eff}}(s_{AA} - s_{aa}) + s_{aa}) \gg 1$. In particular, it breaks down for $s_{Aa} < 0$ and $F = 0$, an important part of the parameter range we are interested in.

To obtain an approximation that holds for $s_{Aa} < 0$, we derive an expression for the expected growth of the mutant allele after the environmental change; this can be used to obtain $p_{\text{est}}(t)$ via an inhomogeneous branching process (see SI Section S6.3.1). The analysis is based on a separation of time scales, assuming that genotype frequencies reach equilibrium proportions instantaneously. We obtain

$$S_A(t) = \frac{n_A(t+1)}{n_A(t)} - 1 = (1 - h_{\text{eff}})s_{aa} + h_{\text{eff}}s_{AA} + (1 - h_{\text{eff}})(s_{AA} - s_{aa})p_A(t), \quad (10)$$

where $p_A(t)$ is the relative frequency of allele A at time t . Comparing selfing and outcrossing populations, the difference in growth rate experienced on average by one copy of the mutant allele is $S_A^{\text{self}} - S_A^{\text{sex}} = (1 - h)F(1 - p_A)(s_{AA} - s_{aa}) = F(1 - p_A)(s_{AA} - s_{Aa}) \geq 0$ for a given allele frequency p_A .

Note that $(S_A^{\text{self}} - S_A^{\text{sex}})/S_A^{\text{self}}$ is a decreasing function in s_{AA} . The stronger the effect of the beneficial allele, the less important is the differential growth rate of selfing and outcrossing populations. In Figure 5, dominance is kept constant at $h' = h = 1/2$, and the fitness effect of the beneficial allele increases along the

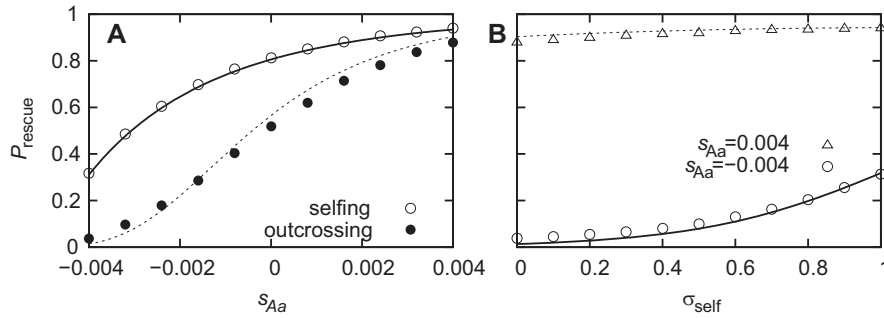


Figure 5. (Panel A) Probability of evolutionary rescue for selfing and outcrossing populations as a function of s_{Aa} when h is fixed at $1/2$ (i.e., the effect of the rescue mutation increases along the x -axis). The plot considers the parameter range of negative or only weakly positive s_{Aa} . The analytical approximations are based on equation (S6.26) and equation (S6.6). Parameter values: $h' = h = \frac{1}{2}$, $\delta_{AA} = -0.01$, $s_{aa} = -0.01$, $u = 5 \cdot 10^{-6}$, $N_0 = 10^5$. (Panel B) Probability of evolutionary rescue as a function of the selfing rate for a weakly and a strongly beneficial mutation. For intermediate dominance ($h' = h = \frac{1}{2}$), selfing significantly increases the probability of population persistence if the mutation is weakly beneficial ($s_{Aa} < 0$), while it has little effect if it is strongly beneficial ($s_{Aa} > 0$). The analytical results are based on equation (S6.26). Parameter values: $h' = h = 0.5$, $\delta_{AA} = -0.01$, $s_{aa} = -0.01$, $u = 5 \cdot 10^{-6}$, $N_0 = 10^5$. The expression for P_{rescue} in equation (S6.26) got evaluated for a discrete set of points that were connected to give a continuous line in the figure. Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

x -axis. Selfing increases rescue considerably when the allele is only slightly beneficial such that s_{Aa} is negative and formation of the mutant homozygote is necessary for rescue. In contrast, there is little difference between selfing and outcrossing populations for a strongly beneficial allele with sufficiently positive s_{Aa} .

Note that for $\sigma_{\text{self}} = 1$, the expected growth rate $S_A(t)$ reduces to s_{AA} since the allele will (almost) certainly exist in a homozygous individual. Consequently, the establishment probability of the mutant is independent of h , as is the frequency in the standing genetic variation (see eq. (11) below). With this, P_{rescue} is approximately independent of the dominance coefficient in a fully selfing population.

Antagonistic effects of selfing before and after the environmental change

Finally, we want to elucidate the consequences of antagonistic effects of selfing on $n_A(0)$ and $p_{\text{est}}^{(A)}$.

In Section S6.2, we show that the number of mutants prior to the environmental change can be approximated deterministically by

$$\bar{n}_A(0) = -\frac{2uN_0}{h'_{\text{eff}}\delta_{AA}} \tag{11}$$

with $h'_{\text{eff}} = h' + F - h'F$ (see also e.g., Glémin 2007). From this approximation, we see that the frequency of the mutant allele in the standing genetic variation decreases with F (and hence with the selfing probability) if the dominance coefficient is between zero and one, but it increases with F if the dominance coefficient is larger than one (i.e., $\delta_{Aa} < \delta_{AA}$). As discussed in the previous paragraph, the effect of selfing on the establishment probability is twofold. Selfing increases the strength of selection on the mutant

allele but also the strength of stochasticity that it experiences. For $s_{Aa} < 0$, efficient formation of the mutant homozygote is crucial for establishment of the mutant allele, and the positive effect of selfing dominates (this is different if $s_{Aa} > 0$ and h is sufficiently large, see eq. (9) and SI Section S6.4).

Figure 6 shows $P_{\text{rescue}}(\sigma_{\text{self}})$ for a switch in the dominance coefficient from $h' = 0.01$ to $h = 0.5$ at the time of environmental

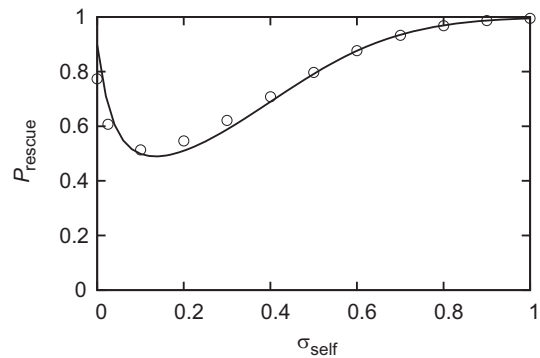


Figure 6. Probability of evolutionary rescue as a function of the selfing probability. The dominance coefficient changes from $h' = 0.01$ to $h = 0.5$ at the time of environmental shift. Outcrossing populations contain the mutant in a high frequency in the standing genetic variation, leading to a high probability of rescue. In selfing population, the initial frequency of the mutation is low but its establishment probability is high due to the efficient generation of the rescue type. The analytical approximation is based on equation (S6.26). The expression for P_{rescue} in equation (S6.26) got evaluated for a discrete set of points that were connected to give a continuous line in the figure. Parameter values: $\delta_{AA} = -0.5$, $s_{aa} = -0.02$, $s_{AA} = 0.01$, $u = 5 \cdot 10^{-6}$, $N_0 = 10^6$. Symbols denote simulation results. Each simulation point is the average of 10^5 replicates.

change. In this case, the probability of rescue is large in outcrossing populations due to the high initial frequency of the mutant allele. In selfing populations, P_{rescue} is large due to the high establishment probability of the mutation. For intermediate selfing, the probability of evolutionary rescue has a minimum. Note that without a switch in the dominance coefficient ($h = h' = 0.01$ or $h = h' = 0.5$), the positive effect of selfing on p_{est} would outweigh the negative effect on the standing genetic variation for all selfing rates, that is $P_{\text{rescue}}(\sigma_{\text{self}})$ would be an increasing function.

Discussion

In this article, we investigated the role of different reproductive modes in evolutionary rescue using a diploid one-locus model. We assumed that the mutant homozygote is the most fit genotype under the perturbed environmental conditions and compared rescue in clonal, selfing, and randomly mating populations.

The role of the dominance coefficient

Whether random mating increases or decreases the probability of evolutionary rescue compared to selfing or clonal reproduction crucially depends on the dominance coefficient of the mutation before and after the environmental change. Dominance coefficients (on an additive scale) can range from negative values to values larger than one. Peters et al. (2003) find great variation in the dominance coefficients of mildly deleterious mutations in *C. elegans*. Likewise, Agrawal and Whitlock (2011) observe a broad variety of dominance coefficients, including over- and underdominance, for knockout mutations in *S. cerevisiae* (some of them beneficial). They moreover find a correlation between the dominance coefficient and the strength of selection; we ignore such a relationship in this article. Again for *S. cerevisiae*, Gerstein et al. (2014) show a shift in the dominance coefficient between two different environments with no correlation between the values. For our study, we assume that the wild-type is the most fit type before the environmental change and the mutant homozygote is the most fit type after. Otherwise, we explore a broad range of dominance coefficients in both phases.

Comparing clonal and sexual reproduction, the dominance coefficient (in discrete-time models on a multiplicative scale) is the factor that decides whether sexual reproduction speeds up or slows down adaptation. A shift in the dominance coefficient upon environmental change can lead to an intermediate minimum or maximum in the probability of rescue as a function of the rate of sex. It is, however, important to note that stochastic effects can be even stronger than the effect of nonmultiplicative fitness. By bringing genotype frequencies closer to Hardy–Weinberg equilibrium, sexual reproduction dampens stochastic fluctuations in the relative frequency of mutant homozygotes. In clonal pop-

ulations, this variation decreases the probability of evolutionary rescue.

For selfing versus randomly mating populations, no simple criterion determines whether selfing promotes or impedes adaptation for a given fitness scheme. Glémin and Ronfort (2013) studied the effect of the dominance coefficient on rescue (setting $h' = h$ in all examples), finding that rescue decreases with the selfing rate for high values of h but increases with the selfing rate for low values of h . Our work can be seen as complementary to Glémin and Ronfort (2013) in that it explores further parameter regimes and moreover puts an emphasis on the differential role of selfing before and after the environmental change. The mutant frequency in the standing genetic variation decreases with the rate of selfing unless homozygotes have a higher fitness than heterozygotes. In contrast, for the establishment of the mutant allele after the environmental change, selfers have an advantage over a broad parameter range due to the efficient formation of the rescue type, leading to a higher effective growth parameter of the beneficial allele. This advantage increases as the dominance coefficient decreases. However, the positive effect of stronger selection on the establishment probability is counteracted by stronger stochasticity. If heterozygotes are fit ($s_{Aa} > 0$) and the dominance coefficient is high, the establishment probability of the mutant allele can indeed be higher in outcrossing than in selfing populations (see Glémin and Ronfort (2013) and SI Section S6.4). Through the interplay of the potentially opposing effects of selfing on the standing genetic variation and the establishment probability of the mutant allele in the new environment, the probability of evolutionary rescue can show an intermediate minimum as a function of the selfing rate (see Figs. 6 and SI Section S6.1). The approximations derived in Glémin and Ronfort (2013) require a high fitness of heterozygotes (at least in populations with a low selfing rate; more precisely s_{Aa}^{eff} needs to be significantly larger than zero). In contrast, we include scenarios where the beneficial allele is only slightly beneficial such that the heterozygote fitness is smaller than or only slightly larger than one. In that case, establishment of the mutant allele is largely contingent on the formation and persistence of homozygotes. For a given dominance coefficient, the benefit of stronger selection in selfing populations increases with decreasing effect of the beneficial allele, and it is particularly strong if the fitness of the heterozygote is smaller than one (see Fig. 5; see also Fig. 6 in Glémin and Ronfort (2013)). Note that unlike randomly mating or clonal populations, the probability of evolutionary rescue in fully selfing populations is insensitive to the dominance coefficient of the mutation for given fitnesses of the homozygote types (see also Fig. 5 in Glémin and Ronfort (2013), cf. also Roux and Reboud (2007)). Last, it is important to point out that we do not consider overdominance after the environmental change. In particular if both homozygotes had fitness smaller than 1 and rescue

relied entirely on the heterozygote, selfers would suffer a great disadvantage.

The population dynamics

In clonal or selfing populations, a slow decay of the wild-type population size enhances the probability of population survival since it increases the total mutational input. The same holds true in randomly mating populations with sufficiently fit heterozygotes as studied by Glémin and Ronfort (2013). However, in randomly mating populations with unfit heterozygotes, the breaking up of mutant homozygotes by random mating has a pronounced negative effect on rescue. A fast eradication of the wild-type can therefore promote rescue in randomly mating populations, while a slow decay can hamper it. This observation is relevant to the evolution of resistance in organisms with biparental sexual reproduction, such as insects or helminths. The fact that the spread of recessive resistance alleles can be constrained by the presence of wild-type individuals has appeared up multiple times in the resistance literature (e.g., Barnes et al. 1995; Hastings 2001). To apply our theory to the problem of choosing the best dosage (high vs low), it is, important to know the dose response curve of all genotypes, since most likely, a higher dose not only affects the wild-type (as in Fig. 2A) but also the mutant genotypes.

Heterozygotes as buffer against environmental change

Heterozygotes, even if they themselves cannot persist long term in the new environment, can serve as a buffer against environmental change. Consider a situation in which the wild-type is lethal under the new conditions. In randomly mating populations, which usually contain heterozygotes at an appreciable frequency, the rescue type can be efficiently generated through mating of heterozygotes after the environmental change. Selfing populations, in contrast, harbor few heterozygotes and (almost) entirely rely on rescue type individuals in the standing genetic variation. This can put them at a significant disadvantage compared to outcrossing populations if the rescue type is strongly deleterious in the original environment. Likewise, rescue can be more likely in a biparental sexual than in a haploid population.

The analogy between segregation and recombination

The role of the rate of sex in a diploid one-locus model is analogous to the role of recombination in a haploid two-locus model. The dominance coefficient (at a multiplicative scale for models in discrete time) corresponds to epistasis, and the inbreeding coefficient corresponds to linkage disequilibrium (up to scaling with the allele frequencies). Just as recombination counteracts deviations from linkage equilibrium, segregation counteracts deviations from Hardy–Weinberg equilibrium. As long as the number of heterozygotes/single mutants is large enough to be well described deterministically, the results are indeed identical.

When random variation in these numbers become important, quantitative differences arise. Then, the probability of rescue is lower in the haploid two-locus case since the frequency of either single mutant is subject to stochastic variation. Stochasticity impairs their ratio, making mating between single mutants less likely (see SI Section S3 and Fig. S3.1). The analogy between the two models is interesting from an experimental point of view. While it is hard to modify the rate of recombination between two loci, it is possible to experimentally control the rate of sex in various organisms such as *S. cerevisiae* or *C. reinhardtii*, making the model predictions experimentally testable.

Limitations and extensions

We chose the most basic setup to address the problem of how the mode of reproduction influences evolutionary rescue. While this approach allows us to gain a clear picture of elementary processes, it makes a number of simplifying assumptions. First, we only consider one locus. An example for such a simple genetic basis is provided by some cases of insecticide resistance. However, adaptation in natural populations is often polygenic. For example successful evolutionary response to climate change normally relies on one or more quantitative traits. With multiple loci, recombination plays an important role. In selfing populations, increased homozygosity (as generated by selfing) alters the action of recombination. Likewise, we neglect background selection that further reduces the variance effective population size in selfing populations (Glémin 2007).

Second, we assume that the rate of sex and the rate of selfing are constant properties, but many species can switch modes of reproduction depending on environmental conditions and the availability of mates. For example when stressed, the diploid form of *S. cerevisiae* starts reproducing sexually, whereas unstressed, it reproduces clonally by budding (Kassir et al. 1988). Likewise, some plant species reproduce by outcrossing in sunny weather (high availability of pollinators) and by selfing under rainy conditions (Stebbins 1957). In the simple model used here, the consequences of a switch in the mating system would strongly depend on the dominance coefficients before and after the environmental change. Also, the mode of reproduction is itself subject to selection and can evolve. For example, Bodbyl Roels and Kelly (2011) show that *Mimulus guttatus*, where the selfing rate is a quantitative trait, evolved increased rates of selfing upon pollinator limitation. Moreover, mating is always guaranteed in our model. However, the mating success of obligate outcrossing individuals often drops with population density since individuals fail to find mates, making rescue less likely to occur. For biparental sexual reproduction, we exclusively consider random mating of individuals. Nonrandom mate choice can considerably influence adaptation. Proulx (1999) show that assortative mating hampers niche expansion in a haploid one-locus two-allele

model, while female choice of locally adapted alleles promotes it. Similar effects would probably occur in our model.

We also assume that the mutation rate is independent of the mode of reproduction but Magni and von Borstel (1962) show for *S. cerevisiae* that the mutation rate differs, depending on whether the cells undergo meiosis or mitosis.

Importantly, for biparental sexual reproduction, we only consider hermaphrodites and do not allow for two genders/mating types that might be differentially affected by environmental change. A simple, yet interesting extension of our model would compare rescue from a mutation on an autosome to one on the X-chromosome. Urdaneta-Marquez et al. (2014) find that an X-linked *dyf-7* haplotype is responsible for resistance against a class of anthelmintics in *Haemonchus contortus*. Based on parameter estimates from this system, they follow the expected genotype frequencies in a classical population genetics model and show that hemizygous resistant males increase the spread of resistance compared to a scenario in which the allele lies on an autosome.

We also chose the simplest scenario on the ecological side: there is no population structure, and the environmental change (assumed to be sudden) hits the entire population at once. A gradual deterioration of the habitat through space and time alters the population dynamics and along with it the role of the segregation and union of gametes in randomly mating populations (see Uecker et al. 2014, for a corresponding haploid model). A relevant modification of the model would incorporate refugia in which the environment remains benign for the wild-type, allowing it to persist. In a recent experimental study, Lagator et al. (2014) explore the combined effect of sex and migration on adaptation to a sink environment in the algae *C. reinhardtii*. While both sex and migration are beneficial during the initial stage of adaptation, the effect of sex on subsequent adaptation depended on the presence or absence of migration. With ongoing migration, sex slowed down adaptation by breaking up adaptive gene combinations (since the genetic basis of adaptation was not determined, it is unclear whether this is due to segregation or recombination). A situation with refugia occurs in agriculture where it is impossible to spray every single leaf with pesticides. Moreover, field margins sometimes remain untreated to contain the pesticide safely within the field or to maintain biodiversity and natural enemies of the pest. In both cases, persistence of the wild-type is a side-effect. However, refugia are often preserved with the explicit goal to maintain a wild-type population to hamper the spread of resistance. The idea behind this “high-dose-refuge” strategy is precisely that mutant homozygotes get broken up through mating with the wild-type. Existing models incorporating this strategy address, for example, resistance in insects against transgenic crops that produce *Bt* toxins (Mallet and Porter 1992; Cerda and Wright 2004) or herbicide resistance in outcrossing versus selfing weeds (Roux and Rebut 2007). Beyond these specific models, a generic model along the lines of the present ar-

ticle could shed light on the influence of refugia on the evolution of resistance (see Comins 1977, for a general, yet mathematically different approach to the problem in obligate sexual insects).

There is no simple answer to the question of which mode of reproduction – clonal reproduction, selfing, or random mating—is best at promoting population survival. The outcome strongly depends on the fitness scheme before and after the environmental change. However, our analysis provides insight into the main principles governing rescue under the three reproductive strategies.

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Supporting Information

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Figure S3.1: Probability of evolutionary rescue as a function of recombination (Panel A) and the probability of sexual reproduction (Panel B) for a harsh environmental change (filled symbols, $s_{ab} = s_{aa} - 1$) and a mild environmental change (empty symbols, $s_{ab} = s_{aa} = -0.01$).

Figure S6.1: Probability of evolutionary rescue as a function of the selfing rate.