Modeling evolutionary rescue

Hildegard Uecker* (ORCiD: 0000-0001-9435-2813), Research Group Stochastic Evolutionary Dynamics, Department of Theoretical Biology, Max Planck Institute for Evolutionary Biology, Plön, Germany
Matthew M. Osmond* (ORCiD: 0000-0001-6170-8182), Department of Ecology and Evolutionary Biology, University of Toronto, Toronto, Canada
Carla Alejandre (ORCiD: 0000-0003-2141-618X), Centro de Astrobiología (CAB), CSIC-INTA, Carretera de Ajalvir km 4, Torrejón de Ardoz, 28850, Madrid, Spain
Ernesto Berríos-Caro (ORCiD: 0000-0002-2080-1273), Center for Advanced Biotechnology and Medicine, Rutgers University, Piscataway, NJ 08854 & Stochastic Evolutionary Dynamics Group, Max Planck Institute for Evolutionary Biology, Plön, Germany & Evolutionary Ecology and Genetics, Christian-Albrechts-University of Kiel, Kiel, Germany
Dale T. Clement (ORCiD: 0000-0001-7327-3323), Department of Biology, Wake Forest University, 834 Wake Forest Rd., Winston Salem, NC 27109 & School of Biological Sciences, Washington State University, Pullman, WA 99164
Peter Czuppon (ORCiD: 0000-0003-1462-7237), Aix Marseille Univ, CNRS, I2M, Marseille, France & Institute for Evolution and Biodiversity, University of Münster, Münster, Germany
Léonard Dekens, Theoretical Biology Lab, The Francis Crick Institute, London NW1 1AT, United Kingdom
Puneeth Deraje, (ORCiD: 0000-0001-6948-7089) Department of Ecology and Evolutionary Biology, University of Toronto, Ontario, Canada
Jeremy A. Draghi, Dept. of Biological Sciences, 4001 Derring Hall, Virginia Tech, Blacksburg, VA, 24060 USA
Asad Hasan, Department of Zoology, University of British Columbia, BC V6T 1Z4, Canada
Robert D. Holt (ORCiD: 0000-0002-6685-547X), Department of Biology, The University of Florida, Gainesville, Florida, USA 32611
Teemu Kuosmanen (ORCiD: 0000-0002-8724-5048), Department of Computer Science, Organismal and Evolutionary Biology Research Programme, University of Helsinki, Helsinki, Finland
Alexander Longcamp, Department of Biological Sciences, Mississippi State University, Mississippi State, MS 39762, USA
Loïc Marrec (ORCiD: 0000-0003-0941-6603), Département de Biologie Computationnelle, Université de Lausanne, Lausanne, Switzerland & Swiss Institute of Bioinformatics, Lausanne, Switzerland
Guillaume Martin, ISEM, Université de Montpellier, CNRS, IRD, Montpellier, France
Christin Nyhoegen (ORCiD: 0000-0002-8447-040X), Freie Universität Berlin, Institute of Pharmacy, Department of Clinical Pharmacy and Biochemistry, Berlin, Germany
Maria E. Orive (ORCiD: 0000-0003-4825-0554), Department of Ecology & Evolutionary Biology, University of Kansas, 1200 Sunnyside Ave., Lawrence, KS 66045 USA
Vrinda Ravi Kumar (ORCiD: 0000-0001-6054-2694), Biology Centre, Czech Academy of Sciences, Branišovská, České Budějovice, Czech Republic 370 05
Ophélie Ronce, ISEM, Univ Montpellier, CNRS, IRD, Montpellier, France
Remus Stana, UT Southwestern Medical Center, Dallas, 5323 Harry Hines Blvd., Dallas, Texas 75390
Lindi M. Wahl (ORCiD: 0000-0003-1163-0940), Mathematics, Western University, London, N6A 5B7, Canada
Masato Yamamichi (ORCiD: 0000-0003-2136-3399), Center for Frontier Research, National Institute of Genetics, 1111 Yata, Mishima, Shizuoka 411-8540, Japan

* *These two authors contributed equally. We had to pick an order.*
Co-corresponding authors: uecker@evolbio.mpg.de, mm.osmond@utoronto.ca

All authors except for the two co-first authors are listed alphabetically.

Abstract

A population that avoids extinction by adapting to environmental change is said to be rescued by evolution. Evolutionary rescue is of fundamental interest in ecology and evolution and of great relevance in conservation, where rescue of endangered species is wanted, and in medicine and agriculture, where rescue (resistance evolution) of pathogens, cancers, and pests is unwanted. Theory plays a key role in understanding and predicting the dynamics and likelihood of rescue. Here, we provide a comprehensive resource on the state-of-the-art of modeling in evolutionary rescue research, including an overview of the current connection between theory and data. The accumulating body of theory includes a large number of complexities, giving us specific insights and shaping our perspective on when rescue is likely. Many of the themes dealt with in general models of evolutionary rescue also appear in the contexts of drug and pesticide resistance, calling for more synergistic interaction. Theoretical and experimental results are broadly consistent. Close ties are still rare but successful examples demonstrate the power of theory. Both simple and complex models are actively used to predict and manage rescue in nature, medicine, and agriculture but challenges remain in connecting what we can measure to what we can model.

Keywords: evolutionary rescue, extinction, modeling, resistance, conservation, evolutionary escape

Contents

1 Introduction

Environmental change can make populations so maladapted they risk extinction. This can be avoided by sufficiently rapid evolution, which is called "evolutionary rescue". The term was coined by Gomulkiewicz and Holt (1995), who used mathematical models to crystallize the underlying logic for rescue following an abrupt environmental change (see Box 1 for one of the author's personal story leading to this paper). Such a scenario causes a population to decline, sparking a race between this population decline and adaptive evolution. Rescue occurs when evolution wins the race, leading to population recovery and a U-shaped 'rescue curve' of population size over time (Figure 1a). Evolution can also rescue populations in gradually changing environments. Here, it takes evolution all the running it can do to keep in the same place (cf. Carroll, 1872): sufficiently rapid evolution permits the population to track the environment and persist (Figure 1b).

When rescue occurs is of fundamental importance in ecology and evolution. In many scenarios of rescue, ecological and evolutionary processes occur on comparable time scales and interact. Evolutionary rescue, and its absence, shape key ecological attributes, such as the fundamental niche and geographic ranges. Conversely, the ecological dynamics that occur in scenarios of rescue can impact evolution, for example affecting the genetic basis of adaptation (Osmond et al., 2020) and selection on key evolutionary parameters, like mutation rates (Gifford et al., 2023).

Evolutionary rescue has great applied relevance. It has attracted attention for more than a century in the context of drug resistance (e.g. Ehrlich, 1907; Bradlow, 1920), where rescue of the pathogen is unwanted (see Alexander Fleming's Nobel lecture, Fleming, 2025). The problem of drug resistance arises for a broad range of pathogens and parasites (bacteria, viruses, fungi, malaria, helminths, etc.) as well as in cancer chemotherapy, directly causing millions of deaths annually (e.g. Murray et al., 2022). Similarly, millions of deaths result from the evolution of pesticide resistance in disease vectors (Ranson and Lissenden, 2016). In agricultural pests, yield losses due to resistant pests cause high economic costs (Varah et al., 2020) and threaten global food security (Hicks et al., 2018). Evolution can also allow pathogens to escape from vaccine-induced or natural immunity and adapt to novel hosts after spillover, leading to emergence. In the future, evolution may allow disease vectors and pests to become resistant to gene-drive-based control strategies. In contrast to medicine and agriculture, in conservation we desire population persistence. Rescue is especially relevant in the context of climate change, which is irreversible on the timescale over which the fate of a population is decided. Relative to background levels prior to human impacts, current rates of extinction are 1000 times higher (Pimm et al., 2014; De Vos et al., 2015). Challenges thus appear in medicine, public health, and agriculture because evolutionary rescue is too likely and in conservation biology because it seems too unlikely to occur.

To be able to sway those likelihoods, it is important to understand which factors influence the probability of rescue, so as to prevent or foster it. For example, in medicine, which drug regimen best eradicates pathogens without selecting for resistance? A long-standing idea is to administer multiple drugs instead of just one (Ehrlich, 1911), which creates a larger evolutionary barrier to resistance. This has proven successful in the treatment of HIV, tuberculosis, and malaria (Medical Research Council, 1950; Fox et al., 1999; Goldberg et al., 2012; WHO, 2024). Despite the conceptual simplicity and compelling logic of the idea and some empirical support, it is, however, not clear whether combination therapy is always superior to mono-therapy and which of the myriad ways of administering multiple drugs is best (e.g. Siedentop et al., 2024). Meanwhile, a major goal in conservation is to preserve and even increase genetic variation that is adaptive in future environments so as to avoid extinction. An emblematic example are coral reefs, which are key for marine biodiversity and heavily affected by climate change. Evolution-informed establishment of marine protected areas is predicted to increase the chances of successful adaptation (see Box 2).

Evolutionary rescue inherently entails both a race and an interaction between evolution and demography. This entangled race can entail complex dynamics that can be difficult to predict, even qualitatively. For example, a stronger stress implies a faster initial demographic decline, reducing the time a rescue mutant has to appear, but facilitating its subsequent spread via competitive release (Uecker et al., 2014; Day and Read, 2016); it is thus unclear when a stronger stress will increase or decrease the probability

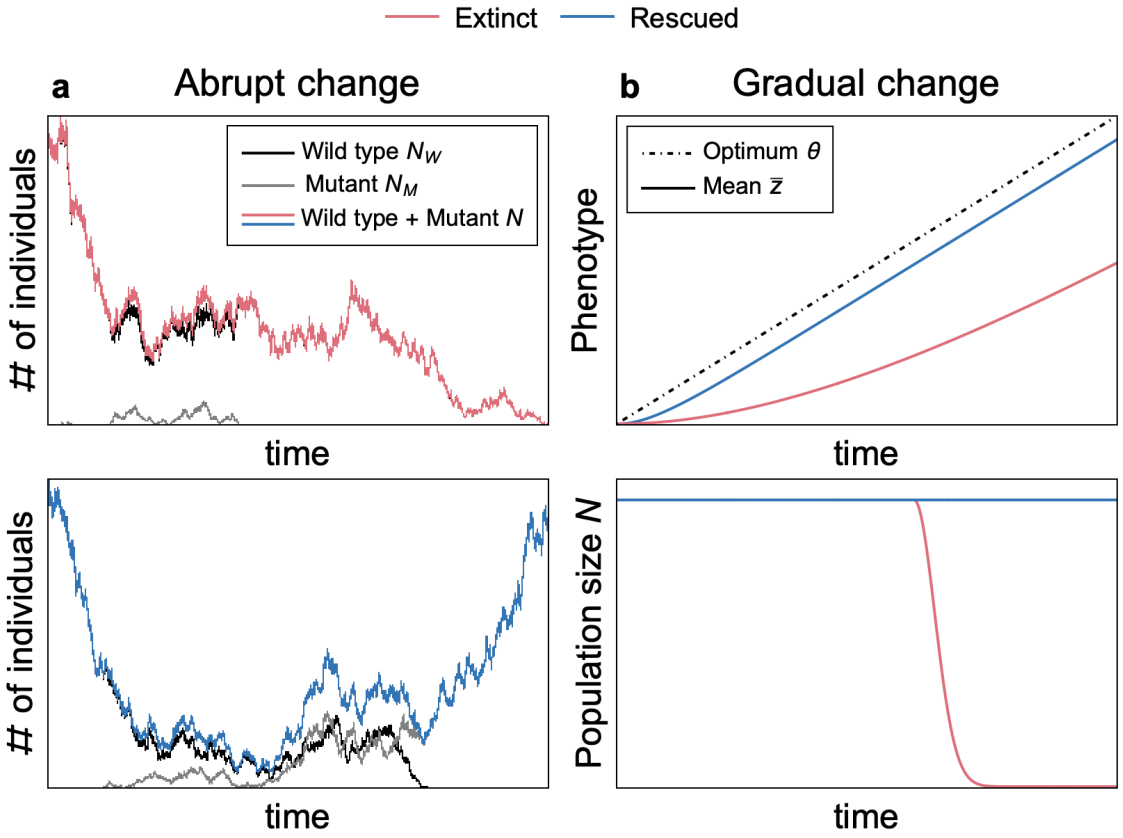

Figure 1: Common models of evolutionary rescue. **(a)** For an abrupt environmental change, we simulate a stochastic branching process in continuous time with a hard carrying capacity. The wild type (black) declines roughly exponentially while producing potential rescue mutants (gray). Rescue occurs, producing a U-shaped trajectory of total population size (blue), if a rescue mutant appears and establishes; otherwise, the population goes extinct (red). **(b)** For a gradual environmental change, we numerically iterate recursion equations describing the expected population mean trait and population size with a linear change in the optimum and a ceiling carrying capacity (see Eqs. 2, 3, 7, 13, and 14 in Bürger and Lynch, 1995). Populations that lag too far behind the optimum go extinct (red); otherwise, the population size remains constant (blue).

of rescue (Alexander et al., 2014). To determine the outcome, one must quantify demographic and evolutionary rates, as well as their interaction. For this, mathematical modeling is essential.

In light of the relevance of mathematical modeling in evolutionary rescue, and the increasing urgency of the issue, a synthesis of the state of the field is timely. Just when evolutionary rescue was becoming an emerging research focus (Gonzalez et al., 2013), the existing eco-evolutionary literature, covering both empirical and theoretical work, was reviewed by Carlson et al. (2014) and by Bell (2017). Two specific aspects of the theory were also reviewed at this time: the similarities between models for medicine and conservation (Alexander et al., 2014) and the rapid evolution of quantitative traits in gradually changing environments (Kopp and Matuszewski, 2014). Since then, the topic of evolutionary rescue has exploded with only a brief recent review within the broader topic of limits to adaptation (Chevin and Bridle, 2025). We here provide a general review of rescue theory, from classical models to the rapidly expanding number of recent advances, and discuss connections between theory and data. Our article is intended to be a resource, structured in several parts. Section 2 introduces two classical modeling approaches – quantitative and population genetics models of rescue – and summarizes their main predictions. In section 3 we call attention to two bodies of literature that include models of evolutionary rescue but have developed independent of the term: theory on Luria-Delbrück experiments and on evolutionary escape of pathogens from drugs, pesticides, and other severe stress. In section 4, we provide a review of the literature, structured by eleven key topics, followed by section 5, where we review application-driven models in conservation and resistance evolution. We highlight connections of theory with empirical systems in Section 6. We end with a discussion of some subtleties in the precise definition of evolutionary rescue in section 7.

2 Fundamental models of rescue

Evolutionary rescue has been modeled within the frameworks of both quantitative and population genetics. We start by outlining the fundamental models for each.

2.1 Quantitative genetics models of rescue

Quantitative genetics models assume a continuous distribution of phenotypes in a population. When fitness is a Gaussian function of an individual's phenotype, the distribution of phenotypes in a population remains normal from one generation to the next and the expected change in the mean phenotype is the product of additive genetic variance and the selection gradient (Lande, 1976). Assuming a constant genetic variance, the mean phenotype across replicates is itself normally distributed, and we can track this full distribution through time (Lande, 1976).

This framework has traditionally been used to model rescue from both an abrupt and gradual environmental change (Box 3). With an abrupt change (i.e., a step-wise shift in the optimum phenotype), if we treat both evolution and demography deterministically, we can solve for the trajectory of population size, quantifying extinction risk by the time it is below a given threshold (Gomulkiewicz and Holt, 1995). With a gradual change, where the optimum phenotype increases linearly (known as the "moving-optimum model"), the expected mean phenotype reaches a steady-state lag behind the optimum (Lynch et al., 1991; Lynch and Lande, 1993; Bürger and Lynch, 1995, recast in terms of thermal performance curves by Huey and Kingsolver, 1993). Populations are predicted to persist in the long run if and only if expected mean fitness at the steady-state lag is above replacement (Figure 1b), which gives a critical rate of environmental change beyond which populations cannot survive. Key quantities in these models are genetic variance and the strength of selection, which speed up evolution but also increase demographic costs (reviewed in Alexander et al., 2014).

2.2 Population genetics models of rescue

Population genetics models of evolutionary rescue assume a discrete set of genotypes and an explicit genetic architecture with feedbacks between allele frequency shifts and population dynamics. As with the quantitative genetics framework, these models can be used to study rescue under all types of environmental change, e.g., the quantitative genetics model with a gradual change in Bürger and Lynch (1995) is accompanied by simulations with explicit genetics. The simplest models consider an abrupt

change and just two genotypes: a "wild type" and a "rescue mutant" (Gomulkiewicz and Holt, 1995; Holt and Gomulkiewicz, 1997; Bell and Collins, 2008; Orr and Unckless, 2008). After the environmental change, the wild type has a negative *per-capita* growth rate, $-r < 0$, and declines to extinction. The rescue mutant, by contrast, has a positive *per-capita* growth rate, $-r + s > 0$, and therefore has a chance to grow to large numbers (Figure 1a).

Rescue contingent on one locus with two alleles is deterministically described by two equations. The first one describes the change in the total population size $\frac{\mathrm{d}N}{\mathrm{d}t} = \bar{m}(q)N$, where $\bar{m}(q)$ is the mean fitness averaged over the two genotypes (three in a diploid model, see Gomulkiewicz and Holt, 1995), which have frequencies $p(t)$ (rescue allele) and $q(t) = 1 - p(t)$ (wild-type allele). The second one describes the evolutionary dynamics, $\frac{\mathrm{d}p}{\mathrm{d}t} = sp(1-p)$ (assuming here a haploid model). Deterministic models of rescue are, for example, applied to determine the time that the population size is dangerously small (Gomulkiewicz and Holt, 1995).

Unlike deterministic models, models that account for stochasticity at least in the rescue mutant dynamics make it possible to explicitly determine the probability of evolutionary rescue vs. population extinction (Holt and Gomulkiewicz, 1997; Orr and Unckless, 2008). If stochastic establishment of rare rescue mutants is independent of their time of appearance, the probability of evolutionary rescue can be expressed as $P_{\mathrm{rescue}} = 1 - \exp\left(-\lambda p_{\mathrm{est}}\right)$, where λ is the sum of the number of rescue mutants in the standing genetic variation or appearing *de novo* during decline of the wild-type population and p_{est} is the stochastic establishment probability of a single rescue mutant (see Box 4).

2.3 Common predictions

At first glance, the fundamental quantitative and population genetics models seem quite disparate. However, while there are some qualitative differences in their underlying dynamics (Box 5), they agree in a number of key predictions.

Rescue is generally more likely for populations that are large at the onset of stress. For both quantitative and population genetics models with a sudden environmental change, larger initial population sizes make the population larger at all times (Eq. B5.1, Box 5), reducing the time spent at high risk of extinction (see figures 5B and 6B in Gomulkiewicz and Holt, 1995). Furthermore, while additive genetic variance is often just a parameter in quantitative genetics models (as assumed in the previous section), it generally increases with population size (see equations 14 and 15 in Bürger and Lynch, 1995), usually facilitating adaptation in both abruptly and gradually changing environments (see below for a caveat). Similarly, in population genetics models of an abrupt change, a larger initial population size implies a larger number of rescue mutants in the standing genetic variation and arising *de novo* during the wild type's decline (see Box 4, and both equation 3 and the unnumbered equation for P_{old} in Orr and Unckless, 2008).

The fundamental models also suggest that rescue is more likely when the environmental change is smaller or slower. In deterministic quantitative and population genetics models with an abrupt change, a smaller environmental change equates to a slower initial population decline, which leads to a higher population size (Eq. B5.1, Box 5) and thus a shorter time at risk (see figure 5A and 6A in Gomulkiewicz and Holt, 1995). In stochastic population genetics models, a more rapid elimination of the wild type, caused by a larger environmental change, leads to fewer rescue mutations (see Box 4 and equation 3 in Orr and Unckless, 2008). With a moving optimum, the population only survives below a critical speed of environmental change (see equation 10 in Bürger and Lynch, 1995).

In both frameworks, greater genetic variation at the onset of stress, $q_0 \cdot (1 - q_0)$ and σ_g^2, speeds up the evolutionary dynamics (Eq. B5.2, Box 5), which in principle aids rescue. However, for both approaches, there is a caveat. In population genetics, both the population size at any point in time (Eq. B5.1a, Box 5) and the probability of evolutionary rescue (Box 4) increase with the initial frequency of the rescue allele $1 - q_0$, implying that a greater variance only aids rescue as long as $q_0 < 1/2$ (which usually applies to rescue scenarios). In quantitative genetics, while the mean population growth rate $\bar{r}(d)$ increases more quickly over time if σ_g^2 is large (Eq. B5.2b, Box 5), a large genetic variance has on the other hand a direct negative effect on $\bar{r}(d)$ through the variance load, $\sigma_z^2/(2\omega^2)$ (Eq. B5.1b, Box 5).

Finally, the rescue probability also increases with the maximum possible growth rate of the population. In both quantitative and population genetics models, a larger maximum growth rate increases mean fitness and thus population size at any given time under an abrupt change (see Eq. B5.1 and Fig. B5.1 in Box 5, and equations 6 and 10 in Gomulkiewicz and Holt, 1995). A larger maximum growth rate also permits a higher critical rate of change in quantitative genetics models for gradual change (see equation 10 in Bürger and Lynch, 1995). In stochastic population genetics models, it increases the establishment probability, p_{est} (see the approximation below equation 1 in Orr and Unckless, 2008).

There are parallels between these fundamental models of rescue and source-sink-theory, which we discuss in Box 6.

3 Foundational rescue theory by other names

The term evolutionary rescue, and most references in the previous section, come from the intersection of evolution and ecology in the 1990s. However, before the term was coined, models of evolutionary rescue have been developed long before in other contexts.

3.1 Luria-Delbrück theory

The Luria-Delbrück experiment – one of the most important experiments in the history of evolutionary biology (Lovett and Sass, 2025) – was designed to determine whether or not mutations occur independently of stress (Luria and Delbrück, 1943). It is still used to estimate mutation rates (Krašovec et al., 2019). In Luria-Delbrück experiments (a.k.a. fluctuation assays), a large number of bacterial populations are each initiated with a few clones and allowed to grow exponentially before being subjected to a lethal stress on separate Petri dishes; the resistant colonies that form on each plate are counted. While performed for a different purpose, Luria-Delbrück experiments are essentially evolutionary rescue experiments – the probability of rescue is simply the fraction of plates with colony growth.

Right from the start, the experiment has been accompanied by theoretical predictions (which were essential to answer the original question), and soon analytical results for the full distribution of mutants in a culture were derived (Lea and Coulson, 1949). Theory has since greatly extended to mitigate various limiting approximations of the early models and improve empirical estimation methods (see Cheek and Antal 2018 for a rigorous stochastic treatment of the basic model and Zheng 1999 for a historical review). A full review of this active field is beyond the scope of the present paper. A few more recent – somewhat subjectively picked – key generalizations are the extension to arbitrary density-dependent or time-varying birth rates (Houchmandzadeh, 2015), the incorporation of cell death, distinct birth and death rates for each type, and non-exponential lifetime distributions (Mazoyer, 2017), and the possibility of multiple mutations along the genome (Cheek and Antal, 2018). The Luria-Delbrück approach has also been adapted to consider plasmid transfer rates instead of mutation rates (Kosterlitz et al., 2022). There are also numerical methods tailored for specific applications, including the estimation of mutation rates towards resistance before and during drug treatment in heterogeneous cancer cell populations (Russo et al., 2022). This rich stochastic and statistical machinery can be viewed as rescue theory. In fact, the probability of seeing any colony counts takes the same functional form as the probability of rescue in classic population genetics models (Box 4). For example, one minus equation 5 in (Luria and Delbrück, 1943) is the probability of rescue from standing genetic variation assuming the establishment probability of a rescue mutation is one. One key difference between Luria-Delbrück theory and many population genetics models is that the latter often assume mutation-selection(-drift) balance prior to the onset of stress (e.g., Orr and Unckless, 2008) while Luria-Delbrück theory does not. The build-up of standing genetic variation during population growth pre-stress – usually not reaching an evolutionary equilibrium – not only reflects the biological reality of the Luria-Delbrück experiment (and presumably many rescue experiments), but is likely also characteristic of many real-life rescue scenarios, such as the spread of resistance mutations during growth of a cancer (modeled e.g., by Coldman and Goldie, 1983). Another difference is that Luria-Delbrück theory typically ignores *de novo* mutation after plating.

3.2 Drug and pesticide resistance and other instances of evolutionary escape of pathogens from severe stress

The evolution of resistance to drugs and pesticides has been extensively modeled for decades, producing a large body of theory on resistance evolution in many organisms in both medicine and agriculture. Many models of resistance evolution are clearly models of evolutionary rescue (e.g., Goldie et al., 1982; Birkhead et al., 1987; Ribeiro and Bonhoeffer, 2000; Alexander and Bonhoeffer, 2012; Nyhoegen et al., 2024) though the term itself may be lacking. Indeed, some models that place themselves into the resistance literature are generally applicable rescue models (e.g., Iwasa et al., 2003, 2004; Madgwick et al., 2024). Others are not models of evolutionary rescue *sensu stricto*. This applies, for example, to many models of pesticide resistance evolution, since eradication of the pest is mostly not possible: not all of a landscape is sprayed with herbicides, not all leaf area can be reached by fungicides, and insects continuously disperse into the field (Roux and Reboud, 2007; Mikaberidze et al., 2014, 2017; Helps et al., 2017, 2020). Similarly, between-host models of drug resistance are often not strictly rescue models, e.g., because new patients keep entering the hospital (Bonhoeffer et al., 1997a; Bergstrom et al., 2004), creating a source-sink situation (Box 6). Conversely, in self-limiting diseases the pathogen population goes extinct even if it evolves resistance – just later (Austin and Anderson, 1999; Day and Read, 2016) (but see the discussion in section 7.3). For many scientific questions, the distinction between a rescue and a non-rescue resistance model is an academic one. A counter example is the so-called high-dose-refuge strategy in which continuous maintenance of a sensitive wild-type population is explicitly part of the resistance management strategy and the size of the wild-type population – which can be manipulated – matters (Comins, 1977; Taylor and Georghiou, 1979; Takahashi et al., 2017). Here and in sections 5.2 and 6.2.1, we discuss resistance models without restricting ourselves to 'true rescue models' but leave out population genetics models that do not consider any demography such as some classic models of insecticide resistance evolution (e.g. MacDonald, 1959; Curtis, 1985).

The overwhelming majority of resistance models consider a discrete set of genotypes, either tracking the agent itself (e.g., bacterial cells) or infected entities (e.g., infected leaf tissue); quantitative genetics models are rare (but see for example Bukkuri et al. 2023b and Taylor and Cunniffe 2023a for quantitative genetics models of resistance in cancer and fungal plant pathogens, respectively). Perhaps unsurprisingly, the fundamental deterministic population genetics model of rescue introduced in section 2.2 has long appeared in the context of resistance evolution. For example, the model of an exponentially decreasing wild-type population (drug sensitive) and an exponentially increasing mutant population (drug resistance) can be found as an explanation for the observed decline and relapse of cancer during treatment in Hokanson et al. (1977) and for experimental results on bacterial dynamics exposed to antibiotics in Li et al. (1994). The joint tracking of population size and allele frequency in a diploid population, as performed by Gomulkiewicz and Holt (1995) and outlined in section 2.2, appears, for instance, in the specific context of insecticide resistance (with a lethal wild-type homozygote and immigration) in Taylor and Georghiou (1979). It is perhaps more surprising that the semi-stochastic approach presented in Box 4 had already been developed and applied in a little cited article by Nissen-Meyer (1966) to calculate the evolution of antibiotic resistance during treatment, allowing for a more complex decay dynamics of the wild type than just exponential decay. Other early studies derive the same functional form for the resistance probability as in Box 4 (i.e., $P_{\text{res}} = 1 - \exp(\dots)$), albeit not accounting for possible stochastic loss of resistant types, i.e., assuming $p_{\text{est}} = 1$ (Goldie and Coldman, 1979; Lipsitch and Levin, 1997). This especially holds for one of the earliest cancer resistance models (Goldie and Coldman, 1979), which determines the number of resistant mutants in an exponentially growing cancer cell population prior to treatment (see also section 3.1 and the review by Altrock et al. 2015). Nevertheless, the potential stochastic loss of resistant mutants has not only been modeled by Nissen-Meyer (1966) but also in other early models such as by Goldie and Coldman (1983) and has been taken into account throughout time sparsely yet recurrently and increasingly often both in stochastic simulations (e.g. Ribeiro and Bonhoeffer, 2000) or analytical models, which are often based on branching process theory (e.g., Iwasa et al., 2003, 2004; Alexander and Bonhoeffer, 2012; Mikaberidze et al., 2017; Gunnarsson et al., 2020; Czuppon et al., 2023; Nyhoegen et al., 2024).

Apart from models of drug resistance, rescue-like scenarios have also long been modeled in the context of adaptation of pathogens to new hosts (see e.g. Antia et al., 2003; Gandon et al., 2013; Elie et al., 2022) as well as in the context of evolutionary escape from vaccine-induced immunity (e.g. McLean,

1995; Restif and Grenfell, 2007; McLeod et al., 2021; Geoffroy et al., 2022; Gandon et al., 2025) or from the natural immune response to cancer (Michelson, 1986) and to viral (and other) infections (e.g. Nowak et al., 1995; Althaus and De Boer, 2008; Fryer et al., 2010; Luo et al., 2012; Nagaraja et al., 2016), including early fully stochastic approaches (Michelson, 1986). For similar reasons as above, many of these models are not strictly rescue models. Last, it should be noted that in this latter literature, as well as sometimes in models of drug resistance (Iwasa et al., 2003) and even in more general models (Iwasa et al., 2004; Serra and Haccou, 2007), the common terminology is "evolutionary escape" or "evasion" rather than "evolutionary rescue" and one may thus find rescue models under these terms.

4 Developments in modeling evolutionary rescue

To review the developments of rescue theory we searched for articles on Web of Science up until May 2025 with the phrase: "evolutionary rescue" AND "model*". We then manually filtered these papers, leaving 156 that we cite in this paper. We complement this literature search with many other relevant articles. Fig. 2 gives a visual summary of 226 articles analyzing rescue models that we review in sections 4 and 5: we see a sharp rise in the number of rescue models over time (panel a) and a citation network analysis detected eight main clusters (panel b).

In this section, we review progress in understanding the influence of key features of the organism, the population, and the environment on evolutionary rescue. We review progress made in application-driven research on evolutionary rescue separately in section 5.

4.1 Genetic architecture

Early models of evolutionary rescue focus on two limiting cases of genetic architecture (see section 2). At one end of the spectrum, population genetics models assume fitness is determined by one locus with two alleles, treating diploids deterministically (Gomulkiewicz and Holt, 1995) or haploids stochastically (Holt and Gomulkiewicz, 1997; Orr and Unckless, 2008). At the other extreme, quantitative genetics models assume fitness is determined by a continuous character. The rate of evolution of the mean trait is determined by the additive genetic variance (Lande, 1976), which depends on the underlying genetic architecture. In the earliest models genetic variance is simply a parameter (Pease et al., 1989; Gomulkiewicz and Holt, 1995). This was extended for gradual environmental changes by deriving the equilibrium genetic variance given a finite number of freely-recombining loci (Lynch and Lande, 1993; Bürger and Lynch, 1995), and later for fully-linked loci in sexuals and asexuals (Bürger, 1999). The effect of genetic covariance between multiple traits on rescue, with either a gradual or abrupt change, was examined by Gomulkiewicz and Houle (2009). For abrupt changes, models with n arbitrarily-linked loci and evolving genetic variance have been numerically iterated and stochastically simulated (Gomulkiewicz et al., 2010).

More recently, the stochastic one-locus two-allele haploid model has been extended analytically to incorporate more alleles (Anciaux et al., 2018; Wahl and Campos, 2023), diploidy (Glémin and Ronfort, 2013; Uecker, 2017; Unckless and Orr, 2020), multiple non-recombining loci (Martin et al., 2013; Osmond et al., 2020; Khatri and Burt, 2022; Alejandre et al., 2024; Freitas and Campos, 2024a,b), and two loci with recombination (Uecker and Hermisson, 2016; Xu, 2023a). This framework has also been developed further to adaptation on plasmids, allowing for horizontal gene transfer (Tazzyman and Bonhoeffer, 2014; Geoffroy and Uecker, 2023) and multiple plasmid copies (Santer and Uecker, 2020; Dewan and Uecker, 2025). A population genetics approach to the moving optimum problem (Kopp and Hermisson, 2007, 2009a,b), originally used to examine the genetic basis of adaptation at rates of change that do not cause population size declines, has since been expanded to examine the effect of pleiotropy (Matuszewski et al., 2014) on the genetic basis of adaptation and the critical rate of environmental change. The quantitative genetics approach has been extended to examine the effect of feedbacks between heritability and population size (Barfield and Holt, 2016) and allow for sex-specific genetic variance (Hangartner et al., 2022). There is also an accumulating number of simulation studies exploring how the number of loci and/or the linkage between them affects rescue (Schiffers et al., 2013; Bourne et al., 2014; Bay et al., 2017; Leidinger et al., 2021; Kardos and Luikart, 2021; Jensen et al., 2022) and its downstream effects on speciation (Yamaguchi et al., 2022).

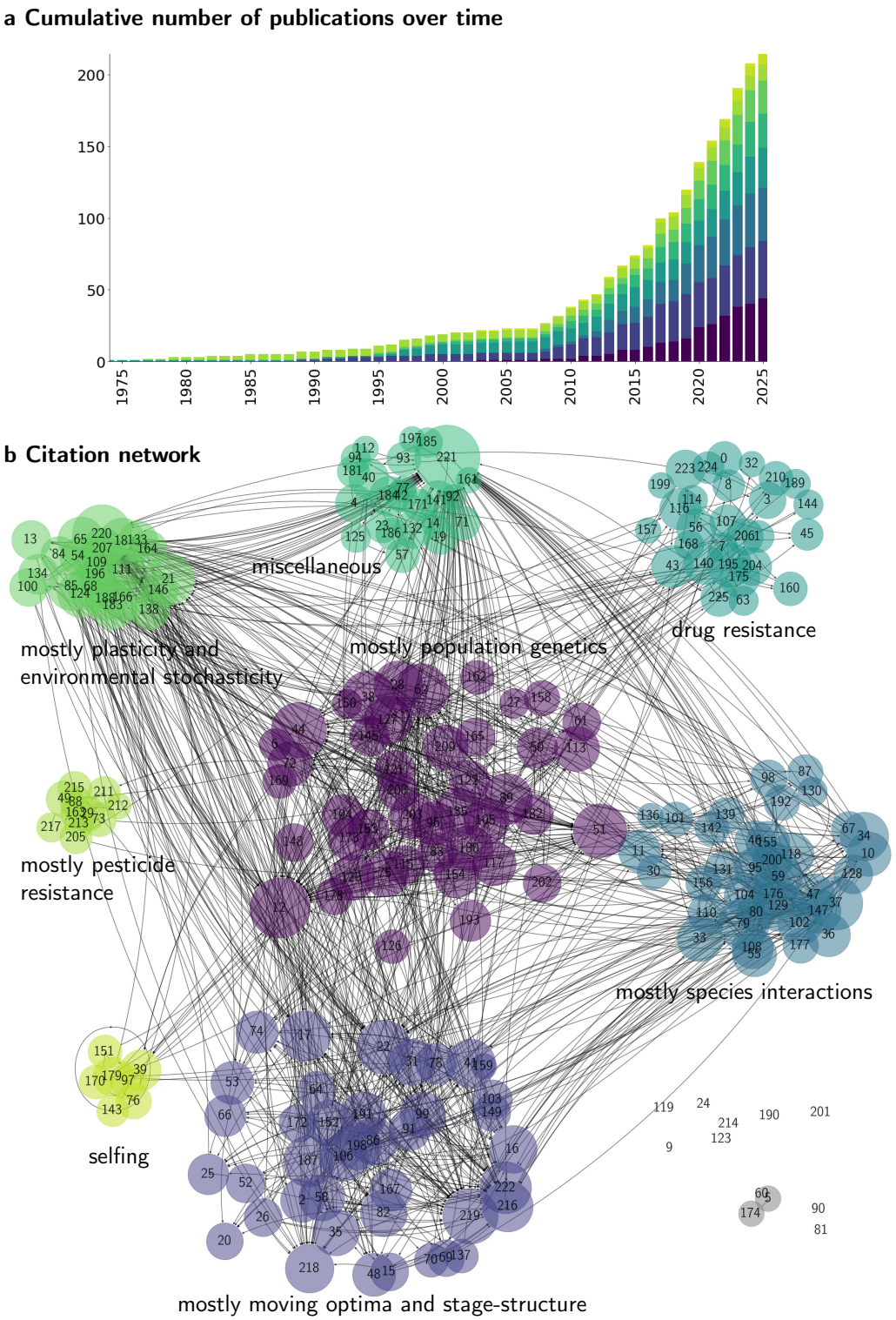

Figure 2: (a) Cumulative number and (b) citation network of papers reviewed in sections 4 and 5. Directed edges point from a paper to the ones it cites. The size of a node is proportional to its degree. The network was partitioned into communities by maximizing the so-called modularity coefficient with the Louvain method; the modularity coefficient quantifies the degree to which the edges fall within communities rather than at random (see Supplementary File S1, section S1 for details). We assigned labels to the communities to give a rough sense of the papers they contain (see Supplementary File S2 for the list of papers in each community). Papers that do not analyze a rescue model or that we could not find on Web of Science are excluded (see File S1, section S1 for details). A series of versions of Figure 2, where each highlights the nodes belonging to a specific subsection in section 4 or 5, can be found in File S2.

The emerging consensus is that there is no easy rule to determine which genetic architecture favours evolutionary rescue. More genetic variance is generally helpful (see section 2.3) but the best architecture will depend on many interacting factors, such as epistasis, dominance, and rates of sex and selfing. At first glance it may appear that there is a large gap in genetic architecture between one-locus and quantitative genetics models. However, the quantitative genetics approach may remain accurate to fairly small numbers of loci (e.g., $n = 50$ in Bürger and Lynch (1995)). More work on multi-locus models, with variable effect sizes, recombination, epistasis, etc., will help clarify the size of the gap and potentially bridge the population and quantitative genetics approaches. For example, Anciaux et al. (2019) show how increasing the mutation rate in Fisher's geometric model of adaptation provides a continuum between a one-locus (Anciaux et al., 2018) and a quantitative genetics model of evolutionary rescue after an abrupt change. A similar continuum arises in moving optimum models; Kopp et al. (2018) show how an adaptive walk of successive substitutions Kopp and Hermisson (2009b); Matuszewski et al. (2014) converges to the continuous process (Ornstein-Uhlenbeck) observed in quantitative genetics models (Lynch and Lande, 1993; Bürger and Lynch, 1995) as the mutation rate increases.

4.2 Standing genetic variation and *de novo* mutation

As outlined in section 2, early models concluded that rescue is generally more likely at higher levels of standing genetic variation and at higher mutation rates. The broad prediction that rescue is more likely for populations with higher genetic variation has remained robust across a number of more complex models (Walters and Berger, 2019; Tanaka and Wahl, 2022; Wahl and Tanaka, 2022; Nordstrom et al., 2023). Similarly, the expectation that rescue probability increases with mutation rate has also proven robust in recent modeling efforts (Orr and Unckless, 2014; Greenspoon and Mideo, 2017; Anciaux et al., 2019; Tanaka and Wahl, 2022; Garnier et al., 2023), although this effect is predicted to break down at (very) high mutation rates if the latter are accompanied by high rates of deleterious mutations (Anciaux et al., 2019; Hinsch et al., 2024) or, for stress-induced mutagenesis, correlated with rapid decline of the wild-type population (Kuosmanen et al., 2021). Models that combine standing variance and new mutation can compare their contributions to rescue to see when one or the other is more important (Orr and Unckless, 2014; Azevedo and Olofsson, 2021; Czuppon et al., 2021), although the distinction can become ambiguous if more than one mutation is needed for rescue (Uecker and Hermisson, 2016). One can also compare the relative contributions of standing genetic variance and new mutation to adaptation in the moving optimum model (Matuszewski et al., 2015). Higher levels of standing genetic variation and higher mutation rates also increase the probability that more than one lineage may contribute to evolutionary rescue, a situation described as a "soft sweep" (Wilson et al., 2017; Osmond and Coop, 2020; Muralidhar and Veller, 2022). Another origin of rescue mutants beyond standing genetic variation or *de novo* appearance is introgression from another population, which has been studied by Baskett and Gomulkiewicz (2011).

A limitation of current theory is that, to date, most models of evolutionary rescue determine the standing genetic variation by mutation-selection(-drift) balance at demographic equilibrium or in an exponentially growing population (Alexander et al., 2014). Yet, both the amount and the type of pre-existing rescue variants will depend on the demographic and evolutionary history of the population, which remains understudied theoretically (but see Greenspoon and Mideo, 2017; Tanaka and Wahl, 2022).

4.3 Non-genetic influences on phenotype

Individuals with the same genotype may exhibit different phenotypes, and hence fitness, due to non-genetic factors, which will therefore influence rescue (Feiner et al., 2021). Early work incorporating non-genetic factors in evolutionary rescue focused on phenotypic plasticity, specifically within-generational plasticity as a linear reaction norm (i.e., phenotype is a linear function of environment, the slope representing the degree of plasticity, Chevin and Lande, 2010; Chevin et al., 2010). The key insight from this work is that adaptive plasticity, and its evolution, reduces extinction risk unless the cost of plasticity is too high (reviewed in Kopp and Matuszewski, 2014; Chevin and Bridle, 2025).

Work on within-generational plasticity has been extended to understand its interactions with environmental stochasticity (Ashander et al., 2016), the type of deterministic environmental change (Scheiner et al., 2017), or both (Scheiner et al., 2020). There have also been efforts to incorporate complexities

such as differences in plasticity between different groups of individuals within a population (Marshall et al., 2016; Hangartner et al., 2022), plasticity in mating system (Xu, 2023b), developmental limits to plasticity (Khare et al., 2024), indirect genetic effects (Murray et al., 2024), and interactions with genetic adaptation (Lambert et al., 2025). A notable development is the incorporation of non-genetic mechanisms other than within-generation phenotypic plasticity, including phenotypic variability (Carja and Plotkin, 2019), cultural adaptation (Fogarty and Kandler, 2020), and trans-generational plasticity (Greenspoon and Spencer, 2021; Harmon and Pfennig, 2021).

Modeling specific non-genetic influences more mechanistically may lead to further insight. For example, the impact of anti-fungal intervention on robust genetic adaptation of bat populations exposed to white-nose syndrome might depend on whether the immune response of exposed individuals is temporary (innate) or long-term (adaptive) (cf. the discussion in Maslo et al., 2017). More mechanistic modeling would also help in understanding the role of epigenetic modifications in rescue, which can cause both phenotypic plasticity and variability, conceivably creating contrasting consequences (O'Dea et al., 2016), as recently shown (Deraje and Osmond, 2025). Elucidating the interactions between specific non-genetic mechanisms and the type of environmental change is an ongoing (Clement et al., 2023) but still largely unexplored research direction. Similarly, interactions between genetic and non-genetic responses to the environment have so far received little attention (but see Lambert et al., 2025; Deraje and Osmond, 2025).

4.4 Reproductive strategies

Reproductive strategies impact both the demographic aspects of evolutionary rescue and the genotypic and phenotypic variation available for natural selection to act upon. Early models considered clonal haploids or randomly mating diploids (Gomulkiewicz and Holt, 1995; Orr and Unckless, 2008). To our knowledge, Glémin and Ronfort (2013) was the first theoretical study explicitly focusing on the role of the reproductive strategy in rescue, comparing outcrossing vs. selfing populations.

Research has continued to look at the effects of selfing on evolutionary rescue, extending the range of the dominance coefficient (Uecker, 2017) and the number of loci underlying adaptation (Xu, 2023a). Evolutionary rescue can also happen directly via the evolution of selfing as a mechanism of reproductive assurance (Cheptou, 2019; Xu, 2022, 2023b; Degottex-Féry and Cheptou, 2023) or a way to avoid reproductive interference (Katsuhara et al., 2021). On the other hand, selfing-rate evolution can lead to extinction (evolutionary suicide) when there is excessive inbreeding depression (Cheptou, 2019; Degottex-Féry and Cheptou, 2023), but evolution can also rescue these populations by purging deleterious mutations (Abu Awad and Billiard, 2017). Another direction of research has considered the rate (or presence/absence) of sex in both one-locus (Uecker, 2017) and quantitative trait (Orive et al., 2017, 2019; Peniston et al., 2021; Garnier et al., 2023) models. There have also been several studies of evolutionary rescue that considered details of biparental sexual reproduction, such as the impact of sexual selection and sexual conflict (Gómez-Llano et al., 2024; Knell and Parrett, 2024), sex determination systems (Blechschmidt et al., 2020), and mate-finding Allee effects for different sexual systems (Deraje and Uecker, 2025).

Together, these studies show how reproductive mode affects rescue via (i) demography, e.g., selfing provides reproductive assurance (Cheptou, 2019) and sexual conflict reduces female fitness (Gómez-Llano et al., 2024), (ii) inherent genetic effects, e.g., sex generates or breaks up advantageous genotypes (Uecker, 2017) and clonality allows the inheritance of non-additive genetic effects (Orive et al., 2017), and (iii) additional effects on evolution, e.g., outcrossing allows for sexual selection, favouring well-adapted individuals (Knell and Parrett, 2024), and populations that reproduce sexually are susceptible to evolutionary tipping points (Osmond and Klausmeier, 2017; Garnier et al., 2023). Moving forward, because reproductive strategies have strong impacts on between-locus interactions, there is considerable interest here, as in the investigation of genetic architecture directly (see above), to investigate the effect of reproductive strategy in n-locus models, which incorporate epistasis and recombination (e.g., the two-locus model of Xu, 2023a). Furthermore, nature offers a great variety in reproductive systems – dioecy, androdioecy, gynodioecy, hermaphroditism – and in mating systems – e.g., monogamy, polygamy, polyandry – the consequences of which have barely been explored in models of evolutionary rescue (Bocedi and Reid, 2017).

4.5 Birth and death

Births and deaths impact not only population growth, but also mutational input, demographic stochasticity, and generation time. This means that the details of birth and death processes matter for rescue.

Models devised for cancer that determine the number of resistance mutations present at the start of treatment (cf. section 3), show that, by increasing the number of cell divisions to reach a given population size, cell death increases the risk of resistance mutations (Iwasa et al., 2006), and this effect is particularly pronounced for the accumulation of mutations to multiple drugs (Komarova and Wodarz, 2005). More recent work has explored how the probability of drug resistance evolution depends on whether a drug reduces birth rates or increases death rates (Marrec and Bitbol, 2020b; Czuppon et al., 2023; Raatz and Traulsen, 2023; Nyhoegen et al., 2024) and whether competition affects birth or death (Czuppon et al., 2023). A key component of these stochastic birth-death models is the probability of mutant establishment. As known from the general evolutionary literature, given the same growth rate (birth minus death), beneficial mutations that cause lower variance in the growth of the mutant population, e.g., caused by lower birth and death rates, are more likely to fix (Gillespie, 1974; Parsons et al., 2018; Bhat and Guttal, 2025; Kuosmanen et al., 2025). This naturally also holds for the establishment probability of rescue mutants (e.g. Czuppon et al., 2023; Nyhoegen et al., 2024).

Increased death has been shown to aid adaptation and persistence in quantitative genetics models with a moving optimum, starting from the point of view of perennial (low adult death) vs. annual (high adult death) life-histories (Zeineddine and Jansen, 2009) (see also the simulations of Kuparinen et al., 2010). Models have since shown that the effect of increased death on persistence depends on how birth and death are impacted by population density and maladaptation (Osmond et al., 2017). More generally, the effects of density and maladaptation on birth and death can have big impacts on population persistence (Klausmeier et al., 2020), largely by modulating generation time (Draghi et al., 2024), and thus the rate of selective events, but also by modulating the strength of demographic stochasticity (Vinton and Vasseur, 2020).

In population genetics models, the probability of mutant establishment is usually calculated assuming mutant individuals do not interact with one another. New mathematical theory is needed to allow for interactions, such as cooperation (e.g., collective antibiotic resistance). The quantitative genetics models show that higher birth and deaths rates can aid persistence by shortening generation times but also reduce persistence by amplifying demographic stochasticity. An analysis of when one effect outweighs the other is missing.

4.6 Density-dependent fitness

Early models of evolutionary rescue largely ignore impacts of population density on fitness. This is in part for analytical tractability but also because extinction vs. rescue will often largely come down to whether a population can grow when rare, where negative density dependence is negligible. Recent studies have examined density dependence, both negative and positive.

Negative density dependence is expected to hinder rescue after an abrupt change by reducing population size (Chevin and Lande, 2010), reducing the number of mutants that arise (Orr and Unckless, 2008), and suppressing mutant growth rates (Orr and Unckless, 2008; Uecker and Hermisson, 2011; Uecker et al., 2014; Wilson et al., 2017; Czuppon et al., 2023). As a result of decreased population sizes, negative density dependence may also reduce rescue probabilities by accelerating the loss of adaptive genetic variation (Nordstrom et al., 2023) and increase the costs for effective conservation efforts in gradually changing environments (Ashander et al., 2019). On the other hand, for the same equilibrium population size, stronger density dependence generates greater demographic compensation as populations become more maladapted, favouring persistence (Reed et al., 2015). Density dependence may turn from negative to positive as a population becomes small (a so-called demographic Allee effect), which is expected to have a negative effect on rescue (as discussed in Gomulkiewicz and Holt, 1995). For strong Allee effects, the population growth rate may be negative below certain size (the Allee threshold), even if it is positive above. In that case evolutionary rescue can occur via the evolution of reduced Allee effects (Kanarek and Webb, 2010; Deraje and Uecker, 2025).

Given the multitude of consequences of negative density dependence, the possibility to evolve to reduce it deserves more attention as well and may have unexpected consequences. For example, after the supply of a resource is suddenly reduced, intensifying competition, plummeting populations can recover by evolving to consume a more abundant resource (Oliveira and Campos, 2024). When a substitutable resource is not available, populations may still evolve to reduce the strength of density-dependence (e.g., via more efficient resource use), but trade-offs with growth at low abundance may ultimately result in higher extinction rates compared to a no-evolution scenario (Engen and Sæther, 2017).

4.7 Frequency-dependent fitness

Models of evolutionary rescue have largely focused on frequency-independent fitness imposed by the environment, where adaptive evolution always increases population mean fitness (reviewed in Svensson and Connallon, 2019). However, fitness can also be frequency-dependent, broadly defined as being dependent on the composition of the population (Lande, 1976), and a few studies have begun to explore how this affects evolutionary rescue.

From classical models we know that changes in the fitness of genotypes due to changes in the composition of the population can speed up or slow down increases in mean fitness, or even cause mean fitness to decline (see Box 1 in Svensson and Connallon, 2019). The immediate consequences for rescue have been made in general (Ferriere and Legendre, 2013; Svensson and Connallon, 2019) and emphasized in the context of populations threatened by pollen limitation (Cheptou, 2019; Degottex-Féry and Cheptou, 2023), where selfing rate evolution may rescue the population or lead to evolutionary suicide (see section 4.4), and rescue via a mutation that allows carriers to repair a degrading habitat through niche construction (Longcamp and Draghi, 2023), where a tragedy of the commons can occur. Frequency dependence has also been shown to affect rescue indirectly, due to interactions between adaptation and sexual conflict (Gómez-Llano et al., 2024) or as a result of cooperation or competition determined by a second, uncorrelated trait in a gradually changing environment (Henriques and Osmond, 2020).

Frequency dependence can thus help or hinder evolutionary rescue. Which is more likely remains an open (and perhaps mostly empirical) question.

4.8 Stage structure

Most populations harbor individuals that differ in their sensitivity to environmental stress, their ecology, and their potential contribution to the evolutionary and demographic future of the population. The consequences of this heterogeneity for rescue can be examined with stage-structured models. For example, simulations of stage-structured tree populations demonstrated that increased adult mortality could actually hasten adaptation in a gradually changing environment (Kuparinen et al., 2010).

One productive line of research in this area was initiated by Barfield et al. (2011), who derived general equations describing the joint dynamics of genotype, phenotype, and population size in stage-structured populations and applied their approach to model rescue following an abrupt environmental change (for an earlier approximation applied specifically to *Trillium*, see Knight et al., 2008). These methods have since been used to investigate the consequences of inherently less efficient selection at older ages on genetic load in changing environments (Cotto and Ronce, 2014) and the consequences for rescue of interactions between stage structure and clonal reproduction (Orive et al., 2017), conflicting selection across stages (Cotto et al., 2019), an inherent trade-off between evolvability and demographic robustness (Schmid et al., 2022), and seed banks (Godineau et al., 2024). Similar techniques have been used to examine the effect of plasticity on rescue of stage-structured populations (Marshall et al., 2016), and individual-based simulations have investigated the interaction of stage structure and evolution on species distribution models (Cotto et al., 2017). A deterministic population genetics model has also looked at the effect of seed banks on rescue in a herbicide context (Lauenroth and Gokhale, 2023).

There seems to be a paucity of stage-structured rescue models with few loci of large effect, especially stochastic ones. It might be promising to apply stage-structured branching process theory to better understand how life history affects the probability of rescue. Integral projection models (Rees and Ellner, 2016) could also be used to allow for more continuous heterogeneity, like body size.

4.9 Spatial structure

When the fitness of a genotype varies in both time and space there are two mechanisms by which a population can persist: tracking its current niche through space via dispersal and evolving its niche in time via evolution.

Spatial structure was a central component of quantitative genetics models very early (Pease et al., 1989), which consider a population in continuous space. Analogous to tracking a moving fitness optimum in time via evolution (Box 3), a population can track a fitness optimum shifting in space via a combination of dispersal and evolution provided the rate of shift is below a critical threshold (Pease et al., 1989). Critical rates have since been calculated for populations tracking a moving cline of fitness optima, either with unlimited ranges of uniform density or as traveling waves of limited range, while considering the complexities of density-dependence and evolving genetic variance (Polechová et al., 2009), multiple traits (Duputié et al., 2012), multiple modes of dispersal (Aguilée et al., 2016), and asexual reproduction (Alfaro et al., 2017). However, the existence of a critical rate of environmental change does not necessarily extend to discrete space, where reducing the rate of environmental change can cause extinction (Dekens, 2024). For a population below its Allee threshold, dispersal can lower the chance of rescue by reducing local population densities (Kanarek and Webb, 2010) and demographic rescue through immigration is a more likely path to population establishment than evolutionary rescue (Kanarek et al., 2015). The evolution of higher within-patch foraging and mating (akin to lower dispersal) can rescue populations with Allee effects after habitat loss (Bagawade et al., 2024).

In population genetics models of rescue, spatial structure was incorporated much later, extending the fundamental population genetics one-locus model (section 2.2) by a deme structure, where demes progressively deteriorate one by one (Uecker et al., 2014; Tomasini and Peischl, 2020; Czuppon et al., 2021; Tomasini and Peischl, 2022). Collectively, these studies provide a detailed treatment of the problem, accounting for a large number of factors such as the speed and extent of environmental deterioration (Uecker et al., 2014), asymmetric migration and habitat choice (Tomasini and Peischl, 2020; Czuppon et al., 2021), population fitness in the favorable habitat (Tomasini and Peischl, 2020), and explicit spatial structure (Tomasini and Peischl, 2022). Further, population subdivision (i.e., less migration) has been shown to permit local fixation of deleterious rescue mutants pre-change, increasing the probability of evolutionary rescue from standing genetic variation (in a model that assumes a simultaneous deterioration of all demes; Fruet et al., 2025). Allowing local environments to diverge post-change, (Mohammadi and Campos, 2025) used Fisher's geometric model with an n-dimensional trait space to study *de novo* rescue of a two-patch meta-population. A one-locus model has also been used to consider rescue from an invading competitor in continuous space (Van Dyken, 2020).

Between one locus and quantitative genetics models there are simulation studies where fitness is determined by traits coded by an intermediate number of loci (Schiffers et al., 2013; Bourne et al., 2014). In these models, a spatially heterogeneous environment is homogeneously affected by climate change, requiring local adaptation (first trait) and adaptation to a warming climate (second trait). It is also possible for dispersal itself to evolve and rescue populations from a shifting environmental gradient or a shifting climate window in a fragmented landscape (Henry et al., 2013; Boeye et al., 2013) or delay extinction with increasing habitat fragmentation (Finand et al., 2024). Rescue through dispersal evolution was also studied in specific biological systems, specifically a butterfly meta-population (Heino and Hanski, 2001), an arthropod threatened by a male-killing endosymbiont, where sex-specific dispersal could evolve (Bonte et al., 2009), or wind-dispersed plants, where dispersal evolution can lead to rescue but also to evolutionary suicide (Travis et al., 2010).

Overall, dispersal has several – often conflicting – effects on evolutionary rescue, which on the positive side include demographic effects and tracking and on the negative side maladaptive gene flow and dispersal into uninhabitable areas. Because of spatial heterogeneity, these models have a strong similarity with source-sink models, where the source and the sink correspond to the favorable and unfavorable spatial locations (see Box 6). Explicit spatial structure is still rare in models with discrete habitat patches and could be extended to account for more complex network structures, which have been shown to affect fixation processes of beneficial alleles in populations of constant size (Yagoobi and Traulsen, 2021). Another interesting direction is to consider migratory species, which can experience multiple

types of environmental change across their life-cycle; maladaptation may be mitigated by phenological evolution.

4.10 Type and temporal dynamics of environmental change

Some form of environmental change is part of virtually any model of evolutionary rescue. The two "classic" scenarios are a single abrupt change or a gradual linear change (see sections 2.1 and 2.2) but periodically changing environments were also already studied in some of the first quantitative genetics models (Lynch et al., 1991; Lande and Shannon, 1996). A key characteristic of environmental change is its severity: the size of an abrupt change and the speed of a gradual change. Furthermore, environmental change can involve several stressors, affecting the number of mutations required for rescue (e.g. Iwasa et al., 2003) or imposing selection on multiple traits (e.g. Gomulkiewicz and Houle, 2009; Chevin, 2013).

Both abrupt and gradual environmental changes have remained central in models of rescue. In the quantitative genetics framework, recent work has especially found that the type of change – abrupt or gradual – affects whether other factors, such as clonality (Orive et al., 2017; Peniston et al., 2021), adult survival in stage-structured populations (Orive et al., 2017), and the initial genetic state of the population (Orive et al., 2019), benefit or hinder rescue. In addition, both population and quantitative genetics models have been extended to explore the consequences of evolution on persistence for other types of change, such as accelerating or decelerating rates of change in moving optimum models (Ashander et al., 2019; Greenspoon and Spencer, 2021), gradual deterioration in population genetics models (Wu et al., 2014; Bertram et al., 2017; Marrec and Bitbol, 2020a), two consecutive changes in the environment (Patil et al., 2025), periodic or random switches between discrete states (Trubenova et al., 2019; Marrec and Bitbol, 2020b; Marrec and Bank, 2023), continuous fluctuations (Wu et al., 2014), regular fluctuations in addition to gradual deterioration (Shibasaki and Yamamichi, 2024), repeated bottlenecks and abrupt pulse disturbances (Martin et al., 2013; Patel et al., 2025), and a one-time pulse disturbance of variable length (Lyberger et al., 2021).

Environmental stochasticity has long been a key component in moving optimum models (Lynch and Lande, 1993; Bürger and Lynch, 1995), which show that uncorrelated fluctuations (white noise) in the optimum phenotype hinder persistence. Populations are better able to adaptively track a fluctuating optimum when the fluctuations are more positively autocorrelated, regardless of the deterministic change in the optimum (Lande and Shannon, 1996; Chevin, 2013). However, stronger positive autocorrelation also creates more variance in population size across replicates, which can decrease the probability of rescue after an abrupt change (Chevin et al., 2017). Overall, fluctuations, and especially positively autocorrelated ones, can increase or decrease the probability of rescue (Peniston et al., 2020). The presence of both environmental and demographic stochasticity causes a larger than multiplicative drop in the probability of rescue (Xu et al., 2023).

Overall, there has been a broadening in the scope of environmental changes considered in evolutionary rescue theory, from a small set of possible changes (i.e., abrupt vs. linear) to something closer to a continuum and this broadening is expected to continue in particular to study rescue in specific contexts. This could for example include environmental change at multiple temporal scales in long-lived species that are affected both by mild but long-lasting stressors and brief but extreme events. One future challenge will be to combine more complex environmental change with spatial structure, such as asynchronous fluctuations across space.

4.11 Species interactions

No species exists in isolation. Correspondingly, a substantial amount of rescue theory has explored the effect of different types of species interactions – competition, predation/parasitism, mutualism – as well as combinations of them.

Competition, being an antagonistic ecological interaction for both species, often hurts persistence, but it may sometimes impose selection that fosters survival. In a changing environment, models have explored the role of spatial structure (de Mazancourt et al., 2008; Norberg et al., 2012; Thompson and Fronhofer, 2019), the additional selection introduced by a competitor (Osmond and de Mazancourt, 2013), trait-matching coevolution (Jones, 2008), the type of coevolution (Northfield and Ives, 2013), asymmetric

competition (Van Den Elzen et al., 2017), and differences in evolutionary rate (Van Eldijk et al., 2020; Leidinger et al., 2021; Bukkuri et al., 2023a). Other models consider rescue from competitive exclusion by an invader, exploring the role of genetic variance (Jones and Gomulkiewicz, 2012), exploitation vs. interference competition (Van Dyken, 2020), reproductive interference (Morita and Yamamichi, 2023), and niche-construction (Longcamp and Draghi, 2025).

Both predation and parasitism have negative ecological effects on the predated and parasitized species but, like competition, the added evolutionary effects can sometimes compensate. Quantitative genetics models have been used to examine the effect of predator-prey interactions and (co)evolution on rescue in gradually changing environments (Jones, 2008; Mellard et al., 2015; Osmond et al., 2017; Vanselow et al., 2022). Quantitative genetics models have also been used to study the effect of predator-prey coevolution on rescue following an abrupt environmental change (Northfield and Ives, 2013; Yamamichi and Miner, 2015; Cortez and Yamamichi, 2019; Raatz et al., 2019), including changes that impose additional selection (Shang et al., 2024), and a population genetics model has examined the special case where only one species evolves (Hermann and Becks, 2022). One can similarly ask how (co)evolution affects persistence when a prey or predator invades a new habitat (Jones and Gomulkiewicz, 2012; DeLong and Belmaker, 2019). Others have examined rescue in a spatial context, considering rescue of a predator after habitat loss (Bagawade et al., 2024) and rescue of host from a male-killing endosymbiont (Bonte et al., 2009). There is also now some theory to understand rescue in communities with more than two species, including 3-species food chains (Kovach-Orr and Fussmann, 2013; Patel and Schreiber, 2015; Wang et al., 2017; Flynn and Skibinski, 2020), two predators competing for one (Fussmann and Gonzalez, 2013) or two (van Velzen, 2023) prey, and emergent food webs (Yacine et al., 2021). Meanwhile for parasitism, models have been used to explore the role of spatial structure (Jiao et al., 2020) and demographic feedbacks (Golas et al., 2021) on the ability of a host to be rescued from a novel pathogen, as well as the negative effect of coevolving parasites on the ability of a host to adaptively colonize a new habitat (Mestre et al., 2024). On the flip side, models have also been used to explore how a pathogen can survive when the host population begins using antibiotics (Greenspoon and Mideo, 2017).

The beneficial ecological effects of mutualism generally help persistence, but complications arise. Models have so far examined the effects of coevolution (Nuismer et al., 2018) and competition (Goldberg and Friedman, 2021) between mutualists on their ability to survive environmental change, as well as the fact that both species may need to adapt to survive (Goldberg and Friedman, 2021) and one partner may disinvest as the other becomes rarer (Northfield and Ives, 2013; Weyerer et al., 2023). Finally, beneficial symbionts might enable (ecological) rescue of the host population, unless they are outcompeted by cheaters (Pillai et al., 2017), as well as facilitate adaptive colonization of a new habitat (Mestre et al., 2024).

One challenge for modeling evolutionary rescue in ecological communities is the number of parameters that can be affected by the environment, evolve, and trade-off with one another. As the complexity of the community increases so does the number of parameters and the farther we get from having a small set of 'standard' models. This makes it harder to gain general intuition. The models above largely focus on the rescue of individual species, but there is also a question of how evolutionary rescue affects broader aspects of a community, such as rank abundance curves (Van Eldijk et al., 2020) and the number of interactions between species (Nuismer et al., 2018). There also seems to be a bias towards models of phenotypic evolution, except in the case of parasites, and especially in larger communities. A further major direction for future research includes models for microbiome-mediated rescue of host populations, involving interactions between multiple symbiont strains or species and accounting for different degrees of heritability and horizontal transfer.

5 Progress in application-driven models of evolutionary rescue

As discussed in the introduction and already addressed in section 3.2, the concept of evolutionary rescue is of great applied relevance. Here we discuss key progress in rescue theory that has been developed in the specific contexts of conservation and drug and pesticide resistance.

5.1 Conservation

Many models of evolutionary rescue are purposefully broad and conceptual. While these can inform conservation strategies, developing more specific rescue models for conservation can help identify which species are most at risk, when sufficiently rapid adaptation is unlikely and interventions are therefore necessary, and which interventions efficiently avoid extinction.

Two of the biggest threats to biodiversity are infectious diseases and warming temperatures. For bat populations with white nose syndrome (Maslo and Fefferman, 2015; Maslo et al., 2017; Jiao et al., 2020) and amphibian populations exposed to *Batrachochytrium dendrobatidis* (Converse et al., 2017; Christie and Searle, 2018; DiRenzo et al., 2018), models have been developed to explore whether genetic variation in tolerance or resistance to infection could rescue the host population and to examine how different interventions (such as treatment of sick animals in Maslo et al. 2017) facilitate or impede evolutionary rescue. Many rescue models developed for conservation in the face of warming temperatures concern the capacity of declining coral reefs to adapt and persist (e.g., McManus et al., 2021). These models are used to explore how the efficiency and optimal design of various conservation actions, such as protected areas (Walsworth et al., 2019), predator control (Condie et al., 2021), or out-planting warm-adapted genotypes (assisted gene flow) (Bay et al., 2017; DeFilippo et al., 2022), depend on the amount of genetic variation for thermal preference that is found within local reefs (see Box 2). Models have also been tailored for other species in warming climates, incorporating complexities such as physiological tolerance (Bush et al., 2016), age-structure (Cotto et al., 2017), and – in a pest management context, but more generally applicable – predator-prey interactions (Ge et al., 2024). Models agnostic to species or stressors are sometimes used to assess the optimal design of conservation interventions, e.g., determining the best time to increase population growth (Ashander et al., 2016) or adaptive gene flow (Kelly and Phillips, 2019; Smart and Phillips, 2023).

These diverse models of evolutionary rescue have broadened our perspective of conservation biology by suggesting many instances where consideration of evolution may modify our recommendations and our practices. For instance, while protecting the coldest coral reefs that can serve as refugia under climate warming is the best strategy when genetic variation for thermal tolerance is ignored, protecting both warm and cold reefs becomes optimal when the spread of adaptive variants is considered (Walsworth et al., 2019; DeFilippo et al., 2022, Box 2). Conversely, these case studies motivated by conservation biology have also enriched our understanding of evolutionary rescue, for instance by showcasing the role of epidemiological feedbacks (Christie and Searle, 2018; Searle and Christie, 2021). Yet, these studies also reveal very large uncertainties associated with predicting evolutionary rescue in any real case study (see section 6.2). Despite recurrent calls to better integrate evolutionary considerations into conservation biology in general (Olivieri et al., 2016) and in population viability models in particular (Pierson et al., 2015), there remains a gap between proof-of-concept theoretical models, which showcase the potential importance of evolution in conservation, and concrete practical guidelines that can support decision in the management of specific endangered species (Funk et al., 2019).

5.2 Drug and pesticide resistance

Providing a full review of the drug and pesticide resistance literature is beyond the scope of this article (for reviews on specific sub-topics see e.g., Tabashnik, 1990; Hastings, 2001; Peck, 2001; van den Bosch and Gilligan, 2008; Rex Consortium, 2010; Zur Wiesch et al., 2011; Foo and Michor, 2014; Renton et al., 2014; Blanquart, 2019; Uecker and Bonhoeffer, 2021; Madgwick and Kanitz, 2024). We here provide a short summary of selected aspects with a particular focus on rescue-relevant aspects, sampling a limited number of older and newer references as examples.

Many if not all of the key topics by which we structured section 4 appear in models in the specific context of resistance evolution, many of them from very early on. The type and temporal dynamics of environmental change (see section 4.10) are especially key topics since they are to a large extent defined by the treatment applied and can thus be controlled. Many studies on resistance evolution have been concerned with identifying strategies to prevent (or delay) the evolution of resistance. One important strategy is the application of multiple drugs or pesticides either together or sequentially or across patients/space (Rex Consortium and others, 2013), for example for the treatment of bacterial infections (e.g., Bonhoeffer et al., 1997a; Lipsitch and Levin, 1997; Austin and Anderson, 1999; Colijn

et al., 2011; Greenspoon and Mideo, 2017; Nyhoegen and Uecker, 2023; Nyhoegen et al., 2024; Delaney et al., 2025) and of cancer (e.g., Goldie et al., 1982; Coldman and Goldie, 1983; Komarova and Wodarz, 2005; Bozic et al., 2013; Gatenby et al., 2020; Patil et al., 2025), or for the administration of fungicides (e.g., Josepovits and Dobrovolszky, 1985; Shaw, 1989; Hobbelen et al., 2011; Mikaberidze et al., 2014; Taylor and Cunniffe, 2023b), insecticides (e.g., Sudo et al., 2018; Helps et al., 2020) and herbicides (e.g. Diggle et al., 2003; Lauenroth and Gokhale, 2023). Similarly, gene drive systems to control disease vectors or agricultural pests can be designed to target multiple sites in the target gene (Khatri and Burt, 2022). Nevertheless, despite extensive work on multi-compound treatments many open questions remain due to the innumerous facets of the problem such as how to measure success of a strategy or the large number of choices regarding for example the modes of action of the compounds or how exactly they are combined. Besides the number of compounds, another fundamental treatment variable is the dose of the drug/pesticide applied as well as the timing of administration (e.g., Nissen-Meyer, 1966; Lipsitch and Levin, 1997; Austin and Anderson, 1999; Foo et al., 2012; Wu et al., 2014; Colijn and Cohen, 2015; Mikaberidze et al., 2017; Scire et al., 2019; Kuosmanen et al., 2021; Patel et al., 2025). Here, a classic conclusion reached by many studies is that resistance evolution is most likely at intermediate doses at which the resistant strain is released from competition with the sensitive strain but not strongly affected by the drug itself (Kouyos et al., 2014). While this may suggest that applying low doses could delay resistance evolution (Day and Read, 2016), recent modeling found that the peak is usually around the minimally effective dose, such that lower doses would compromise the effectiveness of treatment (Czuppon et al., 2023). An intermediate-dose-strategy is noteworthily different from adaptive therapy, which dynamically adjusts treatment to maintain a sensitive cell population small enough to be tolerable for the patient and large enough to competitively suppress resistant cells (see section 6.2.1). The relative importance of *de novo* mutations vs. standing genetic variation is another important topic reviewed in section 4.2 that also keeps being studied in the context of resistance (Bonhoeffer et al., 1997b; Ribeiro and Bonhoeffer, 2000; Komarova and Wodarz, 2005; Greenspoon and Mideo, 2017). The same holds for the role of spatial structure (Comins, 1977; Kepler and Perelson, 1998; Moreno-Gamez et al., 2015; Trubenová et al., 2022; Raatz et al., 2024), cf. section 4.9. Yet another key topic is the genetic architecture of resistance (see also section 4.1), which appears for example in the context of multiple mutations accumulating to escape treatment (Goldie et al., 1982; Iwasa et al., 2003; Igler et al., 2021; Trubenová et al., 2022), recombination in HIV (Kouyos et al., 2009), plasmids in bacteria (Svara and Rankin, 2011; Tazzyman and Bonhoeffer, 2014; Santer and Uecker, 2020; Kippnich et al., 2025), or aneuploidy in cancer (Stana et al., 2025). Non-genetic mechanisms (section 4.3) such as epigenetic phenotypic switching have been considered as well (Gunnarsson et al., 2020, 2023).

A comparison between current and older models shows that early articles already cover many of the themes and factors still studied today. Besides topics already discussed in the previous paragraph, this also includes features such as the dose dependence of the drug effect (pharmacodynamics) and the dynamics of the drug concentration in the body (pharmacokinetics) (Lipsitch and Levin, 1997; Austin and Anderson, 1999), the human immune response (Austin and Anderson, 1999), the dominance of the resistance allele (Comins, 1977; Taylor and Georghiou, 1979) and many more (see also Taylor, 1983; Rex Consortium, 2010). One of the rather recent developments, while not entirely new either (see section 3.2), seems to be a stronger focus on the stochastic establishment of resistant genotypes as a factor in resistance evolution. In this context, the differential effects of treatment on replication and death rates (i.e., the use of bactericidal and bacteriostatic drugs) with and without density-dependent growth has recently received increasing attention (Marrec and Bitbol, 2020b; Czuppon et al., 2023; Raatz and Traulsen, 2023; Nyhoegen et al., 2024); see also section 4.5. Similarly, while the stochastic population genetics approach outlined in Box 4 had long appeared in resistance modeling every now and then (section 3.2), its use has seen a boost over the past decade, presumably driven by spillover from the non-resistance rescue literature. Indeed, the majority of resistance models that appeared in the initial literature search on Web of Science (with the search term "evolutionary rescue") follow this framework. Its growing application especially means that the rarity of extinction as a criterion for treatment success, which was observed by Rex Consortium (2010), might be diminishing. A factor that is still mostly missing from those models is the pharmacokinetics of the drugs (but see Wu et al., 2014).

A restriction of many classic as well as recent models is the distinction of two strains only – sensitive and resistant pathogens/pests – or one mutation per drug/pesticide for treatment with multiple compounds (see above for counter-examples). This is a great simplification since usually many more mutations

provide resistance to low than to high toxin concentrations, and moreover, several mutations may accumulate in the same genome over time. One highly relevant future direction is the development of models that take this diversity of mutations with different dose response curves into account, similar to Fisher's geometric model where the rate of rescue mutations decreases with the distance from the optimum (Anciaux et al., 2018; Osmond et al., 2020). However, models for resistance evolution should ideally account for the typically sigmoidal relationship between the dose and its effect (i.e., the pharmacodynamics; see e.g., Regoes et al. (2004); Foerster et al. (2016) for such dose response curves and their mathematical description); for a rare example see Igler et al. (2021). This is particularly important for studies that focus on the drug or pesticide dose as a treatment variable, where the variability of resistance conferred by different mutations may crucially affect conclusions such as on the dose that maximizes resistance evolution. Another gap is a lack of accounting for pleiotropic effects of resistance mutations that may lead to shifts in ecological interactions. For example, a resistant bacterial strain might have reduced niche overlap with the sensitive strain or other members of the microbial community (Letten et al., 2021), or herbicide resistance can increase or decrease herbivory (Gassmann and Futuyma, 2005; Zhang and Baucom, 2025). The development of models that better integrate the biotic ecological context will be an important future direction.

6 Connecting theory and data

It is of course important to bring theoretical and empirical insights together. In this section, we discuss connections between models and data. In section 6.1, we focus on results from evolution experiments set out to explore the determinants of rescue and discuss in some detail how they relate to the theoretical work reviewed in this article. In section 6.2, we then turn to rescue in natural populations, including pathogens and cancer cell populations, and briefly highlight how models can help to predict or infer rescue.

6.1 The connection between theory and experiments

Whether referred to as evolutionary rescue or not, a large number of rescue experiments have been performed, providing an opportunity to assess how well various aspects of theory have been verified and where new theory is needed. Rescue experiments have mostly been performed with microbes or "near-microscopic" animals (e.g., rotifers) or plants (unicellular algae). Complementing the insights from unicellular models, work on the red flour beetle (*Tribolium castaneum*) and occasionally on the nematode *Caenorhabditis elegans* provides more rare insights in rescue of multicellular animals. Annual plants could in the future also offer a powerful avenue for the exploration and testing of rescue theory in multicellular organisms.

We cannot provide a systematic review of the experimental literature here, which warrants a separate article (older work e.g., reviewed in Bell, 2017). However, since an integration of theoretical and experimental work is essential in making progress, we provide some space to discussing experimental findings, based on a substantial but limited number of studies, and their relationship to theory. We start in section 6.1.1 by providing a summary of experimental work on the key theoretical predictions from section 2.3, followed by tests of more specific factors in section 6.1.2. In section 6.1.3, we briefly present rare examples of studies that combine theory and experiments and finally conclude the section with highlighting several gaps and suggestions for future work that would foster synergies between theoretical and experimental work (section 6.1.4).

6.1.1 Testing key theoretical predictions

The key predictions that are consistent across the fundamental population genetics and quantitative genetics models (outlined in section 2.3) are broadly supported by experiments.

The predicted increase of the probability of rescue with increasing population size has been qualitatively verified in experiments with yeast (Bell and Gonzalez, 2009), bacteria (Ramsayer et al., 2013), and beetles (Hufbauer et al., 2015). A larger initial population size also increases the mean and maximum growth rates of mutants that establish in stressful conditions (Samani and Bell, 2010). Bell and Gonzalez (2009) were likely the first to set out to experimentally replicate the fundamental rescue

model of Gomulkiewicz and Holt (1995) by exposing yeast to high salt concentrations (though similar experiments exist, e.g., *E. coli* exposed to high temperatures; see figure 8 in Bennett and Lenski, 1993 and figure 1 in Mongold et al., 1999). After observing the U-shaped curve of population size over time, which Gomulkiewicz and Holt (1995) predicted as the sum of an exponentially declining wild type and exponentially increasing mutant, they used the model to infer the frequency p_0 of rescue mutants at the time of environmental change. This estimate was consistent with an independent estimate from plating and successfully predicted the initial population size below which rescue becomes unlikely, determined by $p_0 N_0 \approx 1$ (assuming $p_{\text{est}} = 1$). Martin et al. (2013) later used the dataset to show that the dependence of the rescue probability on N_0 is consistent with the functional dependence predicted by the population genetics approach outlined in Box 4.

The second key prediction of rescue theory is that the probability of rescue decreases with the size and speed of environmental change. This prediction has a lot of support. In fact, in one of the earliest known experimental evolution studies (Dallinger, 1887), temperature had to be increased slowly enough to prevent populations of protists from going extinct. A higher probability of rescue (or longer mean persistence time) with a slower or smaller change in the environment, including gradual vs. abrupt changes, has since been observed in asexually-reproducing phages (Bono et al., 2015), protists (Killeen et al., 2017), bacteria (Mongold et al., 1999; Perron et al., 2008; Lindsey et al., 2013; Melero-Jiménez et al., 2022), and yeast (Bell and Gonzalez, 2011; Gonzalez and Bell, 2013), as well as in asexually- and/or sexually-reproducing algae (Lachapelle and Bell, 2012; Petkovic and Colegrave, 2023; Shibasaki and Yamamichi, 2024). Final fitness was also found to be higher after gradual than after an abrupt change (Zhou and Zhang, 2023). However, there are both theoretical (Matuszewski et al., 2015) and experimental results running counter the general prediction. Motivated by Matuszewski et al. (2015), Guzella et al. (2018) demonstrated that slower change can hinder adaptation from the standing genetic variation as genotypes adapted to high stress get lost during slow gradual deterioration.

Rescue is also usually predicted to increase with standing genetic variation. This has been qualitatively verified a relatively large number of times, in asexually-reproducing bacteria (Ramsayer et al., 2013) and yeast (Stelkens et al., 2014), in asexually- and/or sexually-reproducing algae (Lachapelle and Bell, 2012; Bell, 2013), and in sexually-reproducing beetles (Agashe, 2009; Agashe et al., 2011; Hufbauer et al., 2015; Olazcuaga et al., 2023). Rescue is similarly expected to increase with mutation rate, which has been verified in bacteria (Perron et al., 2006; Couce et al., 2015), though exceptions exist (Perron et al., 2006), and asexually-reproducing algae (see UV treatment in Kronholm et al., 2017). Likewise, Gifford et al. (2023) found that a higher initial frequency of mutators in an *E. coli* population increases the probability of antibiotic resistance (rescue).

The fourth key prediction is that the probability of rescue increases with the maximum growth rate in the new environment. We are not aware of an experiment that study this. It could be studied by varying the quality of the media or the stressor but it would be important to control for effects on other factors, like the wild-type decline rate and mutational input.

6.1.2 The connections between experiments and models for the role of other factors in rescue

The effects of many of the factors reviewed in section 4 have also been explored experimentally. There are especially a number of papers on rescue in meta-communities (spatial structure), on the role of sexual reproduction, and on species interactions, but also on several other factors.

Spatial structure. The role of dispersal in evolutionary rescue received early attention from Bell and Gonzalez (2011) and has by now been studied both in asexually and sexually reproducing organisms as well as in species communities.

For asexually reproducing populations, dispersal tends to have a positive effect on rescue (or none, depending on the precise circumstances), as found in meta-populations of single species of yeast (Bell and Gonzalez, 2011) and cyanobacteria (Melero-Jiménez et al., 2022) as well as in communities of different morphotypes of *Pseudomonas fluorescens* (O'Connor et al., 2020). In these studies, meta-populations evolve on a stress gradient where some communities experience benign conditions at least initially before the environment deteriorates either gradually or abruptly. Several of the population genetics models of rescue discussed in section 4.9 have been inspired by Bell and Gonzalez (2011)

and can be considered as simplified versions of these experiments with just two environmental states – benign or deteriorated (with all patches being deteriorated eventually), allowing for some comparisons. Generally consistent with the experimental results, these models find that dispersal mostly aids rescue, although the net effect of strong dispersal can under certain conditions be negative (Uecker et al., 2014; Czuppon et al., 2021; Tomasini and Peischl, 2022). Tomasini and Peischl (2020) derive conditions under which some degree of dispersal (as opposed to none) increases the probability of rescue. The pronounced beneficial effect of dispersal after an abrupt change to lethal conditions from a long period of stasis, as observed in Bell and Gonzalez (2011), is consistent with their theoretical finding that dispersal is beneficial if the intervals between deterioration steps are long and the deteriorated environment is highly stressful to the wild type. The beneficial effect of dispersal observed in experiments is generally thought to arise from dispersal of pre-adapted cells from lower to higher stress levels. This intuition agrees with the finding of Czuppon et al. (2021) that rescue mutants are likely to appear in the benign (rather than in the deteriorated) patches. Finally, we can compare results of models and experiments on the effects of local vs. global dispersal. While local dispersal (dispersing individuals one step up in the stress gradient) is found to be more beneficial than global dispersal in the experiments by Bell and Gonzalez (2011), the model by Tomasini and Peischl (2022) predicts the opposite. Following theoretical results on biased dispersal by Czuppon et al. (2021), the reason for the disagreement could be that local dispersal is unidirectional in Bell and Gonzalez (2011) while it is bidirectional in Tomasini and Peischl (2022). Perhaps more importantly, it is plausible to assume that in the experiments, a dispersing mutant might well be able to grow one stress-level up but not at vastly higher concentrations of the stressor, which will require the accumulation of further mutations – an effect not captured by a model with two genotypes and two environmental states. Overall, the substantial body of literature on either side calls for a synthesis, ideally supported by the co-development of further theory and experiments. On the one hand, the development of population genetics theory allowing for multiple environmental states as well as multi-step rescue, for example using Fisher's geometric model, would help to better link models to experiments. On the other hand, experiments that reduce the stress gradient to only two stress levels – none and high – could help close the gap in our understanding from the other side. Furthermore, theoretical models consider the entire range of dispersal probabilities from 0 to 1, finding that the relationship between dispersal probability and rescue can (but does not have to) be non-monotonic, depending on the fitnesses of genotypes. The experimental meta-community studies, by contrast, do not vary the dispersal probability, and future experiments considering a range of dispersal rates could allow for a comparison to theoretical predictions. In addition to its role in rescue in meta-populations, the related role of (unidirectional) dispersal from a source in adaptation to sinks (Box 6) has been experimentally studied in bacteria adapting to antibiotics (Perron et al., 2007, 2008) and phage adapting to a novel bacterial host (Ching et al., 2013). Varying the number of cells dispersing into the sink, Perron et al. (2007) finds a positive effect of higher dispersal rates on the density of the evolving populations; in Ching et al. (2013), the relationship is non-monotonic and strong dispersal from the source into the sink prevents adaptation, which might be due to negative density dependence as in some parameter regimes in Uecker et al. (2014).

For sexually reproducing organisms, the role of dispersal appears to be more nuanced. The effect of immigration from a source population may change from positive to negative as adaptation proceeds (Lagator et al., 2014b) or can slightly slow down adaptation (Durkee et al., 2024). Similarly, based on the infinitesimal model, Barton and Etheridge (2018) find that low immigration is beneficial because it introduces genetic variation whereas strong immigration can delay adaptation in a sink by pulling the phenotype back to the maladapted source phenotype; high immigration can also increase negative density dependence and hamper adaptation (Gomulkiewicz et al., 1999). Overall, the role of dispersal in rescue of sexually reproducing populations is still underexplored, both experimentally and theoretically. For example, experiments with bi-directional dispersal between different (possibly changing) environments seem to be lacking. On the theory side, while early simulation studies and recent theory have already considered polygenic adaptation in sexually reproducing populations in spatially structured environments (Schiffers et al., 2013; Bourne et al., 2014; Dekens, 2024), a systematic analysis of the interplay between sex and migration would be valuable.

Finally, in meta-populations of communities sourced from nature, dispersal was found to have a positive effect on rescue of soil communities of bacteria and fungi (Low-Décarie et al., 2015), similar to the single-species experiments discussed above, but had no consistent effect on adaptation (or failure thereof) at

either trophic level in a community of predators (zooplankton) and prey species (phytoplankton) (Bell et al., 2019). Rescue theory for co-evolving predator-prey systems in a spatial environment is currently lacking and could help interpret the experiments. More broadly, there is a need for rescue models with interacting species in spatial environments.

Sexual reproduction. The role of sexual reproduction in rescue has experimentally been explored in a series of studies by repeatedly inducing sexual cycles in the unicellular algae *Chlamydomonas reinhardtii* and exposing it either to salt stress (Lachapelle and Bell, 2012; Petkovic and Colegrave, 2023), salt stress in the presence of a competitor (Petkovic and Colegrave, 2019), darkness (Bell, 2013), or herbicides (Lagator et al., 2014b). The consensus of all studies is that sexual reproduction is generally beneficial for rescue but it also had some negative effects by slowing down adaptation to gradually increasing salt concentrations at early stages of the experiment (Lachapelle and Bell, 2012) and in some cases slowing population recovery at late stages of the experiment in the presence of immigration from a source (Lagator et al., 2014b). In the experiments, the positive effect of increased variation (and possibly the avoidance of clonal interference) thus seems to prevail overall, but recombination load might be responsible for the observed negative effects (although the experimental procedure for the sexual cycle could sometimes also itself have harmful effects, as pointed out by Lachapelle and Bell (2012)); see also the high variation in growth rates among F1 lines including some 'rescue lines' observed by Kawaguchi and Yamamichi (2025). The net effect of segregation and recombination have been analysed in one- and two-locus models by Uecker and Hermisson (2016) and Uecker (2017) but an insightful comparison to the experiments would require knowledge of the genotype-fitness landscape. An interesting comparison can, however, be made between the modeling study by Orive et al. (2017) and the experiments by Petkovic and Colegrave (2023), who both compare sexual and asexual reproduction under different rates of environmental deterioration. Orive et al. (2017) finds that increased clonality in populations with both sexual and asexual/clonal reproduction leads to a lower probability of rescue in a gradually deteriorating environment as continuous generation of new genetic variation, better achieved in a sexually reproducing population, is essential for rescue. By contrast, more clonal populations have a higher probability of rescue under an abrupt environmental change since adaptation then relies mostly on the standing genetic variation and pre-existing adaptive genotypes are not broken up in clonal offspring unlike in sexual offspring. In the experiments by Petkovic and Colegrave (2023), purely asexual lines never adapt better than sexual ones. However, while lines with obligate sexual reproduction perform best at intermediate rates of change, the optimal strategy at the most rapid deterioration rate is facultative rather than obligate sex. Similar to Orive et al. (2017), the authors hypothesize that recombination load outweighs the benefits of sex in rapidly deterioration environments where adaptive mutations are too rare to segregate simultaneously.

All the above studies focus on the genetic aspects of sexual vs. asexual reproduction. Another aspect of sexual reproduction is the need for gametes to come in physical contact to form a zygote. Lack of mating at low population densities can be a concern in the experiments since gametes of *Chlamydomonas reinhardtii* might then fail to meet. Many of the experiments discontinue sexual cycles under stress or once population density becomes too low (Bell, 2013; Lachapelle and Bell, 2012; Petkovic and Colegrave, 2023) and / or populations that went extinct due to other reasons than the applied stress are not included into the analysis (Lachapelle and Bell, 2012). (Additional problems may contribute to a stop of sexual cycles since the flagella, needed by gametes for zygote formation, may be lost through salt stress, and the experimental procedures for inducing sexual reproduction are difficult to achieve at very low cell densities; Josianne Lachapelle, personal communication.) Interestingly, Allee effects through failed encounter of gametes have thus not been explored as a negative effect of sexual reproduction in any of the studies. Similarly, mate-finding Allee effects (or Allee effects in general) have received very little attention in models of evolutionary rescue (but see Deraje and Uecker, 2025), highlighting a joint gap in the literature.

Finally, experiments are needed to test theoretical predictions on the role of selfing in rescue (section 4.4), for which the nematode *C. elegans* or short-lived plants could be suitable model systems. For example, Bodbyl Roels and Kelly (2011) utilized pollinator exclusion studies to study the role that rapid evolution of selfing after pollinator loss plays in increasing population fitness, discussing implications for evolutionary rescue.

Species interactions. The effect of species interactions has been empirically investigated at two levels, by exposing either handpicked pairs of species or large natural communities to stress. Considering a parasite-host and a predator-prey pair respectively, Zhang and Buckling (2011) and Hermann and Becks (2022) both explore the role of host / prey evolution on rescue of a parasite / predator population exposed to stress. Zhang and Buckling (2011) found that a population of phages persisted longer under gradual warming (a stress mostly for the phage) when its bacterial host was prevented from evolving. In contrast, Hermann and Becks (2022) showed that evolution in a prey population (algae) could indirectly rescue a declining predator population (rotifers), qualitatively matching their tailored simulations (see also 6.1.3). Such indirect rescue is predicted to occur when there is a strong trade-off between defense and intrinsic growth rate in the prey (Yamamichi and Miner, 2015), which likely played a negligible role in Zhang and Buckling (2011). Adaptation of a parasite (phage) to a new bacterial host was studied by Gandon et al. (2024), showing that the need to overcome multiple resistance mutations in the host hindered phage adaptation in line with a co-developed model (see also 6.1.3). Turning to competitive interactions, (Petkovic and Colegrave, 2019) found that a competing species hindered rescue of phytoplankton exposed to high salt concentrations, consistent with the basic prediction of competition reducing population size, and Bono et al. (2015) observed that evolution could rescue a specialist phage strategy from competitive exclusion by a generalist strategy provided the fraction of hosts inaccessible to the specialist was small enough, reducing the generalist's advantage. This seems broadly consistent with the findings of Van Dyken (2020), that rescue from an invading competitor is more likely when invasion is slower. For a synthetic mutualism between two cross-feeding *E. coli* strains, Melero-Jiménez et al. (2025) found that rescue usually only occurred in one species and happened through breakdown of the mutualism, as the mutualistic strains were more sensitive to stress than an autarch strain. Mutualism breakdown has been predicted by theory (Weyerer et al., 2023), which incorporates a trade-off between investment into the mutualism and independent growth, but the modeled scenario is no close match to Melero-Jiménez et al. (2025). The findings by Melero-Jiménez et al. (2025) as well as Zhang and Buckling (2011) suggest developing new theory that explores the negative pleiotropic costs of biotic adaptation on abiotic adaptation. Experiments with larger, more natural communities follow a two phase design: first expose communities to varying levels of stress (potentially crossed with nutrient concentration and/or dispersal rate) and then expose all communities to a previously lethal stress level. This has been done for a soil microbiome exposed to herbicide (Low-Décarie et al., 2015), a lake microbiome exposed to acidification (Xu et al., 2025), a phytoplankton community exposed to herbicide (Fugère et al., 2020), and a phytoplankton-zooplankton community exposed to acidification (Bell et al., 2019). While some intuition about rescue in large communities can be gained from two-species models (Bell et al., 2019), linking experiments with theory that explores larger networks of interacting species may provide deeper insight.

Other factors. Various other factors have been examined experimentally. One is sequential exposure to different stressors, where pre-exposure to one stressor can slow adaptation (Lagator et al., 2014a) and lower the probability of short-term persistence (Samani and Bell, 2016) and rescue (Lachapelle et al., 2017) when exposed to another. On the other hand, pre-exposure can also accelerate adaptation (Lagator et al., 2014a) and foster rescue contingent on short-term survival (Samani and Bell, 2016). Sequential application (or alternation) of stressors has frequently been modeled in the context of drug and pesticide resistance (see section 5.2), but the objective is usually to determine the overall probability of extinction, making specific assumptions about collateral sensitivity and cross resistance between mutations. More general models of sequential stressors, including demographic impacts on genetic diversity – which have been shown to reduce the chances of subsequent rescue in flour beetles (Olazcuaga et al., 2023) – as well as pleiotropic effects of rescue mutations across environments and physiological responses, may not only help synthesize and generalize the experimental findings. By doing so, they may also be informative for models of drug resistance evolution. Another factor studied is environmental fluctuations, which were found to decrease the probability of rescue in bacteriophage under warming (Hao et al., 2015), as predicted when rescue is likely (Peniston et al., 2020). Environmental fluctuations were also found to slow adaptation of green algae to increasing salt concentrations, but contrastingly improved growth at lethal levels (Shibasaki and Yamamichi, 2024), consistent with a tailored model (Shibasaki and Yamamichi, 2024). Negative density-dependence has been shown to decrease the probability of rescue in flour beetles (Olazcuaga et al., 2024), as expected (Chevin and Lande, 2010; Nordstrom et al., 2023), as has the recessivity of rescue mutations in diploid yeast (Ono

et al., 2024), as predicted (Uecker, 2017). In a long-term experiment, Ravi Kumar et al. (2025) characterized multiple life-history traits of experimental founder populations of flour beetles and tracked the population sizes of adults and larvae after an abrupt switch to a new food source, finding a long-lasting impact of founding population identity on population size and identifying a fast development rate as a particular important trait. The detailed data set calls to be combined with stage-structured models.

6.1.3 Studies combining theory and experiments

Few studies combine theory and experiments. Those that do often present a conceptual model that is neither closely tailored to the experiments nor parameterized by data but is able to explain or reproduce the observed dynamics. For example, Bell et al. (2019) complemented experiments on rescue in communities of phytoplankton and zooplankton stressed by acidification by a predator-prey model that, at least for the chosen parameters, mirrors the dynamics of the experiment. More complex models were developed by Gandon et al. (2024) and Shibasaki and Yamamichi (2024), who both combined theory and experiments. Gandon et al. (2024) built a model of pathogen adaptation to host populations with various resistance profiles, using phages and bacteria with CRISPR-Cas immunity as an elegant experimental system. Shibasaki and Yamamichi (2024) combined a quantitative trait model with experiments of the alga *Chlorella vulgaris* under salt stress to study adaptation to a deteriorating environment superimposed with additional fluctuations in the level of stress. In the following, we discuss two studies in more detail – Hermann and Becks (2022) as a rare example of an experiment (and model) that was directly motivated by preceding theory and Gifford et al. (2023), which closely tailored and quantitatively compared a model to experiments.

The original model of indirect evolutionary rescue (Yamamichi and Miner, 2015) states that when environmental change causes the number of predators to decline, so too does the benefit of costly defense against the predator, leading to the evolution of less defended prey and predator persistence. To see this experimentally, Hermann and Becks (2022) established a chemostat system composed of a rotifer (predator) and two algal clones (prey), one more defended than the other, and exposed it to salt concentrations that harm only the rotifer. They also set up a model to match their experimental system, which in particular assumes two discrete prey types rather than the previously-assumed continuum (Yamamichi and Miner, 2015). Both experiment and theory demonstrated that a sufficient initial frequency of undefended prey allows the predator to persist in harsh environments. While the model reflects the general features of the experimental system, the results are compared only qualitatively.

This is different in the study by Gifford et al. (2023), who investigated the role of mutators in the evolution of multi-drug resistance. Populations of *E. coli* with varying initial mutator frequencies were exposed to either one or two antibiotics. Mutators fostered the emergence of double resistance not only under combination treatment but also under exposure to a single drug. Gifford et al. (2023) then closely tailored a model to these experiments, including careful parameterization, which gave an impressive quantitative agreement (compare their Fig. 1 and 3 and see the statistical comparison in their SI). What is more, the close match between model and experiments showed that the experimentally observed dynamics of multi-drug resistance evolution could be entirely explained by the acquisition of mutations in the respective target genes, enabled by the high mutation rate of the mutator strain. Changes in multi-drug efflux pumps or additional mutation rate evolution, both observed in the experiments, do not need to be invoked, which would have been difficult to conclude experimentally.

Besides these studies that belong to the evolutionary biology literature, there are some specific studies on antibiotic resistance evolution combining models and experiments. For example, Campion et al. (2005) set up models for resistance evolution, taking into account the concentration-dependent effect of the drugs (pharmacodynamics) and the decay of the antibiotic over time (pharmacokinetics), and fits them to data from *in vitro* experiments. The model with the best fit is then applied to predict which treatments would eliminate the bacterial population, which is in turn confirmed by experiments.

6.1.4 Gaps and future suggestions

Many experimental evolutionary rescue studies are based on serial transfer experiments an inherent feature of which are periodic bottlenecks as small inocula are transferred to new medium in regular intervals. Indeed, the stress itself is often not sufficiently strong to suppress growth (e.g., below the

minimal inhibitory concentration for antibiotics) and only leads to population decline in combination with these repeated drastic reductions in the population size. It is well-known that the frequency and size of bottlenecks influence evolutionary dynamics (Raynes et al., 2014; Garoff et al., 2020; Mahrt et al., 2021; Izutsu et al., 2024). While there is substantial theory on the role of bottlenecks in adaptation, these usually are placed in a regime where the wild-type population is not threatened by extinction (Wahl et al., 2002; Wahl and Zhu, 2015; LeClair and Wahl, 2018). Exceptions are the model by Martin et al. (2013), which includes bottlenecks into the basic population genetics framework of one-step rescue after an abrupt change (with multiple rescue alleles) and (Gifford et al., 2023), discussed in the previous section, which closely tailored the model to experiments. Introducing bottlenecks into the existing rescue models with complex genetics or ecology would tie them more closely to experiments and likely bring forward new results.

A key predictor of rescue to a stress is the state of the population when that stress is applied. The state of the population is affected by prior exposure to that stress, prior exposure to other stressors, and demographic history. These factors are explored in many experiments but are generally lacking in theory. In particular, many experiments expose a population to one or more stepwise increases in a stressor before final exposure to a lethal dose (e.g., Samani and Bell, 2010; Lindsey et al., 2013; Gonzalez and Bell, 2013). Similar to evolution on a gradient in space (section 6.1.2), population genetics models with multiple environmental states and multi-step rescue, e.g., as used for adaptation to gradual change (Matuszewski et al., 2015), could be interpreted and applied more in this context. These models capture empirically observed effects such as changes in the rank-order of genotypic fitnesses across environments, e.g., mutations that help with mild stress may be detrimental at higher stresses (Toll-Riera et al., 2022) or the other way round (Mongold et al., 1999; Guzella et al., 2018), and (sign) epistasis, which can cause the selectively-accessible mutational paths to rescue to vary with the rate of environmental change (Lindsey et al., 2013). Such effects also impact standing genetic variance. While many rescue models assume rescue mutants are costly pre-change, experiments show that some rescue mutants are not measurably deleterious (Batarseh et al., 2020) and mutants that rescue populations from harsh changes may not be more deleterious than those that rescue populations from mild changes (Harmand et al., 2017).

Much of evolutionary rescue theory assumes the standing genetic variation is at mutation-selection balance, which may be hard to achieve in experiments and far from the truth in nature. For example, under a simple deterministic model of mutation and selection, $p(t+1) \approx \mu + p(t)(1-s)$, the initial deviation from mutation-selection balance decays like $(1-s)^t$. This means that populations starting with no mutants (e.g., exponentially growing from a single clone) may have average mutant frequencies well below equilibrium for $1/s$ generations, which can be substantial for weakly deleterious mutations. Applying Luria-Delbrück theory to determine pre-change mutants frequencies (see section 3.1) rather than assuming mutation-selection balance could help better connect rescue models to data from evolution experiments. Further, interpreting Luria-Delbrück experiments as evolutionary rescue opens the door to analyzing existing data from fluctuation assays in ways that improve our understanding of rescue. For example, Harmand et al. (2017) performed fluctuation assays with *E. coli* at different concentrations of nalidixic acid. They estimated the mutation rate to resistance as $u = -\ln(P_0)/N_t$, where P_0 is the fraction of plates with no colonies and N_t is the number of cells applied to each plate, and found that it declined like a power-law with drug concentration. This fact can now be used in existing models of rescue (e.g., Orr and Unckless, 2008) for general insight and prediction. More directly, $1 - P_0$ is the probability of rescue. Conversely, rescue theory may be used to improve mutation rate estimates from Luria-Delbrück fluctuation assays. In particular, it could be used to extend Luria-Delbrück theory by the incorporation of *de novo* mutations emerging on the Petri dish in the presence of the stressor. Furthermore, instead of considering a fixed plating efficiency – which is in fact an establishment probability –, plating efficiencies could *a posteriori* be estimated for the various genotypes from seeding experiments (Alexander and MacLean, 2020), and this heterogeneity of plating efficiencies could be incorporated into the modeling framework.

6.2 Predicting and identifying rescue in the wild

We now turn to natural populations, where theory is used to both predict and infer evolutionary rescue. As discussed in section 5, many rescue models have been developed for conservation and drug resistance,

often with the goal of prediction. While in section 5, we focused on the structure and features of models and the relationship to general rescue models, we here focus more on the relationship between models and data, e.g., parameterizing models to make quantitative predictions in specific scenarios. Naturally, there is no strict division between the two sections.

6.2.1 Predicting rescue

There is considerable interest in predicting whether evolution will allow a wild population to persist through environmental change. One popular approach for gradual environmental changes, like climate warming, is to parameterize the critical rate of environmental change derived from a quantitative genetics model with a moving optimum (Box 3). In some cases a point estimate of the critical rate is possible, e.g., with long-term field data (Gienapp et al., 2013). Rescue is then predicted when the critical rate is larger than the forecasted rate of environmental change. Though there are relatively few parameters, there is still typically great uncertainty in their values (e.g., Couper et al., 2021), such as the amount of genetic variation and the width of the fitness function. One way to deal with parameter uncertainty is to calculate a distribution of critical rates from distributions of parameter values, and then ask what is the probability that the critical rate will be greater than the realized rate of environmental change (Radchuk et al., 2019; Diniz-Filho et al., 2019; Souza et al., 2019, 2023). Ideally parameter estimates are also improved with additional experiments or genomic analyses (e.g., Couper et al., 2025). Critical rate predictions rely on knowing which traits and environmental variables determine persistence vs. extinction. A trait-agnostic alternative is to model rates of change in fitness using Fisher's fundamental theorem of natural selection (Fisher, 1930) – populations with mean fitness below replacement are predicted to be rescued when there is sufficient variance in fitness (Kulbaba et al., 2019). The predictive power of a one-time measurement of variance in fitness will be higher after an abrupt change, rather than in a gradually changing environment, as variance in fitness will generally vary with environment (Peschel and Shaw, 2024). A more tailored approach, but one that requires more parameter estimates, is to simulate the demographic and evolutionary dynamics. This can be done at varying levels of complexity, from running ecological niche models for multiple sets of genotypes (Razgour et al., 2019; Nukazawa et al., 2023; Azevedo et al., 2024), to numerically iterating population-mean trait values in species distribution models (Bush et al., 2016), to tracking distributions of trait values and population size with integral projection models (Ge et al., 2024; Clark-Wolf et al., 2024; Anderson et al., 2025), to stochastic individual-based simulations (Fournier-Level et al., 2016; Cotto et al., 2017; Devresse et al., 2025), including those that vary management actions (Bay et al., 2017; Vedder et al., 2022). These simulation approaches can include extensive amounts of data, such as complex genetic bases from genomic prediction (Fournier-Level et al., 2016) and decades of field observations (Clark-Wolf et al., 2024).

Of course, predictions are also desired in the context of drug and pesticide resistance. Models to predict resistance evolution have been developed across systems for example for insects, fungal pathogens, bacteria, or cancer, reviewed with connections to data by Tabashnik (1990); van den Bosch et al. (2015); Blanquart (2019); Scibilia et al. (2025) respectively. Predictions can be made at different scales, e.g., the evolution and spread of antibiotic resistance can be predicted at the scale of individual patients, hospitals, networks of hospitals, and communities (reviewed in Blanquart, 2019) or entire countries (e.g., for tuberculosis by Sharma et al., 2017). Similarly, predictions for resistance of pests to pesticides or pest-resistant crop cultivars can be made at the scale of fields (e.g. Holmes et al., 2022) or the landscape (e.g Papaïx et al., 2018). Many models are tailored to specific species such as Johnsongrass (Holmes et al., 2022), the fungal plant pathogen *Zymoseptoria tritici* (Taylor and Cunniffe, 2023a), species of helminths (Patel et al., 2025) or to specific cancer types such as melanoma (Smalley et al., 2019). Just as the models discussed in the previous paragraph, these models require parameterization or a parameter sensitivity analysis, when reliable estimates are lacking (Tabashnik, 1990; Brady and Enderling, 2019).

Predicting the effect of control strategies is especially of interest (Lässig et al., 2017), and models have a tangible impact in proposing evolution-informed treatments. For example, right from the introduction of *Bt* crops – (usually transgenic) crops that produce *Bacillus thuringiensis* (*Bt*) insecticidal toxins – evolution-informed control has been implemented to prevent the evolution of resistance by applying the refuge strategy (Tabashnik et al., 2008, 2013; United States Environmental Protection Agency,

2026). In this strategy, which had originally been proposed to manage insecticide resistance (see also section 3.2), susceptible non-toxin producing crop plants are planted along with resistant *Bt* cultivars to maintain an insect population sensitive to the toxin. Patterns of insect resistance evolution to the *Bt* toxins (or its absence) are broadly consistent with theoretical predictions (Tabashnik et al., 2013). In evolutionary oncology, a treatment proposed by modeling is adaptive cancer therapy in which treatment is paused once the cancer has shrunk sufficiently and is only resumed once it has regrown to a certain size, thereby suppressing resistance by exploiting competition between resistant and sensitive cells (Gatenby et al., 2009). Adaptive therapy has been modeled for various cancer types such as prostate cancer (Zhang et al., 2017) or melanoma (Smalley et al., 2019), and shows successful results in animal models (Smalley et al., 2019) and clinical trials (Zhang et al., 2017, 2022; West et al., 2023; Scibilia et al., 2025). Both the refuge therapy and adaptive cancer therapy rely on maintenance of a sensitive insect or cell population and therefore resistance evolution does not strictly constitute a rescue scenario. By contrast, the more recently proposed 'two-strike' strategy, where the drug gets switched once the cancer has been reduced to a small size, aims at extinction of the cancer (Gatenby et al., 2020; Patil et al., 2025). This strategy is also already subject to clinical trials (Scibilia et al., 2025). Precision medicine in cancer treatment where evolution is predicted in a given patient is a topic of intense ongoing research (Lipinski et al., 2016) and there are concrete plans to incorporating modeling into treatment in real-time (Scibilia et al., 2025).

6.2.2 Identifying rescue

Identifying whether (and if so how) rescue has occurred in a wild population is difficult. To unambiguously identify rescue, we need to document evolutionary change and, most difficultly, show that without it the population would have gone extinct (Gomulkiewicz and Shaw, 2013). Despite this, there are a number of potential examples of evolutionary rescue in the wild (reviewed in Vander Wal et al., 2013; Carlson et al., 2014) but, even in seemingly clear cases of rescue, uncertainty remains. As an example, in Box 7 we discuss the case of Tasmanian Devils evolving resistance to facial tumours, where models have been used to predict the probability of extinction with and without evolution (Clement et al., 2024). The probability of extinction without evolution is key here as parasites may not always drive non-evolving hosts to extinction (Golas et al., 2021). Empirically-parameterized models have also been used to determine if evolution rescued a native forb from an invading competitor (Dostál, 2022) and the role of a seed bank in preventing demographic recovery of an annual plant to severe drought (Benning et al., 2023). There are a number of other cases of purported rescue where we have both demographic and genetic data (Gignoux-Wolfsohn et al., 2021; Anstett et al., 2024) or phenotypic and genetic data (Salamon et al., 2025) through time; tailoring models for these systems may help determine the link between evolution and persistence.

The strongest evidence of rescue (or rescue-related scenarios) comes from cases of resistance evolution, as here we on purpose manipulate the environment to cause extinction, often monitor the population and evolutionary dynamics, and often have many (uncontrolled) replicates. Concrete examples are Figure 2 in Hokanson et al. (1977) and Figure 2 in Wei et al. (1995), which show U-shaped curves for the dynamics of cancer and viral RNA of HIV respectively. The model of a declining drug-sensitive and an increasing drug-resistant population are used to explain the data in Hokanson et al. (1977) and to obtain parameter estimates in Wei et al. (1995). Similarly, during the Covid pandemic, rescue-like dynamics could be observed in Germany (and presumably many other countries) when interventions were sufficient to suppress the circulating variant, leading to an exponential decline of cases, but the more transmissible alpha-variant was able to spread causing an exponentially growing number of infections, akin to the exponentially decaying wild-type and the exponentially growing mutant population in the basic population genetics model discussed in section 2.2 (see Fig. 4 in Traulsen et al., 2022). Based on the number of cases caused by each variant, the rebound in overall case numbers can be predicted before it occurs.

In many cases we will be lacking demographic and/or evolutionary data during a natural rescue event. However, we may be able to draw conclusions retrospectively by sequencing populations suspected to have undergone rescue and inferring their demography and evolution from genomic data alone. In the simplest scenario, rescue after an abrupt environmental change is a population bottleneck that is ended by a selective sweep, both of which are routinely detected from genomic data. Not surprisingly then,

a number of papers now claim to observe signatures of past evolutionary rescue from contemporary genomes (Oziolor et al., 2019; Garcia-Ulloa II et al., 2021; Fulgione et al., 2022). These studies help determine the timing and extent of the population bottleneck and regions of the genome that were recently under strong selection. Theory developed to determine the expected genomic signatures of rescue by a selective sweep after an abrupt change (Osmond and Coop, 2020) finds that a coincident bottleneck and sweep create different signatures than a sweep in a population of constant size but that this difference is often subtle and, more fundamentally, it will be difficult to determine when an inferred sweep has had a causative effect on the inferred bottleneck, i.e., when evolution impacts demography.

In addition to identifying potential cases of rescue, combining models and data can also characterize how it happens. For example, Pennings (2012) combined data from many sources, stochastic simulations, and a simple model (matching the framework outlined in Box 4) to draw conclusions on the origin of drug resistance – pre-existing or emerging *de novo* – in patients infected with HIV. Based on sequencing data, Feder et al. (2016) detected a correlation between the probability of resistance and the occurrence of soft sweeps, which was shortly after quantified in a general model by Wilson et al. (2017). In general, there is ample data available in the fields of resistance evolution, such as for example on the genetic basis of herbicide resistance and the spatiotemporal history of the underlying alleles (reviewed in Kreiner, 2026), which could be used more by modelers even outside the resistance field.

7 Conceptual coda

When we speak of evolutionary rescue, we think of a population that survives environmental change due to adaptive evolution but that would have gone extinct without evolution (Bell, 2017). While we all have a sense of what this means, the definition is rather vague, and we use this section to discuss three conceptual complications that arise in defining evolutionary rescue.

7.1 What is the meaning of "no evolution"?

We first need to establish a no-evolution scenario for comparison. But what is the meaning of 'no evolution'? For models of evolutionary rescue by *de novo* mutations, we could simply set the mutation rate to zero. Similarly, if a rescue mutant pre-exists at a very low frequency, we could compare to a population without that variant (and without new mutations). When there is more substantial heritable variation in fitness, as in quantitative genetics models, one could remove all variation by giving every individual the mean trait value at the time of environmental change (e.g., Golas et al., 2021; McManus et al., 2021), but this reduces the variance load and would be difficult to achieve in experiments. Alternatively, a no-evolution-by-natural-selection scenario can be imposed by removing heritability. This can be done by choosing the trait value of every offspring either from the distribution at the time of environmental change, from the distribution of environmental effects on phenotype (e.g. Devresse et al., 2025), from the distribution of phenotypes of the parental generation, or by reshuffling phenotypes among individuals (Matz et al., 2020). In experiments, a similar effect to the first option could be achieved by re-sampling individuals from a stock population each time-step (e.g., Zhang and Buckling, 2011). After an abrupt environmental change, no heritability implies a constant mean fitness in a deterministic treatment (e.g., Gomulkiewicz and Holt, 1995). Stochastic models with no heritability, e.g., birth-death processes with non-heritable phenotypic variability (a special case of Carja and Plotkin, 2019), are needed to calculate probabilities of extinction and extinction time distributions.

7.2 Persistence in the absence of evolution

In most situations of rescue we think of extinction being certain in the absence of evolution (left panel of figure 3a), i.e., of situations in which population mean fitness remains below one until extinction (e.g., Gomulkiewicz and Holt, 1995). Then any population that survives is considered rescued and the fraction of surviving replicates is the probability of rescue. But what about scenarios where extinction in the absence of evolution is not certain (right panel of figure 3a)? For example, a parasite might drive a host population to low numbers, reducing its own ability to infect and therefore allowing the host population to rebound (Golas et al., 2021). In the process the host population may go extinct by demographic stochasticity, but extinction is not certain, even in the absence of evolution,

$P(\text{extinction} \mid \text{no evolution}) < 1$. By increasing resistance to the parasite, evolution may reduce the chances of extinction, $P(\text{extinction} \mid \text{evolution}) < P(\text{extinction} \mid \text{no evolution})$ or, phrased differently, increase the chances of persistence, $P(\text{persistence} \mid \text{evolution}) > P(\text{persistence} \mid \text{no evolution})$. In these situations it becomes impossible to know for any given realization if an evolving population's survival was due to evolution.

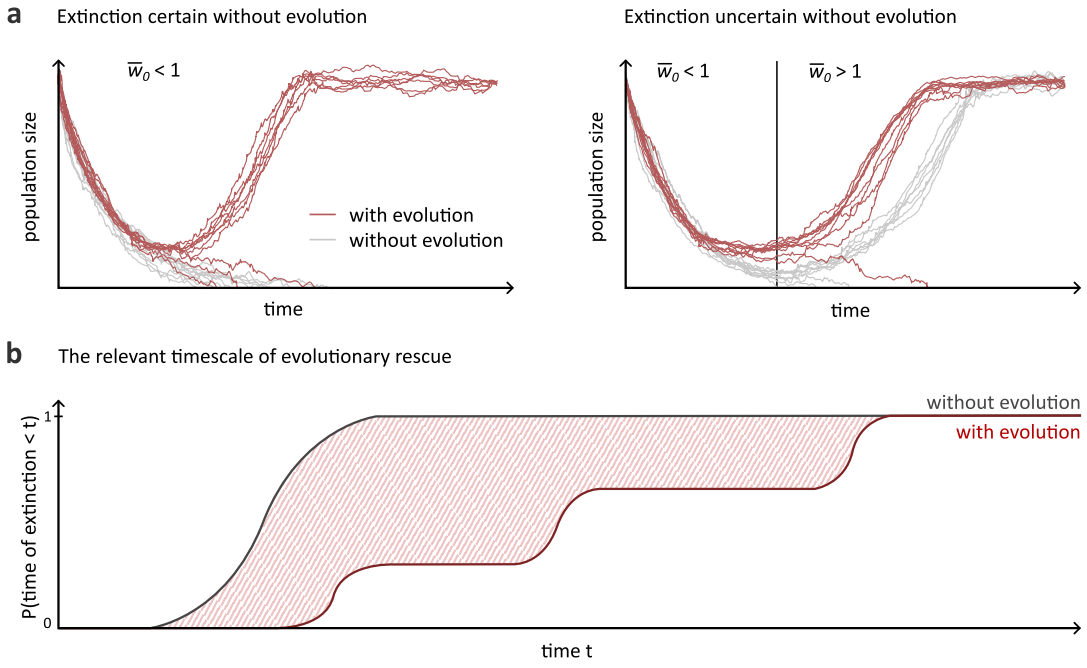

Figure 3: Illustration of conceptual challenges with the definition of evolutionary rescue. Panel a: Population trajectories of replicate populations exposed to environmental change (red lines – with evolution: grey lines – without evolution). If the environment does not improve (i.e., the mean fitness $\bar{w}_0$ of the non-evolving ancestral population remains below 1), all populations go extinct without evolution (left side). By contrast, if the environment improves after some time, lifting $\bar{w}_0$ above 1, some populations may survive even without evolution (right side). However, adaptive evolution increases the chance of survival, and more populations persist. Panel b: Cumulative distribution of extinction times with and without evolution over a long time frame. Following environmental change, both evolving and non-evolving populations persist initially but then the non-evolving population inevitably goes extinct, while the evolving population has a positive chance to survive the change. However, the environment does not stay constant indefinitely and over the course of a series of three environmental changes, even the evolving population goes extinct in the example. When we speak of evolutionary rescue, we usually refer to a specific change, for example the first one in the graph.

How do we quantify the probability of rescue in scenarios where extinction in the absence of evolution is not certain? One option is the excess probability of survival with evolution (Golas et al., 2021). Letting A be persistence with evolution and B be persistence without evolution, this is $P_{\text{excess}} = P(A) - P(B)$. Perhaps more consistent with verbal descriptions of rescue, we can also consider the probability that a given realization survives provided it would have gone extinct without evolution. With complements indicating extinction, this probability is given by

$$\begin{aligned} P_{\text{cond}} &= P(A|B^c) \\ &= P(A \cap B^c)/P(B^c) \\ &= [P(A) - P(B) + P(A^c \cap B)]/P(B^c). \end{aligned} \tag{1}$$

The event $A^c \cap B$ is extinction with evolution but survival without, i.e., evolutionary suicide. If evolutionary suicide cannot occur, P_{cond} corresponds to the excess probability scaled by the extinction

probability in the absence of evolution. Which of the two probabilities, P_{excess} or P_{cond}, we are interested in depends on the context and the precise question we are asking. For example, consider an experiment where out of 100 replicate populations, 90 survived when allowing evolution but only 60 survived when disallowing evolution. When we ask how many of the evolving populations survived due to evolutionary rescue, we would answer by $(90-60)/100 = 30\%$ (disregarding the possibility of evolutionary suicide), which corresponds to P_{excess}. But if we asked about the probability of a population to survive due to evolution if doomed otherwise, we would answer by $3/4$, which is P_{cond}. If the numbers were 40 and 10 instead, P_{cond} would only be $1/3$, while we could still say that 30% of the populations survived thanks to evolution ($P_{\text{excess}} = 30\%$). We could of course ask further questions such as whether a population that survived did so due to evolution or would have survived anyways, which would be $1/3$ and $3/4$ respectively for the two numerical examples.

In either case, we might calculate each of the component probabilities, e.g., $P(A)$ and $P(B)$, by running independent sets of simulations for each. Ideally, however, we would like to know how evolution would have affected the no-evolution simulations and whether any given evolving population would have persisted in the absence of evolution. The issue of appropriate counterfactuals arises in other fields, such as comparing disease spread with and without interventions (Hudgens and Halloran, 2008; Kaminsky et al., 2019), which we could learn from both for the implementation of simulations and the interpretation of empirical data.

7.3 The relevant timescale

Another complication in the definition of rescue is that in the very short term every population persists and in the long run a population (if it did not go extinct) will experience further environmental changes beyond the focal one. When we calculate the probability of rescue we are therefore implicitly choosing a timescale (Martin et al., 2013). Consider a series of abrupt environmental changes, which could be quite different stresses. In the scenario shown in Figure 3b, it takes some time for any population to go extinct after the first change, regardless of evolution, and evolution is insufficient to allow persistence through all changes. In this case what we typically mean by 'the probability of rescue' is the probability of persisting through the first change. To more explicitly determine the timescale of rescue we need to calculate the effect of evolution on persistence over time.

We can start to learn about the relevant timescale of rescue from studies that have calculated distributions of extinction times with evolution, $P(T_{\text{ext}} \leq t) = 1 - P(A_t)$, where A_t denotes persistence up to at least time t. For example, the distribution of extinction times after an abrupt change was calculated for a one-locus two-allele model with standing genetic variation (but without *de novo* mutations) by combining two single-type branching processes (Holt and Gomulkiewicz, 1997). Gomulkiewicz et al. (2017) extended this by considering arbitrarily many types in a continuous branching diffusion and examined the effect of a new mutation present at a given small frequency by the time of environmental change. Anciaux et al. (2019) also used a continuous branching diffusion to calculate extinction times for an asexual population with many types, finding a convenient approximation assuming deterministic evolution. This latter approximation was later applied to sexually-reproducing populations as well (Xu et al., 2023). By comparing to extinction times in matching no-evolution scenarios (see above), $P(B_t)$, these approaches can be used to quantify the effect of evolution on persistence in the short term. For example, Figure 4a shows $P(B_t)$ (dashed blue curve) and $P(A_t)$ (dash-dotted yellow and solid pink curves) from two single-type branching processes (equivalent to Holt and Gomulkiewicz, 1997, but in continuous time), which can be used to calculate Equation 1 over time (since evolutionary suicide is not possible here). When the mutant is beneficial but not able to persist long-term (as its birth rate is smaller than its death rate, $\lambda_m < \mu_m$, yellow curve), evolution may still prolong persistence and both the unconditioned and conditioned excess probabilities, P_{excess} and P_{cond}, become zero eventually (Panels b and c). When the mutant is able to persist in the long-term (as its birth rate is larger than its death rate, $\lambda_m > \mu_m$, pink curve), both probabilities converge to an asymptote, which coincides with the probability of ultimate population survival in the example as extinction is certain in the absence of evolution. To include *de novo* mutations, results from the mathematical literature could be harnessed (Heinzmann, 2009). Branching process models allow indefinite persistence, approximating populations with large carrying capacities; following successful adaptation, longer-term extinction probabilities for

populations with smaller carrying capacities may be derived with help from the ecological literature (Ovaskainen and Meerson, 2010).

In addition to determining the timescale that is relevant for evolutionary rescue, calculating extinction times with and without evolution may also help integrate with experiments because experimental data often contain more information than simply scoring populations as extinct or not.

8 Conclusion/Summary

The concept of evolutionary rescue can be traced back to the confluence of ecological and evolutionary theory in the 1990s. Independently, and under other names, rescue scenarios are modeled in the contexts of drug resistance and Luria-Debrück experiments, with models having appeared decades earlier (e.g., Lea and Coulson, 1949; Nissen-Meyer, 1966). This older literature contains impressive insight and modeling approaches that can inform modern rescue theory. Models of resistance evolution often deal with the same themes as other models of rescue, such as the genetic architecture underlying rescue and the type of stress imperiling persistence. Increased crosstalk between contexts, and between resistance theory for different organisms, would be beneficial. General rescue theory could perhaps play a role in synthesizing theory across organisms as well as in linking theory for resistance evolution and conservation.

Rescue theory has expanded greatly in recent years, exploring the role of many genetic, ecological, and environmental factors. In addition to many specific new insights, such as the complex dependence of rescue on its genetic architecture, this body of theory may have also shifted our perspective on the prospects of rescue. The conclusions from early models of abrupt change (Gomulkiewicz and Holt, 1995; Orr and Unckless, 2008) were pessimistic, suggesting that only large and mildly maladapted populations will be rescued. By considering additional complexities, such as plasticity, spatial structure, and species interactions, more recent rescue theory outlines ways that smaller populations may persist.

A large number of experiments examining evolutionary rescue have now been performed. Despite substantial cross-referencing, theoretical and experimental work has been done mostly independent from one another, often driven by similar interests in the same genetic or ecological factors that are known to be of importance for adaptation from general evolutionary theory. Experimental results are often broadly consistent with theory, both being explained by the same general evolutionary principles. With respect to more specific predictions, the largely independent development of theory and experiment often complicates meaningful comparisons. Close ties between both – e.g., experiments testing a specific idea from a theoretical study or theory tailored to a specific experiment to explain results – are rare. Nevertheless, examples of experiments (or real-world data) matching theory demonstrate the power of models to predict, capture, and explain empirical observations. Besides the co-development of theory and experiments, it would be similarly helpful if more modeling studies presented predictions in ways that make them directly accessible to experimental tests and if more experimental studies set out to test specific theoretical predictions.

Rescue has applied relevance in conservation, medicine, and agriculture. It is particularly noteworthy that application of theory to address contemporary challenges does not necessarily rely on complex models. For example, the fundamental quantitative genetics model for adaptation to gradual change (Lynch and Lande, 1993; Bürger and Lynch, 1995), developed in the 1990s, is used to predict whether a species is expected to survive forecasted climate change. In contexts of resistance, the refuge strategy applied to manage resistance to *Bt* crops traces back to fundamental population genetics models (Comins, 1977; Taylor and Georghiou, 1979). Similarly, the two-strike therapy under clinical trial originated in basic evolutionary models (Gatenby et al., 2020; Patil et al., 2025). Going forward, theory needs to be better informed by data from natural populations. In particular, we can now use genomic tools to explore the genetic underpinnings of evolutionary rescue in the wild, e.g. by identifying QTLs that are directly linked to the phenotype that allows survival in the new environment and by following changes in allele frequencies that may be linked to selection. Connecting what we can measure and observe to what we can model remains a huge continued challenge. While we often lack data to parameterize models for conservation, ample field and clinical data is available from monitoring resistance evolution. This data cannot only be used for applied models in these fields, but could also be informative for general theory.

We hope this review inspires progress in the study of evolutionary rescue, an important topic at the intersection of evolution and ecology of great applied relevance.

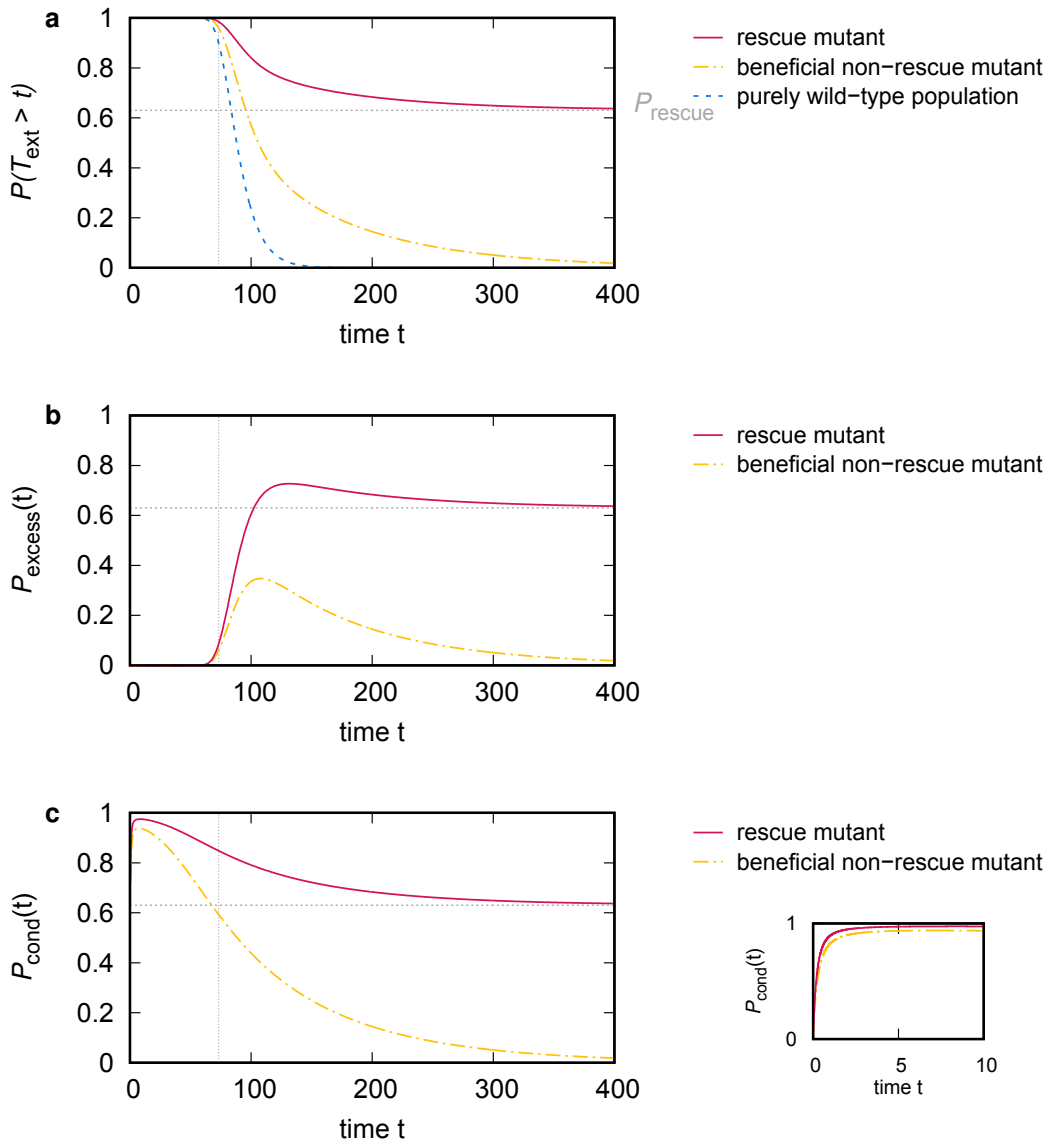

Figure 4: Distribution of persistence times (a), excess probabilities (b), and conditioned excess probabilities over time (c). The graphs compare the following scenarios: extinction of a population (i) composed entirely of wild-type individuals with negative growth rate $-r < 0$ (dashed blue line), (ii) composed of mostly wild-type individuals and a fraction p_0 of beneficial non-rescue mutants with negative growth rate $-r + s_b < 0$ (dash-dotted yellow line), (iii) composed of mostly wild-type individuals and a fraction p_0 of rescue mutants with positive growth rate $-r + s_R > 0$ (solid pink line). No new mutations occur during population decline. The definition of $P_{\mathrm{cond}}(t)$, generalized from Eq. (1), is only practical if the risk of extinction without evolution is not vanishingly small. As visible in the inset of panel c, for small times, when extinction with and without evolution is very small (compare also to panel a), $P_{\mathrm{cond}}(0)$ is zero and then shoots up to values close to 1, which is due to a vanishingly small fraction of extinctions without evolution. For reference, we indicate in the graphs the time at which the extinction risk of a purely wild-type population is 10% (thin vertical line). P_{rescue} denotes the probability of ultimate population survival. Since in the considered scenario, all populations go extinct in the absence of evolution, all proposed measures of rescue converge to this value for large times t. The distributions of persistence times are derived by jointly considering two single-type branching processes, as proposed by Holt and Gomulkiewicz (1997) and executed by Gomulkiewicz et al. (2017) based on branching diffusion. Details can be found in section S2 of Supplementary File S1. Parameters: $p_0 = 0.01$, $s_b = 0.07$, $s_R = 0.09$, $N_0 = 10,000$, $r = 0.08$; all types have the same death rate $\mu = 1.0$.

Box 1: The back story to Gomulkiewicz and Holt (1995), by Bob Holt

The population geneticist Richard Gomulkiewicz (1962-2023) was scheduled to give the plenary at the workshop 'Mathematical Models of Evolutionary Rescue' held in Plön in June 2023. After his tragic, unexpected death on March 23, 2023 (see Holt et al. 2023 for an obituary), the workshop organizers asked me to speak in his place, and in his honor. They suggested that because I had coauthored the paper introducing the term 'evolutionary rescue' (Gomulkiewicz and Holt, 1995), it would be fitting to provide a historical perspective on the origins of that paper, both in my talk, and as this Box in the emergent synthetic review.

Richard and I first met in 1991, when I helped recruit him to join the faculty at the University of Kansas. We hit it off immediately and had complementary research interests and expertise. Richard was a skilled and rigorous applied mathematician with expertise in population and quantitative genetics, and an abiding interest in applied ecology. I am a theoretical ecologist concerned with the integration of ecology and evolution. In conversations during his interview and after his move to Kansas, we mulled over issues of evolution in changing environments, and the task of understanding the ecology and evolution of species' range limits, two areas of inquiry at first glance distinct but in fact linked at a deep conceptual level. We focused on how two papers of mine recently published or in process (Holt, 1990; Holt and Gaines, 1992) might be extended. One had to do with evolution in changing environments, the other, the role of spatial demography in explaining niche conservatism and the evolutionary stability of range limits. Richard was intrigued with this line of collaborative research, tying together seemingly disparate strands of thought, because it provided an arena for him to apply his considerable skill set in theoretical population genetics, and also because of its patent implications for many applied issues.

In Holt (1990) I had reflected on the microevolutionary dimension of climate change. One section of that paper, titled "When does natural selection retard extinction?", included a summary of Pease et al. (1989), possibly the earliest evolutionary rescue model. Their model explored species' persistence via range shifts in continually changing environments, by splicing an evolutionary quantitative genetics model with a reaction-diffusion population dynamic model. The authors (whom Richard knew) considered a species distributed along a smooth environmental gradient; its locally optimal phenotype changed linearly in both space and time. I noted that applied to a closed population (e.g., an island), the deterministic persistence condition was simply that the additive genetic variance in absolute fitness had to equal or exceed the constant rate of environmental decay in average fitness. It occurred to me (and I suggested to Richard) that it would be instructive to examine alternative spatiotemporal scenarios, the simplest being an abrupt step-change in the local environment of a closed population, and to assume heuristically a threshold density below which one could assume extinction was inevitable. We worked through the logical consequences of these assumptions – this led to the 1995 paper (Gomulkiewicz and Holt, 1995).

This scenario also tied in with understanding species' range limits in stable environments. Barring absolute dispersal constraints, a range limit will be ecologically stable only if colonizing episodes (with individuals drawn from persisting populations) landing outside the extant range consistently fail to establish viable populations. Persistent populations are "sources", the habitats with recurrent colonization failures, "sinks". In a paper in the works in 1991 (Holt and Gaines, 1992), I noted (p. 435) two ways a population might suddenly find itself outside its niche (environmental conditions permitting persistence). First, in a closed population, abrupt environmental change could push a population outside its niche – the step-change scenario of Gomulkiewicz and Holt (1995). Second, in spatially open systems, a pulsed dispersal event could take an aliquot of a species from a habitat where it persists just fine (a 'source', where its $r > 0$) into a habitat where the environment lies outside its niche (a 'sink', where $r < 0$), with no further immigration.

This does not fundamentally differ from the first scenario, except in starting conditions (colonizing propagules likely have low abundance and genetic variation, compared to established populations). A range limit along a gradient will be evolutionarily stable, if propagules colonizing beyond that limit routinely decline to extinction, rather than adapting. Each colonizing bout

in effect provides a fresh opportunity for evolutionary rescue – or not. Evolutionary stability of range limits could reflect the fact that rescue is rare or even impossible during colonization in environments outside the current niche of the species.

These papers prompted Richard and I to craft an NSF proposal (funded in early 1996) titled "Niche Conservatism: A Population Dynamic Perspective", which first summarized the 1995 paper, then proposed elaborations, such as applying branching process theory with demographic stochasticity to rescue in clonal species (Holt and Gomulkiewicz, 1997; Gomulkiewicz et al., 1999), examining explicit multilocus models (Gomulkiewicz et al., 2010), and outlining theoretical directions for models of 'black hole' and 'leaky' sinks (see Box 6). Richard moved to Washington State University in 1996, but we continued collaborating, including exploring how our abstract ideas pertained to issues in applied ecology (Holt and Gomulkiewicz, 2004; Holt et al., 2005), and developing general evolutionary theory (Barfield et al., 2011) with implications for evolutionary rescue and many other topics. Beyond our joint work, Richard examined demography as constraints in evolution (Gomulkiewicz and Houle, 2009) and applied evolutionary rescue and source-sink theory to the evolution of antibiotic resistance in microbes (Sokurenko et al., 2006).

From 1995 until 2023, Richard and I (often with the help of my long-term research associate Dr. Michael Barfield) coauthored 15 papers (including one still in review), 13 of which dealt with evolutionary rescue in closed populations, or evolution in source-sink systems. We planned many more. It was an honor and pleasure to engage with Richard Gomulkiewicz's sharp intelligence and engaging persona, and I will be forever grateful to have had the pleasure of this long collaboration.

Box 2: Evolutionary rescue models to inform coral reef conservation

Rising sea temperatures are causing unprecedented declines in coral reefs. Yet, corals harbor genetic variation in heat tolerance (Dziedzic et al., 2019; Drury, 2020) – including local adaptation to a wide range of temperatures across space (Dixon et al., 2015) – and show thus adaptive potential. What role, if any, could evolution play in their struggle for persistence? Eco-evolutionary modeling is key in assessing the scope for coral adaptation and in identifying which conservation strategies may foster it. Recently, models have been applied to assess the potential of large numbers of connected coral reefs to adapt to increasing temperatures (e.g., Walsworth et al., 2019; Matz et al., 2020; McManus et al., 2021). In these models, reefs experience different sea surface temperatures as well as different rates of temperature increases, depending on their geographical locations. Larvae disperse between reefs, and the reefs thus form a network whose structure can, for example, be obtained from ocean circulation models. Assuming various degrees of genetic variance or phenotypic heritability, the models are applied to generate (qualitative) predictions of future coral reef cover and to identify the factors that determine the fate of a reef. All the above studies unanimously find that corals will go extinct in the absence of heritable adaptive variation (and thus evolution) but that evolution can enable at least partial persistence of coral reefs, highlighting the importance of evolutionary rescue in the persistence of coral reefs (see Figure B2.1 below). Besides genetic variation, dispersal of larvae is essential. While gene flow from cold to warm reefs is maladaptive, the positive effect of dispersal seems to dominate: the demographic effect of augmenting local population sizes where necessary and the evolutionary effect of immigration of larvae from warm to cold areas, i.e., larvae that are pre-adapted to warm temperatures to areas that experience warming. Adaptation in cold reefs seems to mostly rely on this immigration while hot reefs adapt from local genetic variation.

The insights from eco-evolutionary modeling result in concrete recommendations for conservation actions, as advocated for in Colton et al. (2022). These recommendations especially concern the choice of reefs for protection from other stress, such as sewage pollution and overfishing, which leads to increased competition from macroalgae, to prevent additional population decline ('marine protected areas'). The models suggest that protecting a diversity of reefs is optimal – cold reefs as climate-change refugia and warm reefs as sources of pre-adapted larvae – and that preserving connectivity to allow for dispersal between reefs is essential. Importantly, ignoring the potential for evolution may lead to the identification of sub-optimal strategies such as the popular 'refugia' strategy, which entirely focuses on the protection of cold reefs. All studies find that adaptation is more likely under slower warming, highlighting a reduction of gas emissions as the most important action on a global scale.

Gathering the scientific knowledge needed for effective conservation programs is the first step to the conservation of coral reefs – the second is to bring this science to action. NGOs contribute to both of these aims. The Coral Reef Alliance (`https://coral.org`) was involved in several of the modeling studies discussed in this box (see also Uecker, 2025). These models clearly show that protecting diversity is key. What is currently missing are good estimates for the adaptive genetic variation present in each reef – a gap in knowledge that the Coral Reef Alliance currently aims to fill (Helen Fox, personal communication). The insights from the above models will then further guide the design of networks of protected reefs. For the eventual establishment of networks of marine protected areas, NGOs advise governments and engage with stakeholders, which for example also includes outreach in local communities.

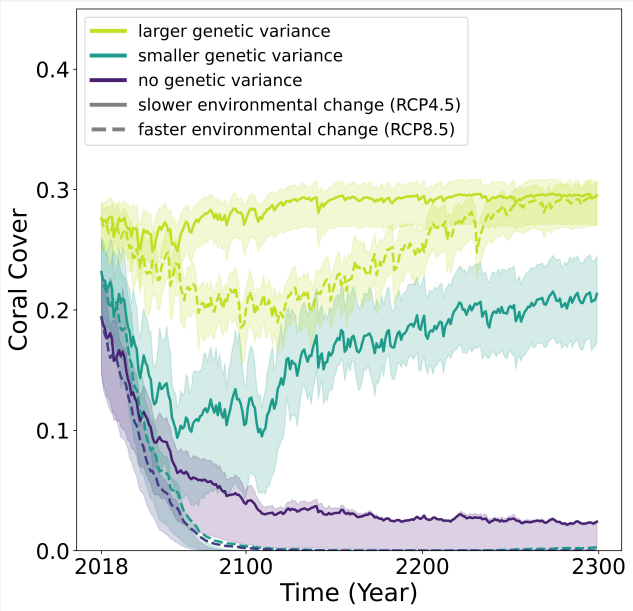

Figure B2.1: Projected coral reef cover in the Caribbean, Southwest Pacific, and Coral Triangle for different levels of genetic variance and climate change scenarios as obtained in the modeling study by McManus et al. (2021). The lines show the mean across all reefs and the error bounds the 25th and 75th percentiles among reefs. The two scenarios modeled correspond to an intermediate reduction in greenhouse emissions over time (RCP 4.5; solid lines) and the worst-case scenario of continued emissions (RCP 8.5; dashed lines); RCP stands for 'Representative Concentration Pathways', which represent projections of future greenhouse gas concentrations under various emission scenarios. The figure shows that without the capacity to evolve ('no genetic variance'), the coral reefs will go extinct, irrespective of the rate of environmental change (purple color). For a large enough genetic variance (light green), the reefs survive for both slow and fast environmental change, while for smaller genetic variance, successful adaptation crucially depends on the rate of environmental change (dark green). Figure adapted from Figure 1 in McManus et al. (2021) based on the data publicly available on Zenodo (doi: 10.5281/zenodo.4784134).

Box 3: The fundamental quantitative genetics models rescue

Let an individual's phenotype be the sum of an additive genetic and environmental component, $z = g + e$, which are independent with means $\bar{g}_t$ and 0 and variances $\sigma^2_{g,t}$ and σ^2_e. Assume non-overlapping generations and that the absolute fitness of an individual with phenotype z is

where $W_{\max}$ is the maximum fitness, $1/\omega^2$ is the strength of stabilizing selection on phenotype, and θ_t is the optimum phenotype in generation t. Assuming z is normally distributed, the population mean viability is

$$\overline{W_t} = W_{\max}\sqrt{\frac{\omega^2}{V_t}}\exp\left[-\frac{(\theta_t - \bar{g}_t)^2}{2V_t}\right], \tag{B3.1}$$

where $V_t = \sigma^2_{g,t}+\sigma^2_e+\omega^2$. Assuming also a constant genetic variance, $\sigma^2_{g,t} = \sigma^2_g$ and $V_t = V$, and an optimum that can change linearly in time, $\theta_t = kt$, the mean genotypic value in generation t is normally distributed with expectation (Lande, 1976; Bürger and Lynch, 1995)

$$\mathbb{E}[\bar{g}_t] = kt - \frac{k}{\phi}[1-(1-\phi)^t] + (1-\phi)^t\bar{g}_0, \tag{B3.2}$$

where $\phi = \sigma^2_g/V$. The variance can also be derived (Lande, 1976; Bürger and Lynch, 1995).

Abrupt environmental change

Following an abrupt environmental change, such as the introduction of a pollutant or antibiotic, a population may suddenly find itself so maladapted that its mean fitness is below replacement, $\overline{W}_t < 1$, causing population decline. Evolutionary rescue occurs when a population persists by evolving fast enough that mean fitness rises above replacement before extinction.

Assuming deterministic evolution, $\bar{g}_t = \mathbb{E}[\bar{g}_t]$, and density-independent deterministic demography, the population size in generation t is

$$N_t = N_0\prod_{i=0}^{t-1}\overline{W}_i.$$

Using (B3.1) and (B3.2) with a static optimum ($k = 0$) initial mean deviation from the optimum $\theta - \bar{g}_0 = \bar{d}_0$, this simplifies to

$$N_t = N_0\left(W_{\max}\sqrt{\frac{\omega^2}{V}}\right)^t\exp\left[-\frac{\bar{d}_0^2}{2V}\frac{1-(1-\phi)^{2t}}{1-(1-\phi)^2}\right].$$

With deterministic demography no population ever truly goes extinct and so instead of asking if a population persists we ask how long a population spends below some critical size, N_c. Setting $N_t = N_c$ and rearranging, the times the population crosses this threshold are the solutions, t, to

$$\ln\frac{N_c}{N_0} = t\ln\left(W_{\max}\sqrt{\frac{\omega^2}{V}}\right) - \frac{\bar{d}_0^2}{2V}\frac{1-(1-\phi)^{2t}}{1-(1-\phi)^2},$$

which is equation 7 of Gomulkiewicz and Holt (1995). The crossing times are found numerically. The more time a population spends below the critical size the less likely it is to be rescued.

Gradual environmental change

Gradual environmental changes, such as climate warming, have typically been modeled as an indefinite linear increase in the phenotype that maximizes an individual's fitness. In most models of this process there is a steady-state where the rate of increase in the mean phenotype (the rate of evolution) matches the rate of increase in the optimum (the rate of environmental change).

If the population mean fitness is above replacement at the steady-state lag, then the population is said to be rescued by evolution. The primary result of most of these analyses is the maximum rate of environmental change that allows a mean fitness above replacement, known as the critical rate.

From (B3.2), after sufficient time the mean genotype has expectation $\bar{g}_\infty = k(t - 1/\phi)$. Assuming deterministic evolution for simplicity, plugging this into (B3.1) gives population mean fitness at steady-state,

$$\overline{W}_\infty = W_{\mathsf{max}}\sqrt{\frac{\omega^2}{V}}\exp\left[-\frac{(k/\phi)^2}{2V}\right]. \tag{B3.3}$$

Setting $\overline{W}_\infty = 1$ and solving for k gives the critical rate of environmental change,

$$k_c = \phi\sqrt{2V\ln\left(W_{\mathsf{max}}\sqrt{\frac{\omega^2}{V}}\right)}, \tag{B3.4}$$

which is equation 10 in Bürger and Lynch (1995) in the absence of genetic drift and environmental stochasticity.

Box 4: The probability of rescue in population genetics models

Population genetics models of evolutionary rescue consider the dynamics of discrete genotypes, among them (at least) one "rescue mutant" that can thrive in the new environment. In the simplest case, there are just two types – the maladapted wild type and the well-adapted mutant. To obtain an analytical approximation for the probability of evolutionary rescue, the mathematical analysis is typically based on the following assumptions and considerations (or generalizations thereof or on similar assumptions for models with discrete generations):

- The dynamics of the wild-type population – which is initially large – are well described deterministically. In the most basic model, the wild-type population decays exponentially until extinction.
- After onset of stress, rescue mutants arise from a (possibly time-inhomogeneous) Poisson process with a (possibly time-dependent) rate $\mu(t)$ (or a constant probability per per cell division) per wild-type individual. This is precisely true in a continuous-time birth-death model.
- Mutants may segregate in the population prior to stress. The distribution can for example be determined by diffusion theory or a birth-death process with immigration.
- Rescue mutants are initially rare, and the rescue mutant population therefore requires a stochastic treatment.
- Mutants reproduce and die independent from each other, also referred to as the branching property. This is often a good assumption in the critical phase of establishment while mutants are rare and unlikely to affect each other. It especially implies that mutant lineages suffer independent fates, i.e., after onset of stress, a mutant lineage founded by a single mutant has a survival or establishment probability p_{est} independent from all other mutant lineages. The establishment probability may depend on the time of appearance t of the founder mutant, $p_{\mathrm{est}}(t)$, since for example the environmental conditions may vary with time. Mathematical branching process theory can be applied to determine p_{est}.

Combining these assumptions, due to the thinning property of the Poisson process, "successful" mutant lineages (i.e., those that escape stochastic loss) appear by a time-inhomogeneous Poisson process with rate $\mu(t) \times p_{\mathsf{est}}(t)$ per wild-type individual after onset of stress. The total number of successful new mutants until extinction of the wild type is thus Poisson distributed with parameter $\int_0^\infty \mu(t) N_w(t) p_{\mathrm{est}}(t) \mathrm{d}t$. It follows that the probability of extinction of all new mutant lineages is given by $e^{-\int_0^\infty \mu(t) N_w(t) p_{\mathrm{est}}(t) \mathrm{d}t}$, and the probability of rescue from *de novo* mutations is thus obtained as

$$P_{\mathrm{rescue}}^{\textit{de novo}} = 1 - e^{-\int_0^\infty \mu(t) N_w(t) p_{\mathrm{est}}(t) \mathrm{d}t} = 1 - e^{-\lambda_{\mathrm{DN}} p_{\mathsf{est}}}, \tag{B4.1}$$

where the last equality holds if p_{est} are independent of time and $\lambda_{\mathrm{DN}} = \int_0^\infty \mu(t) N_w(t) \mathrm{d}t$, e.g., $\lambda_{\mathrm{DN}} = \frac{\mu N_0}{r}$ for an exponentially declining wild-type population, $N_w(t) = N_0 e^{-rt}$, and $\mu(t) = \mu$. If the number of pre-existing rescue mutants can furthermore be approximated by a Poisson distribution with mean λ_{SGV}, we obtain for the total probability of evolutionary rescue

$$P_{\mathrm{rescue}} = 1 - e^{-(\lambda_{\mathrm{SGV}} + \lambda_{\mathrm{DN}}) p_{\mathsf{est}}}. \tag{B4.2}$$

We note that this exponential form of the probability of evolutionary rescue can also be obtained if p_{est} is assumed to be very small without assuming that the numbers of rescue mutants before or after stress are Poisson distributed (e.g., Orr and Unckless, 2008). The first appearance in the literature, with arbitrary wild-type dynamics, is to our knowledge in Nissen-Meyer (1966).

Box 5: Connections between population and quantitative genetics models

While the quantitative and population genetics approaches largely agree in their key predictions, their underlying dynamics may differ. We therefore here compare the dynamics of deterministic population and quantitative genetics models under an abrupt environmental change. This is complicated by the different variables used in the two approaches. To compare we need to make some choices on what aspects of the dynamics to make equal.

We first set the initial and final rate of population size change the same. The rate of change in population size in a continuous-time haploid population genetics model and a continuous-time quantitative genetics model are

$$\text{population genetics:} \quad \frac{\mathrm{d}N}{\mathrm{d}t} = \bar{m}(q)N = ((1-q)s - r)N \tag{B5.1a}$$

$$\text{quantitative genetics:} \quad \frac{\mathrm{d}N}{\mathrm{d}t} = \bar{r}(d)N = \left(r_{\max} - \frac{\sigma_z^2}{2\omega^2} - \frac{d^2}{2\omega^2}\right)N, \tag{B5.1b}$$

where $\bar{m}(q)$ is the mean fitness for the continuous-time haploid population genetics model, averaged over the two genotypes, and $\bar{r}(d)$ is the mean fitness in the continuous-time quantitative genetics model (compare to the discrete-time model in Box 3 with $\bar{r} = \overline{\ln W}$). Thereby, $d = \theta - \bar{z}$ is the mean deviation from the optimum, and $\sigma_z^2 = \sigma_g^2 + \sigma_e^2$ the phenotypic variance. We therefore set $\bar{m}(q_0) = \bar{r}(d_0)$ and $\bar{m}(0) = \bar{r}(0)$ for the comparison.
We also put the evolutionary dynamics on the same timescale by equating the time it takes to reach a mean fitness of 0 in the two models. For this, we consider the evolutionary dynamics (from standing variance only) of the two models, which are approximately

$$\text{population genetics:} \quad \frac{\mathrm{d}q}{\mathrm{d}t} = -q(1-q)s, \tag{B5.2a}$$

$$\text{quantitative genetics:} \quad \frac{\mathrm{d}d}{\mathrm{d}t} = -\sigma_g^2 \frac{d}{\omega^2} \tag{B5.2b}$$

and determine the dynamics of $\bar{m}(q)$ and $\bar{r}(d)$ and thus the time when these turn from negative to positive.
From Equation (B5.2), we see that the population genetics model has a dynamic genetic variance, $q(1-q)$, maximized at $q = 0.5$, and a constant selection strength, s, while the fundamental quantitative genetics model has a constant genetic variance, σ_g^2, and a dynamic selection strength, d/ω^2, that linearly decreases with d. This leads to a key difference in how mean fitness evolves: in the population genetics model the mean fitness increases logistically but it exponentially approaches the maximum from the outset in the quantitative genetics model (Fig. B5.1a and b). The population dynamics differ in two ways (Fig. B5.1c and d). First, on a log scale the dynamics of population size in the population genetics model is roughly V-shaped, due to the exponential decline of the wild type and the exponential increase of the mutant. Meanwhile the dynamics of population size in the quantitative genetics model is more U-shaped, as the population spends more time with an intermediate mean phenotype and hence fitness. Second, the population genetics model tends to reach lower population sizes because evolution is initially slower when the mutant is rare and there is consequently limited genetic variance. This is caused by how we chose to standardize the models, by equating the time to a mean fitness of 0. We could alternatively set the initial genetic variance for fitness equal in the two models (see also Gomulkiewicz et al., 2010). This flips the second conclusion when the rescue allele is initially rare, as evolution initially speeds up over time in the population genetics model but slows down in the quantitative genetics model.

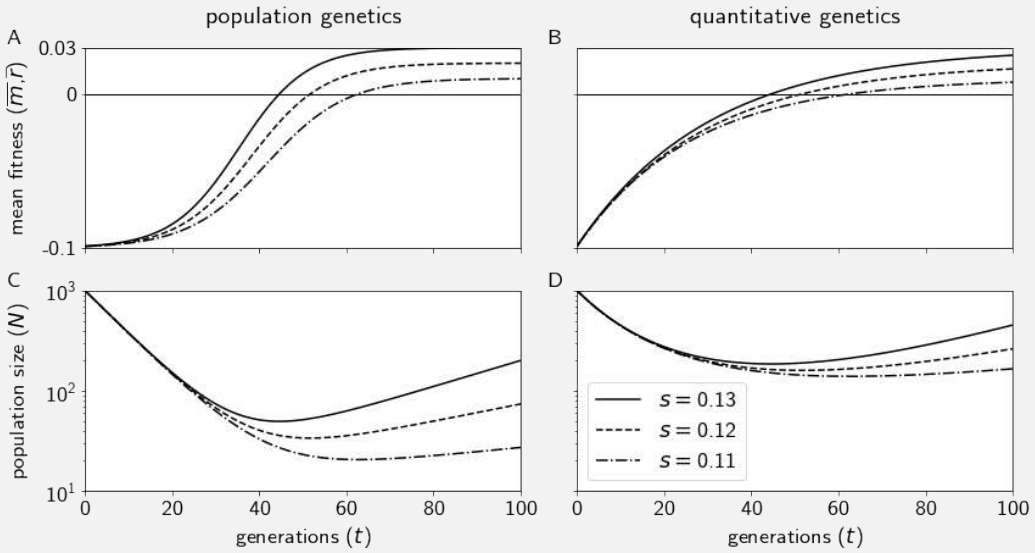

Figure B5.1: Comparing population genetics (A,C) and quantitative genetics (B,D) models (Eq. (B5.1)–(B5.2) above). The quantitative genetics model is parameterized by equating initial mean fitness, final mean fitness, and the time to reach a mean fitness of 0 with those in the population genetics model. In each panel, lines are shown corresponding to three values of the selective strength, s, in the population genetics model. Parameters: $r = 0.1, q_0 = 0.99$, $N_0 = 10^3$.

Box 6: Parallels between source-sink theory and evolutionary rescue theory

Recurrent immigration allows populations to persist in unfavorable environments. The analogue of rescue in this source-sink scenario is adaptation to the sink environment, sufficient to permit persistence without further evolution were immigration cut off. The quantitative question is how rapidly such adaptation occurs. Because this question has inspired some key work on evolutionary rescue (Box 1), here we summarize key insights from evolutionary source-sink models (reviewed in Kawecki, 2008; Holt, 2011) and point out parallels with evolutionary rescue theory. First, consider black-hole sinks (Holt and Gaines, 1992), where there is no migration from sink to source.

1) In single-locus models, there is an absolute (rather than relative) fitness criterion for the spread of a rare allele in a sink with recurrent immigration (Holt and Gomulkiewicz, 1997; Gomulkiewicz et al., 1999; LoFaro and Gomulkiewicz, 1999). The harsher the environment, the larger the effect a mutant must have on fitness for it to spread. One therefore needs to focus on the upper tail of the distribution of mutational effects on fitness, as in evolutionary rescue (Anciaux et al., 2018). 2) Recurrent immigration has multiple, contrasting evolutionary consequences. It can infuse adaptive genetic variation (Gomulkiewicz et al., 1999; Barton, 2001) but it can also hamper adaptation because maladapted immigrants compete and mate with better adapted residents (Gomulkiewicz et al., 1999; Barton and Etheridge, 2018). In evolutionary rescue, the rate of population decline has a similar effect. A slower rate of wild-type decline increases the cumulative number of mutations that arise before the population goes extinct (Orr and Unckless, 2008) but can also hinder rescue by increasing competition (Day and Read, 2016) or mating (Uecker and Hermisson, 2016; Uecker, 2017) between wild-type and rescue genotypes. 3) Temporal variation in selection can facilitate local adaptation in a sink, particularly if the environment is positively autocorrelated (Holt et al., 2004). This is because a stretch of less severe conditions can allow the population size to grow, breaking the population out of a positive feedback loop between small population size and weak local adaptation relative to the magnitude of gene swamping (Holt et al., 2003). Temporal variation in the environment can also facilitate evolutionary rescue in very harsh environments (Peniston et al., 2020), by increasing the expected cumulative number of wild-type individuals and thus the mutational input.

With leaky sinks (Holt and Gaines, 1992), bidirectional dispersal leads to a weighted averaging of selection across habitats, so that the fate of a novel mutation is determined by trade-offs in fitness among habitats (Holt and Gaines, 1992; Holt, 1996; Rousset, 1999; Kawecki and Holt, 2002). The harsher the sink the lower its weight will be and the more it will be discounted by selection. For a single population facing a novel environment, there is no analogy to going back to the source as an individual cannot go back in time. However, a harsher environmental change can increase the trade-off between fitness in the pre- and post-change environments (e.g., in fitness-landscape models, Anciaux et al., 2018), reducing the probability of rescue by standing genetic variation.

Box 7: Rescue in the wild? Tasmanian devils and the devil facial tumor disease

Tasmanian devil (*Sarcophilus harrisii*) populations have declined by over 80% due to the devil facial tumor disease (DFTD), a fatal transmissible cancer. Devils have been the focus of intense research, including decades of trapping and spotlight surveys (Jones et al., 2007; Lachish et al., 2007; Hamede et al., 2012; Lazenby et al., 2018), as well as many genomic studies (reviewed in Storfer et al., 2025) and demographic models (McCallum et al., 2009; Beeton and McCallum, 2011; Siska et al., 2018; Wells et al., 2019; Durrant et al., 2021; Cunningham et al., 2021; Clement et al., 2024). Despite severe initial declines, long-infected populations appear to have stabilized at low abundance (Lazenby et al., 2018; Cunningham et al., 2021). Simultaneously, there is strong evidence for rapid devil evolution in response to DFTD. To what degree, then, are Tasmanian devils an example of evolutionary rescue?

Is evolution sufficient to prevent Tasmanian devil extinction? Evidence for DFTD-induced rapid evolution in devils includes selection on genomic regions containing immune-related genes (Epstein et al., 2016; Hubert et al., 2018; Stahlke et al., 2021), one- and two-species genome-wide association studies (Margres et al., 2018; Gallinson et al., 2024) linking devil genetic variation, as well as the interaction between devil and tumor genomes, to phenotypic variation in several disease-related traits, and a estimates of substantial heritability in DFTD infection among devils (Strickland et al., 2024). However, whether evolution is sufficient to enable rescue is less clear; no empirical study has directly linked these evolutionary changes to changes in devil fitness (but see Wells et al. 2017). Eco-evolutionary modeling by Clement et al. (2024) predicted that coevolution contributes positively to long-term devil persistence, but that this effect is highly sensitive to rate of evolution of DFTD (for evidence of DFTD evolution see Kwon et al. 2020; Patton et al. 2020; Stammnitz et al. 2023). Moreover, devil population sizes were predicted to remain low and recover slowly, if at all.

Is evolution necessary to prevent Tasmanian devil extinction? DFTD is transmitted by biting behavior during feeding and mating (Hamede et al., 2008, 2009, 2013; Hamilton et al., 2019, 2020), suggesting a strong frequency-dependent component to transmission. This frequency-dependence, combined with DFTD's high lethality, led to initial predictions of high devil extinction risk (McCallum et al., 2009; Beeton and McCallum, 2011). However, DFTD transmission has declined in the intervening years (Patton et al., 2020) and more recent non-evolutionary models predict lower extinction probabilities (Siska et al., 2018; Wells et al., 2019; Cunningham et al., 2021). It is unclear whether these new predictions result from better data and more refined models or if they implicitly reflect the effect of rapid evolution. There are also ecological mechanisms that could potentially promote devil persistence. For example, behavioral changes may reduce transmission, as infected individuals have been shown to interact less frequently with conspecifics as their disease burden increases (Hamilton et al., 2020). Additionally, spatial modeling (Siska et al., 2018; Durrant et al., 2021) suggests that metapopulation effects could allow the population to persist at low densities.

Data availability

Supplementary File S2 has been uploaded to `https://github.com/mmosmond/rescue-review-network.git`.

Author contributions

Conceptualization: Peter Czuppon, Robert D. Holt, Guillaume Martin, Maria E. Orive, Matthew Osmond, Ophélie Ronce, Hildegard Uecker, Lindi Wahl, Masato Yamamichi

Formal analysis: Matthew Osmond, Hildegard Uecker

Investigation: Carla Alejandre, Ernesto Berríos-Caro, Dale Clement, Peter Czuppon, Puneeth Deraje, Jeremy Draghi, Asad Hasan, Robert D. Holt, Maria E. Orive, Matthew Osmond, Vrinda Ravi Kumar, Teemu Kuosmanen, Loïc Marrec, Guillaume Martin, Christin Nyhoegen, Ophélie Ronce, Hildegard Uecker, Lindi Wahl, Masato Yamamichi

Project administration: Matthew Osmond, Hildegard Uecker

Software: Léonard Dekens, Alexander Longcamp

Validation: everyone

Visualization: Léonard Dekens, Alexander Longcamp, Christin Nyhoegen, Matthew Osmond, Hildegard Uecker

Writing – original draft: Ernesto Berríos-Caro, Dale Clement, Peter Czuppon, Puneeth Deraje, Jeremy Draghi, Asad Hasan, Robert D. Holt, Maria E. Orive, Matthew Osmond, Vrinda Ravi Kumar, Loïc Marrec, Guillaume Martin, Christin Nyhoegen, Ophélie Ronce, Hildegard Uecker, Lindi Wahl, Masato Yamamichi

Writing – review & editing: everyone

Funding

The authors acknowledge funding from a large number of sources, specifically: Carla Alejandre: grants PID2021-122936NB-I00 and PID2024-159684NB-I00 funded by the Spanish Ministry of Science and Innovation/State Agency of Research MCIN AEI/10.13039/501100011033 and "ERDF A way of making Europe", and from the Consejería de Educación, Ciencia y Universidades de la Comunidad de Madrid through grant PIPF-2023/TEC29607; Ernesto Berríos-Caro: German Science Foundation (DFG) through a Walter Benjamin Position grant, GZ: BE 8013/1-1, Projektnummer: 512851323; Dale T. Clement: NSF DMS 2327799 (to N. K.), NSF DEB 2027446 (to A. S.); Léonard Dekens: Francis Crick Institute, which receives its core funding from Cancer Research UK (CC2240), the UK Medical Research Council (CC2240), and the Wellcome Trust, United Kingdom (CC2240); Asad Hasan: Natural Sciences and Engineering Research Council of Canada Doctoral Postgraduate Scholarship (PGS–D 601214); Robert D. Holt: National Science Foundation, DEB-1923513, and the joint NIFA-NSF-NIH Ecology and Evolution of Infectious Disease (EEID) award 2023-67015-40544, and the University of Florida Foundation; Guillaume Martin: project ANR-18-CE45-0019 RESISTE; Maria Orive: National Science Foundation DEB-1923495 and the University of Kansas; Matthew Osmond: Natural Sciences and Engineering Research Council of Canada, grant RGPIN–2021-03207; Vrinda Ravi Kumar: Czech VEDA Fellowships (project number CZ.02.01.01/00/22_010/0008117); Ophélie Ronce: Agence Nationale de la Recherche grant FloRes ANR22-CE02_0010; Lindi Wahl: Natural Sciences and Engineering Research Council of Canada, grant RGPIN-2019-06294; Masato Yamamichi: Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Scientific Research (KAKENHI) JP19K16223, JP20KK0169, JP21H02560, JP22H02688, JP22H04983, and JP25K02340, Australian Research Council (ARC) Discovery Project DP220102040, Japan Science and Technology Agency (JST) Core Research for Evolutional Science and Technology (CREST) JPMJCR23N5, Inamori Research Grant 2024, and Research Organization of Information and Systems (ROIS) Research Grant of Strategic Research Project

2024-SRP-10; Hildegard Uecker and Matthew Osmond: Workshop program of the Max Planck Institute for Evolutionary Biology.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This review article was initiated at the Workshop 'Mathematical models of evolutionary rescue', which took place in June 2023 at the Max Planck Institute for Evolutionary Biology in Plön. We would like to thank all workshop participants for their contributions. We are furthermore grateful to the institute's Workshop program for funding the workshop and Maren Lehmann and Corinna Plohmann for support with the organisation and logistics. We are grateful to Helen Fox (Conservation Science Director at the Coral Reef Alliance) for providing us with insights into the work of the Coral Reef Alliance, which entered Box 2, to Josianne Lachapelle, Graham Bell, and Andrew Gonzalez for answering very specific questions about their experiments, and to Alexey Mikaberidze for providing helpful references for the introduction. We thank Richard Gomulkiewicz for his many insights on evolutionary rescue and even more so for his humanity. He will always be missed.

References

Abu Awad, D. and Billiard, S. (2017). The double edged sword: The demographic consequences of the evolution of self-fertilization. *Evolution*, 71(5):1178–1190.

Agashe, D. (2009). The stabilizing effect of intraspecific genetic variation on population dynamics in novel and ancestral habitats. *The American Naturalist*, 174(2):255–267.

Agashe, D., Falk, J. J., and Bolnick, D. I. (2011). Effects of founding genetic variation on adaptation to a novel resource. *Evolution*, 65(9):2481–2491.

Aguilée, R., Raoul, G., Rousset, F., and Ronce, O. (2016). Pollen dispersal slows geographical range shift and accelerates ecological niche shift under climate change. *Proceedings of the National Academy of Sciences*, 113(39):E5741–E5748.

Alejandre, C., Calle-Espinosa, J., and Iranzo, J. (2024). Synergistic epistasis among cancer drivers can rescue early tumors from the accumulation of deleterious passengers. *PLOS Computational Biology*, 20:e1012081.

Alexander, H. K. and Bonhoeffer, S. (2012). Pre-existence and emergence of drug resistance in a generalized model of intra-host viral dynamics. *Epidemics*, 4(4):187–202.

Alexander, H. K. and MacLean, R. C. (2020). Stochastic bacterial population dynamics restrict the establishment of antibiotic resistance from single cells. *Proceedings of the National Academy of Sciences*, 117(32):19455–19464.

Alexander, H. K., Martin, G., Martin, O. Y., and Bonhoeffer, S. (2014). Evolutionary rescue: linking theory for conservation and medicine. *Evolutionary Applications*, 7(10):1161–1179.

Alfaro, M., Berestycki, H., and Raoul, G. (2017). The effect of climate shift on a species submitted to dispersion, evolution, growth, and nonlocal competition. *SIAM Journal on Mathematical Analysis*, 49(1):562–596.

Althaus, C. L. and De Boer, R. J. (2008). Dynamics of immune escape during HIV/SIV infection. *PLoS Computational Biology*, 4(7):e1000103.

Altrock, P. M., Liu, L. L., and Michor, F. (2015). The mathematics of cancer: integrating quantitative models. *Nature Reviews Cancer*, 15(12):730–745.

Anciaux, Y., Chevin, L.-M., Ronce, O., and Martin, G. (2018). Evolutionary rescue over a fitness landscape. *Genetics*, 209(1):265–279.

Anciaux, Y., Lambert, A., Ronce, O., Roques, L., and Martin, G. (2019). Population persistence under high mutation rate: from evolutionary rescue to lethal mutagenesis. *Evolution*, 73(8):1517–1532.

Anderson, J. T., DeMarche, M. L., Denney, D. A., Breckheimer, I., Santangelo, J., and Wadgymar, S. M. (2025). Adaptation and gene flow are insufficient to rescue a montane plant under climate change. *Science*, 388(6746):525–531.

Anstett, D. N., Anstett, J., Sheth, S. N., Moxley, D., Jahani, M., Huang, K., Todesco, M., Jordan, R., Lazaro-Guevara, J. M., Rieseberg, L. H., et al. (2024). Evolutionary rescue during extreme drought. *bioRxiv*.

Antia, R., Regoes, R. R., Koella, J. C., and Bergstrom, C. T. (2003). The role of evolution in the emergence of infectious diseases. *Nature*, 426(6967):658–661.

Ashander, J., Chevin, L.-M., and Baskett, M. L. (2016). Predicting evolutionary rescue via evolving plasticity in stochastic environments. *Proceedings of the Royal Society B: Biological Sciences*, 283(1839):20161690.

Ashander, J., Thompson, L. C., Sanchirico, J. N., and Baskett, M. L. (2019). Optimal investment to enable evolutionary rescue. *Theoretical Ecology*, 12(2):165–177.

Austin, D. and Anderson, R. (1999). Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 354(1384):721–738.

Azevedo, J. A., Faurby, S., Colli, G. R., Antonelli, A., and Werneck, F. P. (2024). Deforestation limits evolutionary rescue under climate change in amazonian lizards. *Diversity and Distributions*, 30(7):e13860.

Azevedo, R. B. and Olofsson, P. (2021). A branching process model of evolutionary rescue. *Mathematical Biosciences*, 341:108708.

Bagawade, R., van Benthem, K. J., and Wittmann, M. J. (2024). Multi-scale effects of habitat loss and the role of trait evolution. *Ecology and Evolution*, 14(1):e10799.

Barfield, M. and Holt, R. D. (2016). Evolutionary rescue in novel environments: towards improving predictability. *Evolutionary Ecology Research*, 17(6):771–786.

Barfield, M., Holt, R. D., and Gomulkiewicz, R. (2011). Evolution in stage-structured populations. *The American Naturalist*, 177(4):397–409.

Barton, N. H. (2001). Adaptation at the edge of a species' range. In *Integrating Ecology and Evolution in a Spatial Context*, pages 365–392. Cambridge University Press.

Barton, N. H. and Etheridge, A. (2018). Establishment in a new habitat by polygenic adaptation. *Theoretical Population Biology*, 122:110–127.

Baskett, M. L. and Gomulkiewicz, R. (2011). Introgressive hybridization as a mechanism for species rescue. *Theoretical Ecology*, 4(2):223–239.

Batarseh, T. N., Hug, S. M., Batarseh, S. N., and Gaut, B. S. (2020). Genetic mutations that drive evolutionary rescue to lethal temperature in *escherichia coli*. *Genome Biology and Evolution*, 12(11):2029–2044.

Bay, R. A., Rose, N. H., Logan, C. A., and Palumbi, S. R. (2017). Genomic models predict successful coral adaptation if future ocean warming rates are reduced. *Science Advances*, 3(11):e1701413.

Beeton, N. and McCallum, H. (2011). Models predict that culling is not a feasible strategy to prevent extinction of Tasmanian devils from facial tumour disease. *Journal of Applied Ecology*, 48(6):1315–1323.

Bell, G. (2013). Evolutionary rescue of a green alga kept in the dark. *Biology Letters*, 9(1):20120823.

Bell, G. (2017). Evolutionary rescue. *Annual Review of Ecology, Evolution, and Systematics*, 48:605–627.

Bell, G. and Collins, S. (2008). Adaptation, extinction and global change. *Evolutionary Applications*, 1(1):3–16.

Bell, G., Fugère, V., Barrett, R., Beisner, B., Cristescu, M., Fussmann, G., Shapiro, J., and Gonzalez, A. (2019). Trophic structure modulates community rescue following acidification. *Proceedings of the Royal Society B*, 286(1904):20190856.

Bell, G. and Gonzalez, A. (2009). Evolutionary rescue can prevent extinction following environmental change. *Ecology Letters*, 12(9):942–948.

Bell, G. and Gonzalez, A. (2011). Adaptation and evolutionary rescue in metapopulations experiencing environmental deterioration. *Science*, 332(6035):1327–1330.

Bennett, A. F. and Lenski, R. E. (1993). Evolutionary adaptation to temperature II. Thermal niches of experimental lines of *escherichia coli*. *Evolution*, 47(1):1–12.

Benning, J. W., Faulkner, A., and Moeller, D. A. (2023). Rapid evolution during climate change: demographic and genetic constraints on adaptation to severe drought. *Proceedings of the Royal Society B*, 290(1998):20230336.

Bergstrom, C. T., Lo, M., and Lipsitch, M. (2004). Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proceedings of the National Academy of Sciences*, 101(36):13285–13290.

Bertram, J., Gomez, K., and Masel, J. (2017). Predicting patterns of long-term adaptation and extinction with population genetics. *Evolution*, 71(2):204–214.

Bhat, A. S. and Guttal, V. (2025). Eco-evolutionary dynamics for finite populations and the noise-induced reversal of selection. *The American Naturalist*, 205(1):1–19.

Birkhead, B. G., Rankin, E. M., Gallivan, S., Dones, L., and Rubens, R. D. (1987). A mathematical model of the development of drug resistant to cancer chemotherapy. *European Journal of Cancer and Clinical Oncology*, 23(9):1421–1427.

Blanquart, F. (2019). Evolutionary epidemiology models to predict the dynamics of antibiotic resistance. *Evolutionary Applications*, 12(3):365–383.

Blechschmidt, J., Wittmann, M. J., and Bluml, C. (2020). Climate change and green turtle sex ratio - preventing possible extinction. *Genes*, 11(5):588.

Bocedi, G. and Reid, J. M. (2017). Feed-backs among inbreeding, inbreeding depression in sperm traits, and sperm competition can drive evolution of costly polyandry. *Evolution*, 71(12):2786–2802.

Bodbyl Roels, S. A. and Kelly, J. K. (2011). Rapid evolution caused by pollinator loss in *mimulus guttatus*. *Evolution*, 65(9):2541–2552.

Boeye, J., Travis, J. M., Stoks, R., and Bonte, D. (2013). More rapid climate change promotes evolutionary rescue through selection for increased dispersal distance. *Evolutionary Applications*, 6(2):353–364.

Bonhoeffer, S., Lipsitch, M., and Levin, B. R. (1997a). Evaluating treatment protocols to prevent antibiotic resistance. *Proceedings of the National Academy of Sciences*, 94(22):12106–12111.

Bonhoeffer, S., May, R. M., Shaw, G. M., and Nowak, M. A. (1997b). Virus dynamics and drug therapy. *Proceedings of the National Academy of Sciences*, 94(13):6971–6976.

Bono, L. M., Gensel, C. L., Pfennig, D. W., and Burch, C. L. (2015). Evolutionary rescue and the coexistence of generalist and specialist competitors: an experimental test. *Proceedings of the Royal Society B: Biological Sciences*, 282(1821):20151932.

Bonte, D., Hovestadt, T., and Poethke, H.-J. (2009). Sex-specific dispersal and evolutionary rescue in metapopulations infected by male killing endosymbionts. *BMC Evolutionary Biology*, 9(1):16.

Bourne, E. C., Bocedi, G., Travis, J. M., Pakeman, R. J., Brooker, R. W., and Schiffers, K. (2014). Between migration load and evolutionary rescue: dispersal, adaptation and the response of spatially structured populations to environmental change. *Proceedings of the Royal Society B: Biological Sciences*, 281(1778):20132795.

Bozic, I., Reiter, J. G., Allen, B., Antal, T., Chatterjee, K., Shah, P., Moon, Y. S., Yaqubie, A., Kelly, N., Le, D. T., et al. (2013). Evolutionary dynamics of cancer in response to targeted combination therapy. *eLife*, 2:e00747.

Bradlow, B. (1920). The use and abuse of the sulphonamides in general practice. *South African Medical Journal*, 18(9):161–163.

Brady, R. and Enderling, H. (2019). Mathematical models of cancer: when to predict novel therapies, and when not to. *Bulletin of Mathematical Biology*, 81(10):3722–3731.

Bukkuri, A., Pienta, K. J., Amend, S. R., Austin, R. H., Hammarlund, E. U., and Brown, J. S. (2023a). The contribution of evolvability to the eco-evolutionary dynamics of competing species. *Ecology and Evolution*, 13(10):e10591.

Bukkuri, A., Pienta, K. J., Hockett, I., Austin, R. H., Hammarlund, E. U., Amend, S. R., and Brown, J. S. (2023b). Modeling cancer's ecological and evolutionary dynamics. *Medical Oncology*, 40(4):109.

Bürger, R. (1999). Evolution of genetic variability and the advantage of sex and recombination in changing environments. *Genetics*, 153(2):1055–1069.

Bürger, R. and Lynch, M. (1995). Evolution and extinction in a changing environment: a quantitative-genetic analysis. *Evolution*, 49(1):151–163.

Bush, A., Mokany, K., Catullo, R., Hoffmann, A., Kellermann, V., Sgrò, C., McEvey, S., and Ferrier, S. (2016). Incorporating evolutionary adaptation in species distribution modelling reduces projected vulnerability to climate change. *Ecology Letters*, 19(12):1468–1478.

Campion, J. J., McNamara, P. J., and Evans, M. E. (2005). Pharmacodynamic modeling of ciprofloxacin resistance in *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, 49(1):209–219.

Carja, O. and Plotkin, J. B. (2019). Evolutionary rescue through partly heritable phenotypic variability. *Genetics*, 211(3):977–988.

Carlson, S. M., Cunningham, C. J., and Westley, P. A. (2014). Evolutionary rescue in a changing world. *Trends in Ecology & Evolution*, 29(9):521–530.

Carroll, L. (1872). *Through the looking-glass, and what Alice found there*. Macmillan and Co.

Cheek, D. and Antal, T. (2018). Mutation frequencies in a birth–death branching process. *The Annals of Applied Probability*, 28(6):3922–3947.

Cheptou, P.-O. (2019). Does the evolution of self-fertilization rescue populations or increase the risk of extinction? *Annals of Botany*, 123(2):337–345.

Chevin, L.-M. (2013). Genetic constraints on adaptation to a changing environment. *Evolution*, 67(3):708–721.

Chevin, L.-M. and Bridle, J. (2025). Impacts of limits to adaptation on population and community persistence in a changing environment. *Philosophical Transactions B*, 380(1917):20230322.

Chevin, L.-M., Cotto, O., and Ashander, J. (2017). Stochastic evolutionary demography under a fluctuating optimum phenotype. *The American Naturalist*, 190(6):786–802.

Chevin, L.-M. and Lande, R. (2010). When do adaptive plasticity and genetic evolution prevent extinction of a density-regulated population? *Evolution*, 64(4):1143–1150.

Chevin, L.-M., Lande, R., and Mace, G. M. (2010). Adaptation, plasticity, and extinction in a changing environment: towards a predictive theory. *PLOS Biology*, 8(4):e1000357.

Ching, J., Musheyev, S. A., Chowdhury, D., Kim, J. A., Choi, Y., and Dennehy, J. J. (2013). Migration enhances adaptation in bacteriophage populations evolving in ecological sinks. *Evolution*, 67(1):10–17.

Christie, M. R. and Searle, C. L. (2018). Evolutionary rescue in a host–pathogen system results in coexistence not clearance. *Evolutionary Applications*, 11(5):681–693.

Clark-Wolf, T., Boersma, P. D., Plard, F., Rebstock, G. A., and Abrahms, B. (2024). Increasing environmental variability inhibits evolutionary rescue in a long-lived vertebrate. *Proceedings of the National Academy of Sciences*, 121(34):e2406314121.

Clement, D. T., Gallinson, D. G., Hamede, R. K., Jones, M. E., Margres, M. J., McCallum, H., and Storfer, A. (2024). Coevolution promotes the coexistence of Tasmanian devils and a fatal, transmissible cancer. *Evolution*, 79(1):100–118.

Clement, D. T., Neylan, I. P., Roberts, N. J., Schreiber, S. J., Trimmer, P. C., and Sih, A. (2023). Evolutionary history mediates population response to rapid environmental change through within-generational and transgenerational plasticity. *The American Naturalist*, 201(5):E90–E109.

Coldman, A. and Goldie, J. (1983). A model for the resistance of tumor cells to cancer chemotherapeutic agents. *Mathematical Biosciences*, 65(2):291–307.

Colijn, C. and Cohen, T. (2015). How competition governs whether moderate or aggressive treatment minimizes antibiotic resistance. *eLife*, 4:e10559.

Colijn, C., Cohen, T., Ganesh, A., and Murray, M. (2011). Spontaneous emergence of multiple drug resistance in tuberculosis before and during therapy. *PLOS ONE*, 6(3):e18327.

Colton, M. A., McManus, L. C., Schindler, D. E., Mumby, P. J., Palumbi, S. R., Webster, M. M., Essington, T. E., Fox, H. E., Forrest, D. L., Schill, S. R., et al. (2022). Coral conservation in a warming world must harness evolutionary adaptation. *Nature Ecology & Evolution*, 6(10):1405–1407.

Comins, H. N. (1977). The development of insecticide resistance in the presence of migration. *Journal of Theoretical Biology*, 64(1):177–197.

Condie, S. A., Anthony, K. R., Babcock, R. C., Baird, M. E., Beeden, R., Fletcher, C. S., Gorton, R., Harrison, D., Hobday, A. J., Plagányi, É. E., et al. (2021). Large-scale interventions may delay decline of the great barrier reef. *Royal Society Open Science*, 8(4):201296.

Converse, S. J., Bailey, L. L., Mosher, B. A., Funk, W. C., Gerber, B. D., and Muths, E. (2017). A model to inform management actions as a response to chytridiomycosis-associated decline. *EcoHealth*, 14:144–155.

Cortez, M. H. and Yamamichi, M. (2019). How (co)evolution alters predator responses to increased mortality: extinction thresholds and hydra effects. *Ecology*, 100(10):e02789.

Cotto, O. and Ronce, O. (2014). Maladaptation as a source of senescence in habitats variable in space and time. *Evolution*, 68(9):2481–2493.

Cotto, O., Sandell, L., Chevin, L.-M., and Ronce, O. (2019). Maladaptive shifts in life history in a changing environment. *The American Naturalist*, 194(4):558–573.

Cotto, O., Wessely, J., Georges, D., Klonner, G., Schmid, M., Dullinger, S., Thuiller, W., and Guillaume, F. (2017). A dynamic eco-evolutionary model predicts slow response of alpine plants to climate warming. *Nature Communications*, 8(1):15399.

Couce, A., Rodríguez-Rojas, A., and Blázquez, J. (2015). Bypass of genetic constraints during mutator evolution to antibiotic resistance. *Proceedings of the Royal Society B: Biological Sciences*, 282(1804):20142698.

Couper, L. I., Dodge, T. O., Hemker, J. A., Kim, B. Y., Exposito-Alonso, M., Brem, R. B., Mordecai, E. A., and Bitter, M. C. (2025). Evolutionary adaptation under climate change: *Aedes sp.* demonstrates potential to adapt to warming. *Proceedings of the National Academy of Sciences*, 122(2):e2418199122.

Couper, L. I., Farner, J. E., Caldwell, J. M., Childs, M. L., Harris, M. J., Kirk, D. G., Nova, N., Shocket, M., Skinner, E. B., Uricchio, L. H., et al. (2021). How will mosquitoes adapt to climate warming? *eLife*, 10:e69630.

Cunningham, C. X., Comte, S., McCallum, H., Hamilton, D. G., Hamede, R., Storfer, A., Hollings, T., Ruiz-Aravena, M., Kerlin, D. H., Brook, B. W., Hocking, G., and Jones, M. E. (2021). Quantifying 25 years of disease-caused declines in Tasmanian devil populations: host density drives spatial pathogen spread. *Ecology Letters*, 24(5):958–969.

Curtis, C. (1985). Theoretical models of the use of insecticide mixtures for the management of resistance. *Bulletin of Entomological Research*, 75(2):259–266.

Czuppon, P., Blanquart, F., Uecker, H., and Débarre, F. (2021). The effect of habitat choice on evolutionary rescue in subdivided populations. *The American Naturalist*, 197(6):625–643.

Czuppon, P., Day, T., Débarre, F., and Blanquart, F. (2023). A stochastic analysis of the interplay between antibiotic dose, mode of action, and bacterial competition in the evolution of antibiotic resistance. *PLOS Computational Biology*, 19(8):e1011364.

Dallinger, W. H. (1887). The president's address. *Journal of the Royal Microscopical Society*, 7(2):185–199.

Day, T. and Read, A. F. (2016). Does high-dose antimicrobial chemotherapy prevent the evolution of resistance? *PLOS Computational Biology*, 12(1):e1004689.

de Mazancourt, C., Johnson, E., and Barraclough, T. G. (2008). Biodiversity inhibits species' evolutionary responses to changing environments. *Ecology Letters*, 11(4):380–388.

De Vos, J. M., Joppa, L. N., Gittleman, J. L., Stephens, P. R., and Pimm, S. L. (2015). Estimating the normal background rate of species extinction. *Conservation Biology*, 29(2):452–462.

DeFilippo, L. B., McManus, L. C., Schindler, D. E., Pinsky, M. L., Colton, M. A., Fox, H. E., Tekwa, E., Palumbi, S. R., Essington, T. E., and Webster, M. M. (2022). Assessing the potential for demographic restoration and assisted evolution to build climate resilience in coral reefs. *Ecological Applications*, 32(7):e2650.

Degottex-Féry, F. and Cheptou, P.-O. (2023). A model for evolutionary rescue through plant mating system. *Evolutionary Ecology*, 37:893–908.

Dekens, L. (2024). Sharp habitat shifts, evolutionary tipping points and rescue: Quantifying the perilous path of a specialist species towards a refugium in a changing environment. *Theoretical Population Biology*, 160:25–48.

Delaney, O., Letten, A. D., and Engelstädter, J. (2025). Optimal antimicrobial dosing combinations when drug-resistance mutation rates differ. *Evolution*, page qpaf123.

DeLong, J. P. and Belmaker, J. (2019). Ecological pleiotropy and indirect effects alter the potential for evolutionary rescue. *Evolutionary Applications*, 12(3):636–654.

Deraje, P. and Osmond, M. M. (2025). Quasi epigenetic equilibrium: the implications of plasticity and variability on evolution and extinction. *bioRxiv*, page 2025.08.27.672696.

Deraje, P. and Uecker, H. (2025). How do mate-finding Allee effects affect evolutionary rescue? *bioRxiv*, pages 2025–09.

Devresse, L., Way, F., Postic, T., de Coligny, F., and Morin, X. (2025). Evolutionary rescue in a mixed beech–fir forest: insights from a quantitative-genetics approach in a process-based model. *Oikos*, page e11661.

Dewan, I. and Uecker, H. (2025). Evolutionary rescue of bacterial populations by heterozygosity on multicopy plasmids. *Journal of Mathematical Biology*, 90(3):1–34.

Diggle, A. J., Neve, P., and Smith, F. P. (2003). Herbicides used in combination can reduce the probability of herbicide resistance in finite weed populations. *Weed Research*, 43(5):371–382.

Diniz-Filho, J. A. F., Souza, K. S., Bini, L. M., Loyola, R., Dobrovolski, R., Rodrigues, J. F. M., Lima-Ribeiro, S., Terribile, L. C., Rangel, T. F., Bione, I., et al. (2019). A macroecological approach to evolutionary rescue and adaptation to climate change. *Ecography*, 42(6):1124–1141.

DiRenzo, G. V., Zipkin, E. F., Grant, E. H. C., Royle, J. A., Longo, A. V., Zamudio, K. R., and Lips, K. R. (2018). Eco-evolutionary rescue promotes host–pathogen coexistence. *Ecological Applications*, 28(8):1948–1962.

Dixon, G. B., Davies, S. W., Aglyamova, G. V., Meyer, E., Bay, L. K., and Matz, M. V. (2015). Genomic determinants of coral heat tolerance across latitudes. *Science*, 348(6242):1460–1462.

Dostál, P. (2022). Evolution of plasticity prevents postinvasion extinction of a native forb. *Proceedings of the National Academy of Sciences of the United States of America*, 119(32):e2118866119.

Draghi, J. A., McGlothlin, J. W., and Kindsvater, H. K. (2024). Demographic feedbacks during evolutionary rescue can slow or speed adaptive evolution. *Proceedings of the Royal Society B: Biological Sciences*, 291(2016):20231553.

Drury, C. (2020). Resilience in reef-building corals: The ecological and evolutionary importance of the host response to thermal stress. *Molecular Ecology*, 29(3):448–465.

Duputié, A., Massol, F., Chuine, I., Kirkpatrick, M., and Ronce, O. (2012). How do genetic correlations affect species range shifts in a changing environment?: Multivariate adaptation and range shifts. *Ecology Letters*, 15(3):251–259.

Durkee, L. F., Olazcuaga, L., Melbourne, B. A., and Hufbauer, R. A. (2024). Immigration delays but does not prevent adaptation following environmental change: experimental evidence. *Journal of Evolutionary Biology*, 37(6):665–676.

Durrant, R., Hamede, R. K., Wells, K., and Lurgi, M. (2021). Disruption of metapopulation structure reduces Tasmanian devil facial tumour disease spread at the expense of abundance and genetic diversity. *Pathogens*, 10(12):1592.

Dziedzic, K. E., Elder, H., Tavalire, H., and Meyer, E. (2019). Heritable variation in bleaching responses and its functional genomic basis in reef-building corals (*Orbicella faveolata*). *Molecular Ecology*, 28(9):2238–2253.

Ehrlich, P. (1907). The Harben Lectures 1907, Experimental researches on specific therapeutics. *Journal of the Royal Institute of Public Health*, 15(7):385–403.

Ehrlich, P. (1911). Aus Theorie und Praxis der Chemotherapie. *Folia Serologica*, 7:697–714.

Elie, B., Selinger, C., and Alizon, S. (2022). The source of individual heterogeneity shapes infectious disease outbreaks. *Proceedings of the Royal Society B*, 289(1974):20220232.

Engen, S. and Sæther, B.-E. (2017). Extinction risk and lack of evolutionary rescue under resource depletion or area reduction. *The American Naturalist*, 190(1):73–82.

Epstein, B., Jones, M., Hamede, R. K., Hendricks, S., McCallum, H., Murchison, E. P., Schönfeld, B., Wiench, C., Hohenlohe, P., and Storfer, A. (2016). Rapid evolutionary response to a transmissible cancer in Tasmanian devils. *Nature Communications*, 7(1):12684.

Feder, A. F., Rhee, S.-Y., Holmes, S. P., Shafer, R. W., Petrov, D. A., and Pennings, P. S. (2016). More effective drugs lead to harder selective sweeps in the evolution of drug resistance in hiv-1. *eLife*, 5:e10670.

Feiner, N., Brun-Usan, M., and Uller, T. (2021). Evolvability and evolutionary rescue. *Evolution & Development*, 23(4):308–319.

Ferriere, R. and Legendre, S. (2013). Eco-evolutionary feedbacks, adaptive dynamics and evolutionary rescue theory. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120081.

Finand, B., Monnin, T., and Loeuille, N. (2024). Evolution of dispersal and the maintenance of fragmented metapopulations. *Oikos*, 2024(2):e10490.

Fisher, R. A. (1930). *The genetical theory of natural selection*. Claredon Press.

Fleming, S. A. (26 Nov 2025). Nobel Lecture. NobelPrize.org. Nobel Prize Outreach 2025. `https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/`. Accessed 2925-11-25.

Flynn, K. J. and Skibinski, D. O. (2020). Exploring evolution of maximum growth rates in plankton. *Journal of Plankton Research*, 42(5):497–513.

Foerster, S., Unemo, M., Hathaway, L. J., Low, N., and Althaus, C. L. (2016). Time-kill curve analysis and pharmacodynamic modelling for in vitro evaluation of antimicrobials against neisseria gonorrhoeae. *BMC microbiology*, 16(1):216.

Fogarty, L. and Kandler, A. (2020). The fundamentals of cultural adaptation: implications for human adaptation. *Scientific Reports*, 10(1):14318.

Foo, J., Chmielecki, J., Pao, W., and Michor, F. (2012). Effects of pharmacokinetic processes and varied dosing schedules on the dynamics of acquired resistance to erlotinib in EGFR-mutant lung cancer. *Journal of Thoracic Oncology*, 7(10):1583–1593.

Foo, J. and Michor, F. (2014). Evolution of acquired resistance to anti-cancer therapy. *Journal of Theoretical Biology*, 355:10–20.

Fournier-Level, A., Perry, E. O., Wang, J. A., Braun, P. T., Migneault, A., Cooper, M. D., Metcalf, C. J. E., and Schmitt, J. (2016). Predicting the evolutionary dynamics of seasonal adaptation to novel climates in *Arabidopsis thaliana*. *Proceedings of the National Academy of Sciences of the United States of America*, 113(20):E2812–E2821.

Fox, W., Ellard, G. A., and Mitchison, D. A. (1999). Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *The International Journal of Tuberculosis and Lung Disease*, 3(10):S231–S279.

Freitas, O. and Campos, P. R. (2024a). The role of epistasis in evolutionary rescue. *The European Physical Journal E*, 47(7):49.

Freitas, O. and Campos, P. R. (2024b). Understanding evolutionary rescue and parallelism in response to environmental stress. *Evolution*, 78(8):1453–1463.

Fruet, C., Müller, E. L., Loverdo, C., and Bitbol, A.-F. (2025). Spatial structure facilitates evolutionary rescue by drug resistance. *PLOS Computational Biology*, 21(4):e1012861.

Fryer, H. R., Frater, J., Duda, A., Roberts, M. G., Investigators, S. T., Phillips, R. E., and McLean, A. R. (2010). Modelling the evolution and spread of HIV immune escape mutants. *PLoS Pathogens*, 6(11):e1001196.

Fugère, V., Hébert, M.-P., Da Costa, N. B., Xu, C. C., Barrett, R. D., Beisner, B. E., Bell, G., Fussmann, G. F., Shapiro, B. J., Yargeau, V., et al. (2020). Community rescue in experimental phytoplankton communities facing severe herbicide pollution. *Nature Ecology & Evolution*, 4(4):578–588.

Fulgione, A., Neto, C., Elfarargi, A. F., Tergemina, E., Ansari, S., Göktay, M., Dinis, H., Döring, N., Flood, P. J., Rodriguez-Pacheco, S., et al. (2022). Parallel reduction in flowering time from de novo mutations enable evolutionary rescue in colonizing lineages. *Nature Communications*, 13(1):1461.

Funk, W., Forester, B. R., Converse, S. J., Darst, C., and Morey, S. (2019). Improving conservation policy with genomics: a guide to integrating adaptive potential into us endangered species act decisions for conservation practitioners and geneticists. *Conservation Genetics*, 20:115–134.

Fussmann, G. F. and Gonzalez, A. (2013). Evolutionary rescue can maintain an oscillating community undergoing environmental change. *Interface Focus*, 3(6):20130036.

Gallinson, D. G., Kozakiewicz, C. P., Rautsaw, R. M., Beer, M. A., Ruiz-Aravena, M., Compte, S., Hamilton, D. G., Kerlin, D. H., McCallum, H., Hamede, R. K., Jones, M. E., Storfer, A., McMinds, R., and Margres, M. J. (2024). Intergenomic signatures of coevolution between Tasmanian devils and an infectious cancer. *Proceedings of the National Academy of Sciences*, 121(12):e2307780121.

Gandon, S., Guillemet, M., Gatchitch, F., Nicot, A., Renaud, A. C., Tremblay, D. M., and Moineau, S. (2024). Building pyramids against the evolutionary emergence of pathogens. *Proceedings of the Royal Society B*, 291(2018):20231529.

Gandon, S., Hochberg, M. E., Holt, R. D., and Day, T. (2013). What limits the evolutionary emergence of pathogens? *Philosophical transactions of the Royal Society B: biological sciences*, 368(1610):20120086.

Gandon, S., Lambert, A., Voinson, M., Day, T., and Parsons, T. L. (2025). The speed of vaccination rollout and the risk of pathogen adaptation. *Journal of the Royal Society Interface*, 22(228):20250060.

Garcia-Ulloa II, M., Elena Escalante, A., Moreno-Letelier, A., Eguiarte, L. E., and Souza, V. (2021). Evolutionary rescue of an environmental *Pseudomonas otitidis* in response to anthropogenic perturbation. *Frontiers in Microbiology*, 11:563885.

Garnier, J., Cotto, O., Bouin, E., Bourgeron, T., Lepoutre, T., Ronce, O., and Calvez, V. (2023). Adaptation of a quantitative trait to a changing environment: New analytical insights on the asexual and infinitesimal sexual models. *Theoretical Population Biology*, 152:1–22.

Garoff, L., Pietsch, F., Huseby, D. L., Lilja, T., Brandis, G., and Hughes, D. (2020). Population bottlenecks strongly influence the evolutionary trajectory to fluoroquinolone resistance in *Escherichia coli*. *Molecular Biology and Evolution*, 37(6):1637–1646.

Gassmann, A. and Futuyma, D. (2005). Consequence of herbivory for the fitness cost of herbicide resistance: photosynthetic variation in the context of plant–herbivore interactions. *Journal of Evolutionary Biology*, 18(2):447–454.

Gatenby, R. A., Artzy-Randrup, Y., Epstein, T., Reed, D. R., and Brown, J. S. (2020). Eradicating metastatic cancer and the eco-evolutionary dynamics of anthropocene extinctions. *Cancer Research*, 80:613–623.

Gatenby, R. A., Silva, A. S., Gillies, R. J., and Frieden, B. R. (2009). Adaptive therapy. *Cancer research*, 69(11):4894–4903.

Ge, X., Newman, J. A., and Griswold, C. K. (2024). Geographic variation in evolutionary rescue under climate change in a crop pest–predator system. *Evolutionary Applications*, 17(7):e13750.

Geoffroy, F., Traulsen, A., and Uecker, H. (2022). Vaccination strategies when vaccines are scarce: On conflicts between reducing the burden and avoiding the evolution of escape mutants. *Journal of the Royal Society Interface*, 19(191):20220045.

Geoffroy, F. and Uecker, H. (2023). Limits to evolutionary rescue by conjugative plasmids. *Theoretical Population Biology*, 154:102–117.

Gienapp, P., Lof, M., Reed, T. E., McNamara, J., Verhulst, S., and Visser, M. E. (2013). Predicting demographically sustainable rates of adaptation: can great tit breeding time keep pace with climate change? *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120289.

Gifford, D. R., Berríos-Caro, E., Joerres, C., Suñé, M., Forsyth, J. H., Bhattacharyya, A., Galla, T., and Knight, C. G. (2023). Mutators can drive the evolution of multi-resistance to antibiotics. *PLoS Genetics*, 19(6):e1010791.

Gignoux-Wolfsohn, S. A., Pinsky, M. L., Kerwin, K., Herzog, C., Hall, M., Bennett, A. B., Fefferman, N. H., and Maslo, B. (2021). Genomic signatures of selection in bats surviving white-nose syndrome. *Molecular Ecology*, 30(22):5643–5657.

Gillespie, J. H. (1974). Natural selection for within-generation variance in offspring number. *Genetics*, 76(3):601.

Glémin, S. and Ronfort, J. (2013). Adaptation and maladaptation in selfing and outcrossing species: New mutations versus standing variation. *Evolution*, 67(1):225–240.

Godineau, C., Theodorou, K., and Spigler, R. B. (2024). Effect of the seed bank on evolutionary rescue in small populations: univariate and multivariate demogenetic dynamics. *The American Naturalist*, 204(3):221–241.

Golas, B. D., Goodell, B., and Webb, C. T. (2021). Host adaptation to novel pathogen introduction: Predicting conditions that promote evolutionary rescue. *Ecology Letters*, 24(10):2238–2255.

Goldberg, D. E., Siliciano, R. F., and Jacobs, W. R. (2012). Outwitting evolution: fighting drug-resistant TB, malaria, and HIV. *Cell*, 148(6):1271–1283.

Goldberg, Y. and Friedman, J. (2021). Positive interactions within and between populations decrease the likelihood of evolutionary rescue. *PLoS Computational Biology*, 17(2):e1008732.

Goldie, J. and Coldman, A. (1979). A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treatment Reports*, 63(11-12):1727–1733.

Goldie, J. and Coldman, A. (1983). Quantitative model for multiple levels of drug resistance in clinical tumors. *Cancer Treat Rep*, 67(10):923–931.

Goldie, J., Coldman, A., and Gudauskas, G. (1982). Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treatment Reports*, 66(3):439–449.

Gómez-Llano, M., Faria, G. S., García-Roa, R., Noble, D. W., and Carazo, P. (2024). Male harm suppresses female fitness, affecting the dynamics of adaptation and evolutionary rescue. *Evolution Letters*, 8(1):149–160.

Gomulkiewicz, R. and Holt, R. D. (1995). When does evolution by natural selection prevent extinction? *Evolution*, 49:201–207.

Gomulkiewicz, R., Holt, R. D., and Barfield, M. (1999). The effects of density dependence and immigration on local adaptation and niche evolution in a black-hole sink environment. *Theoretical Population Biology*, 55(3):283–296.

Gomulkiewicz, R., Holt, R. D., Barfield, M., and Nuismer, S. L. (2010). Genetics, adaptation, and invasion in harsh environments. *Evolutionary Applications*, 3(2):97–108.

Gomulkiewicz, R. and Houle, D. (2009). Demographic and genetic constraints on evolution. *The American Naturalist*, 174(6):E218–E229.

Gomulkiewicz, R., Krone, S. M., and Remien, C. H. (2017). Evolution and the duration of a doomed population. *Evolutionary Applications*, 10(5):471–484.

Gomulkiewicz, R. and Shaw, R. G. (2013). Evolutionary rescue beyond the models. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120093.

Gonzalez, A. and Bell, G. (2013). Evolutionary rescue and adaptation to abrupt environmental change depends upon the history of stress. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120079.

Gonzalez, A., Ronce, O., Ferriere, R., and Hochberg, M. E. (2013). Evolutionary rescue: an emerging focus at the intersection between ecology and evolution. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120404.

Greenspoon, P. B. and Mideo, N. (2017). Evolutionary rescue of a parasite population by mutation rate evolution. *Theoretical Population Biology*, 117:64–75.

Greenspoon, P. B. and Spencer, H. G. (2021). Avoiding extinction under nonlinear environmental change: models of evolutionary rescue with plasticity. *Biology Letters*, 17(12):20210459.

Gunnarsson, E. B., De, S., Leder, K., and Foo, J. (2020). Understanding the role of phenotypic switching in cancer drug resistance. *Journal of Theoretical Biology*, 490:110162.

Gunnarsson, E. B., Foo, J., and Leder, K. (2023). Statistical inference of the rates of cell proliferation and phenotypic switching in cancer. *Journal of Theoretical Biology*, 568:111497.

Guzella, T. S., Dey, S., Chelo, I. M., Pino-Querido, A., Pereira, V. F., Proulx, S. R., and Teotónio, H. (2018). Slower environmental change hinders adaptation from standing genetic variation. *PLOS Genetics*, 14(11):e1007731.

Hamede, R., Lachish, S., Belov, K., Woods, G., Kreiss, A., PEARSE, A.-M., Lazenby, B., Jones, M., and McCALLUM, H. (2012). Reduced effect of Tasmanian devil facial tumor disease at the disease front. *Conservation Biology*, 26(1):124–134.

Hamede, R. K., Mccallum, H., and Jones, M. (2008). Seasonal, demographic and density-related patterns of contact between Tasmanian devils (*Sarcophilus harrisii*): Implications for transmission of devil facial tumour disease. *Austral Ecology*, 33(5):614–622.

Hamede, R. K., McCallum, H., and Jones, M. (2009). Contact networks in a wild Tasmanian devil (Sarcophilus harrisii) population: using social network analysis to reveal seasonal variability in social behaviour and its implications for transmission of devil facial tumour disease. *Ecology Letters*, 12(11):1147–1157.

Hamede, R. K., McCallum, H., and Jones, M. (2013). Biting injuries and transmission of Tasmanian devil facial tumour disease. *Journal of Animal Ecology*, 82(1):182–190.

Hamilton, D. G., Jones, M. E., Cameron, E. Z., Kerlin, D. H., McCallum, H., Storfer, A., Hohenlohe, P. A., and Hamede, R. K. (2020). Infectious disease and sickness behaviour: tumour progression affects interaction patterns and social network structure in wild Tasmanian devils. *Proceedings of the Royal Society B: Biological Sciences*, 287(1940):20202454.

Hamilton, D. G., Jones, M. E., Cameron, E. Z., McCallum, H., Storfer, A., Hohenlohe, P. A., and Hamede, R. K. (2019). Rate of intersexual interactions affects injury likelihood in Tasmanian devil contact networks. *Behavioral Ecology*, 30(4):1087–1095.

Hangartner, S., Sgrò, C. M., Connallon, T., and Booksmythe, I. (2022). Sexual dimorphism in phenotypic plasticity and persistence under environmental change: An extension of theory and meta-analysis of current data. *Ecology Letters*, 25(6):1550–1565.

Hao, Y.-Q., Brockhurst, M. A., Petchey, O. L., and Zhang, Q.-G. (2015). Evolutionary rescue can be impeded by temporary environmental amelioration. *Ecology Letters*, 18(9):892–898.

Harmand, N., Gallet, R., Jabbour-Zahab, R., Martin, G., and Lenormand, T. (2017). Fisher's geometrical model and the mutational patterns of antibiotic resistance across dose gradients. *Evolution*, 71(1):23–37.

Harmon, E. A. and Pfennig, D. W. (2021). Evolutionary rescue via transgenerational plasticity: Evidence and implications for conservation. *Evolution & Development*, 23(4):292–307.

Hastings, I. M. (2001). Modelling parasite drug resistance: lessons for management and control strategies. *Tropical Medicine & International Health*, 6(11):883–890.

Heino, M. and Hanski, I. (2001). Evolution of migration rate in a spatially realistic metapopulation model. *The American Naturalist*, 157(5):495–511.

Heinzmann, D. (2009). Extinction times in multitype Markov branching processes. *Journal of Applied Probability*, 46(1):296–307.

Helps, J., Paveley, N., and Van Den Bosch, F. (2017). Identifying circumstances under which high insecticide dose increases or decreases resistance selection. *Journal of Theoretical Biology*, 428:153–167.

Helps, J. C., Paveley, N. D., White, S., and van den Bosch, F. (2020). Determinants of optimal insecticide resistance management strategies. *Journal of Theoretical Biology*, 503:110383.

Henriques, G. J. and Osmond, M. M. (2020). Cooperation can promote rescue or lead to evolutionary suicide during environmental change. *Evolution*, 74(7):1255–1273.

Henry, R. C., Bocedi, G., and Travis, J. M. (2013). Eco-evolutionary dynamics of range shifts: Elastic margins and critical thresholds. *Journal of Theoretical Biology*, 321:1–7.

Hermann, R. J. and Becks, L. (2022). Change in prey genotype frequency rescues predator from extinction. *Royal Society Open Science*, 9(6):220211.

Hicks, H. L., Comont, D., Coutts, S. R., Crook, L., Hull, R., Norris, K., Neve, P., Childs, D. Z., and Freckleton, R. P. (2018). The factors driving evolved herbicide resistance at a national scale. *Nature Ecology & Evolution*, 2(3):529–536.

Hinsch, M., Robertson, D. L., and Silverman, E. (2024). Evolutionary rescue effect can disappear under non-neutral mutations–a reply to Zhang et al. (2022). *Nature Communications*, 15:10676.

Hobbelen, P., Paveley, N., and Van den Bosch, F. (2011). Delaying selection for fungicide insensitivity by mixing fungicides at a low and high risk of resistance development: A modeling analysis. *Phytopathology*, 101(10):1224–1233.

Hokanson, J. A., Brown, B. W., Thompson, J. R., Drewinko, B., and Alexanian, R. (1977). Tumor growth patterns in multiple myeloma. *Cancer*, 39(3):1077–1084.

Holmes, K. H., Lindquist, J. L., Rebarber, R., Werle, R., Yerka, M., and Tenhumberg, B. (2022). Modeling the evolution of herbicide resistance in weed species with a complex life cycle. *Ecological Applications*, 32(1):e02473.

Holt, R. D. (1990). The microevolutionary consequences of climate change. *Trends in Ecology & Evolution*, 5(9):311–315.

Holt, R. D. (1996). Demographic constraints in evolution: towards unifying the evolutionary theories of senescence and niche conservatism. *Evolutionary Ecology*, 10:1–11.

Holt, R. D. (2011). Evolution in source-sink environments: implications for niche conservatism. In Liu, J., Hull, V., Morzillo, A. T., and Wiens, J. A., editors, *Sources, Sinks and Sustainability*, pages 23–57. Cambridge University Press, Cambridge, UK.

Holt, R. D., Barfield, M., and Gomulkiewicz, R. (2004). Temporal variation can facilitate niche evolution in harsh sink environments. *The American Naturalist*, 164(2):187–200.

Holt, R. D., Barfield, M., and Gomulkiewicz., R. (2005). Theories of niche conservatism and evolution: Could exotic species be potential tests? In Sax, D. F., Stachowicz, J. J., and Gaines, S. D., editors, *Species Invasions: Insights into Ecology, Evolution and Biogeography*, pages 259–290. Sinauer Associates, Sunderland, MA.

Holt, R. D. and Gaines, M. S. (1992). Analysis of adaptation in heterogeneous landscapes: implications for the evolution of fundamental niches. *Evolutionary Ecology*, 6:433–447.

Holt, R. D. and Gomulkiewicz, R. (1997). The evolution of species' niches: a population dynamic perspective. In Othmer, H. G., Adler, F. R., Lewis, M. A., , and Dallon, J. C., editors, *Case Studies in Mathematical Modelling: Ecology, Physiology, and Cell Biology*, pages 25–50. Prentice Hall Englewood Cliffs, NJ.

Holt, R. D. and Gomulkiewicz, R. (2004). Conservation implications of niche conservatism and evolution in heterogeneous environments. In *Evolutionary Conservation Biology*, pages 244–264. Cambridge University Press.

Holt, R. D., Gomulkiewicz, R., and Barfield, M. (2003). The phenomenology of niche evolution via quantitative traits in a 'black-hole'sink. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 270(1511):215–224.

Holt, R. D., Hastings, A., and Nuismer, S. L. (2023). Richard S. Gomulkiewicz (1962–2023). *Nature Ecology & Evolution*, 7(10):1562–1563.

Houchmandzadeh, B. (2015). General formulation of Luria-Delbrück distribution of the number of mutants. *Phys. Rev. E*, 92:012719.

Hubert, J.-N., Zerjal, T., and Hospital, F. (2018). Cancer- and behavior-related genes are targeted by selection in the Tasmanian devil (*Sarcophilus harrisii)*. *PLOS ONE*, 13(8):e0201838.

Hudgens, M. G. and Halloran, M. E. (2008). Toward causal inference with interference. *Journal of the american statistical association*, 103(482):832–842.

Huey, R. B. and Kingsolver, J. G. (1993). Evolution of resistance to high temperature in ectotherms. *The American Naturalist*, 142:S21–S46.

Hufbauer, R. A., Szűcs, M., Kasyon, E., Youngberg, C., Koontz, M. J., Richards, C., Tuff, T., and Melbourne, B. A. (2015). Three types of rescue can avert extinction in a changing environment. *Proceedings of the National Academy of Sciences*, 112(33):10557–10562.

Igler, C., Rolff, J., and Regoes, R. (2021). Multi-step vs. single-step resistance evolution under different drugs, pharmacokinetics, and treatment regimens. *eLife*, 10:e64116.

Iwasa, Y., Michor, F., and Nowak, M. A. (2003). Evolutionary dynamics of escape from biomedical intervention. *Proceedings of the Royal Society B: Biological Sciences*, 270(1533):2573–2578.

Iwasa, Y., Michor, F., and Nowak, M. A. (2004). Evolutionary dynamics of invasion and escape. *Journal of Theoretical Biology*, 226(2):205–214.

Iwasa, Y., Nowak, M. A., and Michor, F. (2006). Evolution of resistance during clonal expansion. *Genetics*, 172(4):2557–2566.

Izutsu, M., Lake, D. M., Matson, Z. W., Dodson, J. P., and Lenski, R. E. (2024). Effects of periodic bottlenecks on the dynamics of adaptive evolution in microbial populations. *Microbiology*, 170(9):001494.

Jensen, A. J., Hagen, I. J., Czorlich, Y., Bolstad, G. H., Bremset, G., Finstad, B., Hindar, K., Skaala, Ø., and Karlsson, S. (2022). Large-effect loci mediate rapid adaptation of salmon body size after river regulation. *Proceedings of the National Academy of Sciences*, 119(44):e2207634119.

Jiao, J., Gilchrist, M. A., and Fefferman, N. H. (2020). The impact of host metapopulation structure on short-term evolutionary rescue in the face of a novel pathogenic threat. *Global Ecology and Conservation*, 23:e01174.

Jones, A. G. (2008). A theoretical quantitative genetic study of negative ecological interactions and extinction times in changing environments. *BMC Evolutionary Biology*, 8:119.

Jones, E. I. and Gomulkiewicz, R. (2012). Biotic interactions, rapid evolution, and the establishment of introduced species. *The American Naturalist*, 179(2):E28–E36.

Jones, M. E., Jarman, P. J., Lees, C. M., Hesterman, H., Hamede, R. K., Mooney, N. J., Mann, D., Pukk, C. E., Bergfeld, J., and McCallum, H. (2007). Conservation management of Tasmanian devils in the context of an emerging, extinction-threatening disease: devil facial tumor disease. *EcoHealth*, 4:326–337.

Josepovits, G. and Dobrovolszky, A. (1985). A novel mathematical approach to the prevention of fungicide resistance. *Pesticide science*, 16(1):17–22.

Kaminsky, J., Keegan, L. T., Metcalf, C. J. E., and Lessler, J. (2019). Perfect counterfactuals for epidemic simulations. *Philosophical Transactions of the Royal Society B*, 374(1776):20180279.

Kanarek, A. R. and Webb, C. T. (2010). Allee effects, adaptive evolution, and invasion success. *Evolutionary Applications*, 3(2):122–135.

Kanarek, A. R., Webb, C. T., Barfield, M., and Holt, R. D. (2015). Overcoming Allee effects through evolutionary, genetic, and demographic rescue. *Journal of Biological Dynamics*, 9(1):15–33.

Kardos, M. and Luikart, G. (2021). The genetic architecture of fitness drives population viability during rapid environmental change. *The American Naturalist*, 197(5):511–525.

Katsuhara, K. R., Tachiki, Y., Iritani, R., and Ushimaru, A. (2021). The eco-evolutionary dynamics of prior selfing rates promote coexistence without niche partitioning under conditions of reproductive interference. *Journal of Ecology*, 109:3916–3928.

Kawaguchi, Y. W. and Yamamichi, M. (2025). A single episode of sexual reproduction can produce large variation in population growth rates under dual stressors. *Journal of Evolutionary Biology*, page voaf041.

Kawecki, T. J. (2008). Adaptation to marginal habitats. *Annual Review of Ecology, Evolution, and Systematics*, 39(1):321–342.

Kawecki, T. J. and Holt, R. D. (2002). Evolutionary consequences of asymmetric dispersal rates. *The American Naturalist*, 160(3):333–347.

Kelly, E. and Phillips, B. (2019). How many and when? optimising targeted gene flow for a step change in the environment. *Ecology Letters*, 22(3):447–457.

Kepler, T. B. and Perelson, A. S. (1998). Drug concentration heterogeneity facilitates the evolution of drug resistance. *Proceedings of the National Academy of Sciences*, 95(20):11514–11519.

Khare, S. B., Holt, R. D., and Scheiner, S. M. (2024). The genetics of phenotypic plasticity. xviii. developmental limits restrict adaptive plasticity. *Evolution*, 78(11):1761–1773.

Khatri, B. S. and Burt, A. (2022). A theory of resistance to multiplexed gene drive demonstrates the significant role of weakly deleterious natural genetic variation. *Proceedings of the National Academy of Sciences*, 119(32):e2200567119.

Killeen, J., Gougat-Barbera, C., Krenek, S., and Kaltz, O. (2017). Evolutionary rescue and local adaptation under different rates of temperature increase: a combined analysis of changes in phenotype expression and genotype frequency in *paramecium* microcosms. *Molecular Ecology*, 26(7):1734–1746.

Kippnich, J., Benz, F., Uecker, H., and Baumdicker, F. (2025). Effectiveness of CRISPR-Cas in sensitizing bacterial populations with plasmid-encoded antimicrobial resistance. *Genetics*, 231(3):iyaf192.

Klausmeier, C. A., Osmond, M. M., Kremer, C. T., and Litchman, E. (2020). Ecological limits to evolutionary rescue. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 375(1814):20190453.

Knell, R. J. and Parrett, J. M. (2024). Alternative reproductive tactics and evolutionary rescue. *Evolution Letters*, 8(4):539–549.

Knight, T. M., Barfield, M., and Holt, R. D. (2008). Evolutionary dynamics as a component of stage-structured matrix models: an example using trillium grandiflorum. *The American Naturalist*, 172(3):375–392.

Komarova, N. L. and Wodarz, D. (2005). Drug resistance in cancer: principles of emergence and prevention. *Proceedings of the National Academy of Sciences*, 102(27):9714–9719.

Kopp, M. and Hermisson, J. (2007). Adaptation of a quantitative trait to a moving optimum. *Genetics*, 176(1):715–719.

Kopp, M. and Hermisson, J. (2009a). The genetic basis of phenotypic adaptation i: fixation of beneficial mutations in the moving optimum model. *Genetics*, 182(1):233–249.

Kopp, M. and Hermisson, J. (2009b). The genetic basis of phenotypic adaptation ii: the distribution of adaptive substitutions in the moving optimum model. *Genetics*, 183(4):1453–1476.

Kopp, M. and Matuszewski, S. (2014). Rapid evolution of quantitative traits: theoretical perspectives. *Evolutionary Applications*, 7(1):169–191.

Kopp, M., Nassar, E., and Pardoux, E. (2018). Phenotypic lag and population extinction in the moving-optimum model: insights from a small-jumps limit. *Journal of Mathematical Biology*, 77:1431–1458.

Kosterlitz, O., Muñiz Tirado, A., Wate, C., Elg, C., Bozic, I., Top, E. M., and Kerr, B. (2022). Estimating the transfer rates of bacterial plasmids with an adapted Luria–Delbrück fluctuation analysis. *PLoS Biology*, 20(7):e3001732.

Kouyos, R. D., Fouchet, D., and Bonhoeffer, S. (2009). Recombination and drug resistance in hiv: population dynamics and stochasticity. *Epidemics*, 1(1):58–69.

Kouyos, R. D., Metcalf, C. J. E., Birger, R., Klein, E. Y., Abel zur Wiesch, P., Ankomah, P., Arinaminpathy, N., Bogich, T. L., Bonhoeffer, S., Brower, C., et al. (2014). The path of least resistance: aggressive or moderate treatment? *Proceedings of the Royal Society B: Biological Sciences*, 281(1794):20140566.

Kovach-Orr, C. and Fussmann, G. F. (2013). Evolutionary and plastic rescue in multitrophic model communities. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120084.

Krašovec, R., Richards, H., Gomez, G., Gifford, D., Mazoyer, A., and Knight, C. (2019). Measuring microbial mutation rates with the fluctuation assay. *Journal of Visualized Experiments : JoVE*, (153).

Kreiner, J. M. (2026). The genetic architecture and spatiotemporal dynamics of adaptation across human-modified landscapes. *New Phytologist*, 249(2):744–750.

Kronholm, I., Bassett, A., Baulcombe, D., and Collins, S. (2017). Epigenetic and genetic contributions to adaptation in *chlamydomonas*. *Molecular Biology and Evolution*, 34(9):2285–2306.

Kulbaba, M. W., Sheth, S. N., Pain, R. E., Eckhart, V. M., and Shaw, R. G. (2019). Additive genetic variance for lifetime fitness and the capacity for adaptation in an annual plant. *Evolution*, 73(9):1746–1758.

Kuosmanen, T., Cairns, J., Noble, R., Beerenwinkel, N., Mononen, T., and Mustonen, V. (2021). Drug-induced resistance evolution necessitates less aggressive treatment. *PLOS Computational Biology*, 17(9):e1009418.

Kuosmanen, T., Särkkä, S., and Mustonen, V. (2025). Turnover shapes evolution of birth and death rates. *Evolution*, 79(8):1456–1468.

Kuparinen, A., Savolainen, O., and Schurr, F. M. (2010). Increased mortality can promote evolutionary adaptation of forest trees to climate change. *Forest Ecology and Management*, 259(5):1003–1008.

Kwon, Y. M., Gori, K., Park, N., Potts, N., Swift, K., Wang, J., Stammnitz, M. R., Cannell, N., Baez-Ortega, A., Comte, S., Fox, S., Harmsen, C., Huxtable, S., Jones, M., Kreiss, A., Lawrence, C., Lazenby, B., Peck, S., Pye, R., Woods, G., Zimmermann, M., Wedge, D. C., Pemberton, D., Stratton, M. R., Hamede, R. K., and Murchison, E. P. (2020). Evolution and lineage dynamics of a transmissible cancer in Tasmanian devils. *PLOS Biology*, 18(11):e3000926.

Lachapelle, J. and Bell, G. (2012). Evolutionary rescue of sexual and asexual populations in a deteriorating environment. *Evolution*, 66(11):3508–3518.

Lachapelle, J., Colegrave, N., and Bell, G. (2017). The effect of selection history on extinction risk during severe environmental change. *Journal of Evolutionary Biology*, 30(10):1872–1883.

Lachish, S., Jones, M., and McCallum, H. (2007). The impact of disease on the survival and population growth rate of the Tasmanian devil. *Journal of Animal Ecology*, 76(5):926–936.

Lagator, M., Colegrave, N., and Neve, P. (2014a). Selection history and epistatic interactions impact dynamics of adaptation to novel environmental stresses. *Proceedings of the Royal Society B: Biological Sciences*, 281(1794):20141679.

Lagator, M., Morgan, A., Neve, P., and Colegrave, N. (2014b). Role of sex and migration in adaptation to sink environments. *Evolution*, 68(8):2296–2305.

Lambert, A., Achaz, G., Le Rouzic, A., and Loison, L. (2025). The Baldwin effect reloaded: Intermediate levels of phenotypic plasticity favor evolutionary rescue. *The American Naturalist*, 206(5):418–434.

Lande, R. (1976). Natural selection and random genetic drift in phenotypic evolution. *Evolution*, 30(2):314–334.

Lande, R. and Shannon, S. (1996). The role of genetic variation in adaptation and population persistence in a changing environment. *Evolution*, 50(1):434–437.

Lässig, M., Mustonen, V., and Walczak, A. M. (2017). Predicting evolution. *Nature Ecology & Evolution*, 1(3):0077.

Lauenroth, D. and Gokhale, C. S. (2023). Theoretical assessment of persistence and adaptation in weeds with complex life cycles. *Nature Plants*, 9(8):1267–1279.

Lazenby, B. T., Tobler, M. W., Brown, W. E., Hawkins, C. E., Hocking, G. J., Hume, F., Huxtable, S., Iles, P., Jones, M. E., Lawrence, C., Thalmann, S., Wise, P., Williams, H., Fox, S., and Pemberton, D. (2018). Density trends and demographic signals uncover the long-term impact of transmissible cancer in Tasmanian devils. *Journal of Applied Ecology*, 55(3):1368–1379.

Lea, D. E. and Coulson, C. A. (1949). The distribution of the numbers of mutants in bacterial populations. *Journal of Genetics*, 49(3):264–285.

LeClair, J. S. and Wahl, L. M. (2018). The impact of population bottlenecks on microbial adaptation. *Journal of Statistical Physics*, 172(1):114–125.

Leidinger, L., Vedder, D., and Cabral, J. S. (2021). Temporal environmental variation may impose differential selection on both genomic and ecological traits. *Oikos*, 120(7):1100–1115.

Letten, A. D., Hall, A. R., and Levine, J. M. (2021). Using ecological coexistence theory to understand antibiotic resistance and microbial competition. *Nature Ecology & Evolution*, 5(4):431–441.

Li, R. C., Nix, D. E., and Schentag, J. J. (1994). Pharmacodynamic modeling of bacterial kinetics: β-lactam antibiotics against *escherichia coli*. *Journal of Pharmaceutical Sciences*, 83(7):970–975.

Lindsey, H. A., Gallie, J., Taylor, S., and Kerr, B. (2013). Evolutionary rescue from extinction is contingent on a lower rate of environmental change. *Nature*, 494(7438):463–467.

Lipinski, K. A., Barber, L. J., Davies, M. N., Ashenden, M., Sottoriva, A., and Gerlinger, M. (2016). Cancer evolution and the limits of predictability in precision cancer medicine. *Trends in Cancer*, 2(1):49–63.

Lipsitch, M. and Levin, B. R. (1997). The population dynamics of antimicrobial chemotherapy. *Antimicrobial Agents and Chemotherapy*, 41(2):363–373.

LoFaro, T. and Gomulkiewicz, R. (1999). Adaptation versus migration in demographically unstable populations. *Journal of Mathematical Biology*, 38:571–584.

Longcamp, A. and Draghi, J. (2023). Evolutionary rescue via niche construction: Infrequent construction can prevent post-invasion extinction. *Theoretical Population Biology*, 153:37–49.

Longcamp, A. and Draghi, J. (2025). Evolutionary rescue of niche constructors from habitat exploitation: Fecundity costs can promote rescue. *Evolution*, 79(12):2667–2681.

Lovett, S. T. and Sass, T. H. (2025). The nature of mutation: a legacy of bacterial genetics. *Genetics*, 231(3):iyaf144.

Low-Décarie, E., Kolber, M., Homme, P., Lofano, A., Dumbrell, A., Gonzalez, A., and Bell, G. (2015). Community rescue in experimental metacommunities. *Proceedings of the National Academy of Sciences*, 112(46):14307–14312.

Luo, S., Reed, M., Mattingly, J. C., and Koelle, K. (2012). The impact of host immune status on the within-host and population dynamics of antigenic immune escape. *Journal of The Royal Society Interface*, 9(75):2603–2613.

Luria, S. E. and Delbrück, M. (1943). Mutations of bacteria from virus sensitivity to virus resistance. *Genetics*, 28(6):491–511.

Lyberger, K. P., Osmond, M. M., and Schreiber, S. J. (2021). Is evolution in response to extreme events good for population persistence? *The American Naturalist*, 198(1):44–52.

Lynch, M., Gabriel, W., and Wood, A. M. (1991). Adaptive and demographic responses of plankton populations to environmental change. *Limnology and Oceanography*, 36(7):1301–1312.

Lynch, M. and Lande, R. (1993). Evolution and extinction in response to environmental change. In *Biotic Interactions and Global Change*, pages 234–250. Sinauer Associates.

MacDonald, G. (1959). The dynamics of resistance to insecticides by anophelines. *Rivista di Parassitologia*, 20:305–315.

Madgwick, P. G. and Kanitz, R. (2024). What is the value of rotations to insecticide resistance management? *Pest Management Science*, 80(4):1671–1680.

Madgwick, P. G., Tunstall, T., and Kanitz, R. (2024). Evolutionary rescue in resistance to pesticides. *Proceedings B*, 291(2025):20240805.

Mahrt, N., Tietze, A., Künzel, S., Franzenburg, S., Barbosa, C., Jansen, G., and Schulenburg, H. (2021). Bottleneck size and selection level reproducibly impact evolution of antibiotic resistance. *Nature Ecology & Evolution*, 5(9):1233–1242.

Margres, M. J., Jones, M. E., Epstein, B., Kerlin, D. H., Comte, S., Fox, S., Fraik, A. K., Hendricks, S. A., Huxtable, S., Lachish, S., Lazenby, B., O'Rourke, S. M., Stahlke, A. R., Wiench, C. G., Hamede, R. K., Schönfeld, B., McCallum, H., Miller, M. R., Hohenlohe, P. A., and Storfer, A. (2018). Large-effect loci affect survival in Tasmanian devils (*Sarcophilus harrisii*) infected with a transmissible cancer. *Molecular Ecology*, 27(21):4189–4199.

Marrec, L. and Bank, C. (2023). Evolutionary rescue in a fluctuating environment: periodic versus quasi-periodic environmental changes. *Proceedings of the Royal Society B: Biological Sciences*, 290(1999):20230770.

Marrec, L. and Bitbol, A.-F. (2020a). Adapt or perish: Evolutionary rescue in a gradually deteriorating environment. *Genetics*, 216(2):573–583.

Marrec, L. and Bitbol, A.-F. (2020b). Resist or perish: fate of a microbial population subjected to a periodic presence of antimicrobial. *PLOS Computational Biology*, 16(4):e1007798.

Marshall, D. J., Burgess, S. C., and Connallon, T. (2016). Global change, life-history complexity and the potential for evolutionary rescue. *Evolutionary Applications*, 9(9):1189–1201.

Martin, G., Aguilée, R., Ramsayer, J., Kaltz, O., and Ronce, O. (2013). The probability of evolutionary rescue: towards a quantitative comparison between theory and evolution experiments. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120088.

Maslo, B. and Fefferman, N. H. (2015). A case study of bats and white-nose syndrome demonstrating how to model population viability with evolutionary effects. *Conservation Biology*, 29(4):1176–1185.

Maslo, B., Gignoux-Wolfsohn, S. A., and Fefferman, N. H. (2017). Success of wildlife disease treatment depends on host immune response. *Frontiers in Ecology and Evolution*, 5:28.

Matuszewski, S., Hermisson, J., and Kopp, M. (2014). Fisher's geometric model with a moving optimum. *Evolution*, 68(9):2571–2588.

Matuszewski, S., Hermisson, J., and Kopp, M. (2015). Catch me if you can: adaptation from standing genetic variation to a moving phenotypic optimum. *Genetics*, 200(4):1255–1274.

Matz, M. V., Treml, E. A., and Haller, B. C. (2020). Estimating the potential for coral adaptation to global warming across the Indo-West Pacific. *Global Change Biology*, 26(6):3473–3481.

Mazoyer, A. (2017). Time inhomogeneous mutation models with birth date dependence. *Bulletin of Mathematical Biology*, 79(12):2929–2953.

McCallum, H., Jones, M., Hawkins, C., Hamede, R. K., Lachish, S., Sinn, D. L., Beeton, N., and Lazenby, B. (2009). Transmission dynamics of Tasmanian devil facial tumor disease may lead to disease-induced extinction. *Ecology*, 90(12):3379–3392.

McLean, A. R. (1995). Vaccination, evolution and changes in the efficacy of vaccines: a theoretical framework. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 261(1362):389–393.

McLeod, D. V., Wahl, L. M., and Mideo, N. (2021). Mosaic vaccination: How distributing different vaccines across a population could improve epidemic control. *Evolution Letters*, 5(5):458–471.

McManus, L. C., Forrest, D. L., Tekwa, E. W., Schindler, D. E., Colton, M. A., Webster, M. M., Essington, T. E., Palumbi, S. R., Mumby, P. J., and Pinsky, M. L. (2021). Evolution and connectivity influence the persistence and recovery of coral reefs under climate change in the Caribbean, Southwest Pacific, and Coral Triangle. *Global Change Biology*, 27(18):4307–4321.

Medical Research Council (1950). Treatment of pulmonary tuberculosis with streptomycin and para-amino-salicylic acid. *The British Medical Journal*, 2:1073–1085.

Melero-Jiménez, I. J., Martín-Clemente, E., Reul, A., García-Sánchez, M. J., Flores-Moya, A., and Bañares-España, E. (2022). Dispersal of populations and environmental deterioration rate influence evolutionary rescue under selection by salinity in the freshwater cyanobacterium *microcystis aeruginosa*. *European Journal of Phycology*, 57(1):96–106.

Melero-Jiménez, I. J., Sorokin, Y., Merlin, A., Li, J., Couce, A., and Friedman, J. (2025). Mutualism breakdown underpins evolutionary rescue in an obligate cross-feeding bacterial consortium. *Nature Communications*, 16(1):3482.

Mellard, J. P., De Mazancourt, C., and Loreau, M. (2015). Evolutionary responses to environmental change: trophic interactions affect adaptation and persistence. *Proceedings of the Royal Society B: Biological Sciences*, 282(1805):20141351.

Mestre, A., Butlin, R. K., Hortal, J., and Rafajlović, M. (2024). Adaptive colonization across a parasitism–mutualism gradient. *Evolution Letters*, 8(3):340–350.

Michelson, S. (1986). Comparison of stochastic models for tumor escape. In *Immunology and Epidemiology: Proceedings of an International Conference held in Mogilany, Poland, February 18–25, 1985*, pages 82–119. Springer.

Mikaberidze, A., McDonald, B. A., and Bonhoeffer, S. (2014). Can high-risk fungicides be used in mixtures without selecting for fungicide resistance? *Phytopathology*, 104(4):324–331.

Mikaberidze, A., Paveley, N., Bonhoeffer, S., and van den Bosch, F. (2017). Emergence of resistance to fungicides: the role of fungicide dose. *Phytopathology*, 107(5):545–560.

Mohammadi, A. and Campos, P. R. (2025). Geometric insights into evolutionary rescue dynamics in a two-deme model. *Evolution*, 79(5):752–764.

Mongold, J. A., Bennett, A. F., and Lenski, R. E. (1999). Evolutionary adaptation to temperature. VII. Extension of the upper thermal limit of *escherichia coli*. *Evolution*, 53(2):386–394.

Moreno-Gamez, S., Hill, A. L., Rosenbloom, D. I., Petrov, D. A., Nowak, M. A., and Pennings, P. S. (2015). Imperfect drug penetration leads to spatial monotherapy and rapid evolution of multidrug resistance. *Proceedings of the National Academy of Sciences*, 112(22):E2874–E2883.

Morita, K. and Yamamichi, M. (2023). How does the magnitude of genetic variation affect ecological and reproductive character displacement? *Population Ecology*, 65(4):220–230.

Muralidhar, P. and Veller, C. (2022). Dominance shifts increase the likelihood of soft selective sweeps. *Evolution*, 76(5):966–984.

Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., et al. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325):629–655.

Murray, M., Wright, J., and Araya-Ajoy, Y. G. (2024). Evolutionary rescue from climate change: male indirect genetic effects on lay-dates and their consequences for population persistence. *Evolution Letters*, 8(1):137–148.

Nagaraja, P., Alexander, H. K., Bonhoeffer, S., and Dixit, N. M. (2016). Influence of recombination on acquisition and reversion of immune escape and compensatory mutations in HIV-1. *Epidemics*, 14:11–25.

Nissen-Meyer, S. (1966). Analysis of effects of antibiotics on bacteria by means of stochastic models. *Biometrics*, 22(4):761–780.

Norberg, J., Urban, M. C., Vellend, M., Klausmeier, C. A., and Loeuille, N. (2012). Eco-evolutionary responses of biodiversity to climate change. *Nature Climate Change*, 2:747–751.

Nordstrom, S. W., Hufbauer, R. A., Olazcuaga, L., Durkee, L. F., and Melbourne, B. A. (2023). How density dependence, genetic erosion and the extinction vortex impact evolutionary rescue. *Proceedings of the Royal Society B: Biological Sciences*, 290(2011):20231228.

Northfield, T. D. and Ives, A. R. (2013). Coevolution and the effects of climate change on interacting species. *PLOS Biology*, 11(10):e1001685.

Nowak, M. A., May, R. M., and Sigmund, K. (1995). Immune responses against multiple epitopes. *Journal of Theoretical Biology*, 175(3):325–353.

Nuismer, S. L., Week, B., and Aizen, M. A. (2018). Coevolution slows the disassembly of mutualistic networks. *The American Naturalist*, 192(4):490–502.

Nukazawa, K., Chiu, M.-C., Kazama, S., and Watanabe, K. (2023). Contrasting adaptive genetic consequences of stream insects under changing climate. *Science of the Total Environment*, 872:162258.

Nyhoegen, C., Bonhoeffer, S., and Uecker, H. (2024). The many dimensions of combination therapy: How to combine antibiotics to limit resistance evolution. *Evolutionary Applications*, 17:e13764.

Nyhoegen, C. and Uecker, H. (2023). Sequential antibiotic therapy in the laboratory and in the patient. *Journal of The Royal Society Interface*, 20(198):20220793.

O'Connor, L. M., Fugère, V., and Gonzalez, A. (2020). Evolutionary rescue is mediated by the history of selection and dispersal in diversifying metacommunities. *Frontiers in Ecology and Evolution*, 8:517434.

Olazcuaga, L., Lincke, B., DeLacey, S., Durkee, L. F., Melbourne, B. A., and Hufbauer, R. A. (2023). Population demographic history and evolutionary rescue: Influence of a bottleneck event. *Evolutionary Applications*, 16(8):1483–1495.

Olazcuaga, L., Melbourne, B. A., Nordstrom, S. W., and Hufbauer, R. A. (2024). Density dependence impedes evolutionary rescue. *bioRxiv*, pages 2024–12.

Oliveira, V. M. and Campos, P. R. (2024). Resource-based modelling approach to studying evolutionary rescue. *Physical Review E*, 110(3):034406.

Olivieri, I., Tonnabel, J., Ronce, O., and Mignot, A. (2016). Why evolution matters for species conservation: perspectives from three case studies of plant metapopulations. *Evolutionary Applications*, 9(1):196–211.

Ono, J., Kuzmin, A., Miller, L., and Otto, S. P. (2024). The limit to evolutionary rescue depends on ploidy in yeast exposed to nystatin. *Canadian Journal of Microbiology*, 70(9):394–404.

Orive, M. E., Barfield, M., Fernandez, C., and Holt, R. D. (2017). Effects of clonal reproduction on evolutionary lag and evolutionary rescue. *The American Naturalist*, 190(4):469–490.

Orive, M. E., Holt, R. D., and Barfield, M. (2019). Evolutionary rescue in a linearly changing environment: Limits on predictability. *Bulletin of Mathematical Biology*, 81:4821–4839.

Orr, H. A. and Unckless, R. L. (2008). Population extinction and the genetics of adaptation. *The American Naturalist*, 172(2):160–169.

Orr, H. A. and Unckless, R. L. (2014). The population genetics of evolutionary rescue. *PLOS Genetics*, 10(8):e1004551.

Osmond, M. M. and Coop, G. (2020). Genetic signatures of evolutionary rescue by a selective sweep. *Genetics*, 215(3):813–829.

Osmond, M. M. and de Mazancourt, C. (2013). How competition affects evolutionary rescue. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120085.

Osmond, M. M. and Klausmeier, C. A. (2017). An evolutionary tipping point in a changing environment. *Evolution*, 71(12):2930–2941.

Osmond, M. M., Otto, S. P., and Klausmeier, C. A. (2017). When predators help prey adapt and persist in a changing environment. *The American Naturalist*, 190(1):83–98.

Osmond, M. M., Otto, S. P., and Martin, G. (2020). Genetic paths to evolutionary rescue and the distribution of fitness effects along them. *Genetics*, 214(2):493–510.

Ovaskainen, O. and Meerson, B. (2010). Stochastic models of population extinction. *Trends in Ecology & Evolution*, 25(11):643–652.

Oziolor, E. M., Reid, N. M., Yair, S., Lee, K. M., Guberman VerPloeg, S., Bruns, P. C., Shaw, J. R., Whitehead, A., and Matson, C. W. (2019). Adaptive introgression enables evolutionary rescue from extreme environmental pollution. *Science*, 364(6439):455–457.

O'Dea, R. E., Noble, D. W., Johnson, S. L., Hesselson, D., and Nakagawa, S. (2016). The role of non-genetic inheritance in evolutionary rescue: epigenetic buffering, heritable bet hedging and epigenetic traps. *Environmental Epigenetics*, 2(1):dvv014.

Papaïx, J., Rimbaud, L., Burdon, J. J., Zhan, J., and Thrall, P. H. (2018). Differential impact of landscape-scale strategies for crop cultivar deployment on disease dynamics, resistance durability and long-term evolutionary control. *Evolutionary Applications*, 11(5):705–717.

Parsons, T. L., Lambert, A., Day, T., and Gandon, S. (2018). Pathogen evolution in finite populations: slow and steady spreads the best. *Journal of The Royal Society Interface*, 15(147):20180135.

Patel, S., Lyberger, K., Vegvari, C., and Gulbudak, H. (2025). Eco-evolutionary dynamics of anthelmintic resistance in soil-transmitted helminths. *Theoretical Population Biology*, 163:80–90.

Patel, S. and Schreiber, S. J. (2015). Evolutionarily driven shifts in communities with intraguild predation. *The American Naturalist*, 186(5):E98–E110.

Patil, S., Ahmed, A., Viossat, Y., and Noble, R. (2025). Preventing evolutionary rescue in cancer using two-strike therapy. *Genetics*, page iyaf255.

Patton, A. H., Lawrance, M. F., Margres, M. J., Kozakiewicz, C. P., Hamede, R. K., Ruiz-Aravena, M., Hamilton, D. G., Comte, S., Ricci, L. E., Taylor, R. L., Stadler, T., Leaché, A., McCallum, H., Jones, M. E., Hohenlohe, P. A., and Storfer, A. (2020). A transmissible cancer shifts from emergence to endemism in Tasmanian devils. *Science*, 370(6522):eabb9772.

Pease, C. M., Lande, R., and Bull, J. (1989). A model of population growth, dispersal and evolution in a changing environment. *Ecology*, 70(6):1657–1664.

Peck, S. L. (2001). Antibiotic and insecticide resistance modeling–is it time to start talking? *Trends in Microbiology*, 9(6):286–292.

Peniston, J. H., Barfield, M., Gonzalez, A., and Holt, R. D. (2020). Environmental fluctuations can promote evolutionary rescue in high-extinction-risk scenarios. *Proceedings of the Royal Society B: Biological Sciences*, 287(1932):20201144.

Peniston, J. H., Barfield, M., Holt, R. D., and Orive, M. E. (2021). Environmental fluctuations dampen the effects of clonal reproduction on evolutionary rescue. *Journal of Evolutionary Biology*, 34:710–722.

Pennings, P. S. (2012). Standing genetic variation and the evolution of drug resistance in HIV. *PLoS Computational Biology*, 8(6):e1002527.

Perron, G., Gonzalez, A., and Buckling, A. (2008). The rate of environmental change drives adaptation to an antibiotic sink. *Journal of Evolutionary Biology*, 21(6):1724–1731.

Perron, G. G., Gonzalez, A., and Buckling, A. (2007). Source–sink dynamics shape the evolution of antibiotic resistance and its pleiotropic fitness cost. *Proceedings of the Royal Society B: Biological Sciences*, 274(1623):2351–2356.

Perron, G. G., Zasloff, M., and Bell, G. (2006). Experimental evolution of resistance to an antimicrobial peptide. *Proceedings of the Royal Society B: Biological Sciences*, 273(1583):251–256.

Peschel, A. R. and Shaw, R. G. (2024). Comparing the predicted versus realized rate of adaptation of *Chamaecrista fasciculata* to climate change. *The American Naturalist*, 203(1):14–27.

Petkovic, N. and Colegrave, N. (2019). Sex increases the probability of evolutionary rescue in the presence of a competitor. *Journal of Evolutionary Biology*, 32(11):1252–1261.

Petkovic, N. and Colegrave, N. (2023). The effects of sex on extinction dynamics of *chlamydomonas reinhardtii* depend on the rate of environmental change. *Journal of Evolutionary Biology*, 36(12):1783–1795.

Pierson, J. C., Beissinger, S. R., Bragg, J. G., Coates, D. J., Oostermeijer, J. G. B., Sunnucks, P., Schumaker, N. H., Trotter, M. V., and Young, A. G. (2015). Incorporating evolutionary processes into population viability models. *Conservation Biology*, 29(3):755–764.

Pillai, P., Gouhier, T. C., and Vollmer, S. V. (2017). Ecological rescue of host-microbial systems under environmental change. *Theoretical Ecology*, 10(1):51–63.

Pimm, S. L., Jenkins, C. N., Abell, R., Brooks, T. M., Gittleman, J. L., Joppa, L. N., Raven, P. H., Roberts, C. M., and Sexton, J. O. (2014). The biodiversity of species and their rates of extinction, distribution, and protection. *Science*, 344(6187):1246752.

Polechová, J., Barton, N., and Marion, G. (2009). Species' range: Adaptation in space and time. *The American Naturalist*, 174(5):E186–E204.

Raatz, M., de Azevedo-Lopes, A., Drabik, K., Traulsen, A., and Waclaw, B. (2024). Pathogen non-planktonic phases within the urinary tract impact early infection and resistance evolution. *The ISME Journal*, 18(1):wrae191.

Raatz, M. and Traulsen, A. (2023). Promoting extinction or minimizing growth? The impact of treatment on trait trajectories in evolving populations. *Evolution*, 77(6):1408–1421.

Raatz, M., van Velzen, E., and Gaedke, U. (2019). Co-adaptation impacts the robustness of predator–prey dynamics against perturbations. *Ecology and Evolution*, 9(7):3823–3836.

Radchuk, V., Reed, T., Teplitsky, C., van de Pol, M., Charmantier, A., Hassall, C., Adamík, P., Adriaensen, F., Ahola, M. P., Arcese, P., et al. (2019). Adaptive responses of animals to climate change are most likely insufficient. *Nature communications*, 10(1):3109.

Ramsayer, J., Kaltz, O., and Hochberg, M. E. (2013). Evolutionary rescue in populations of *Pseudomonas fluorescens* across an antibiotic gradient. *Evolutionary Applications*, 6(4):608–616.

Ranson, H. and Lissenden, N. (2016). Insecticide resistance in african anopheles mosquitoes: a worsening situation that needs urgent action to maintain malaria control. *Trends in Parasitology*, 32(3):187–196.

Ravi Kumar, V., Buddh, S., Singhal, S., Prakash, A., and Agashe, D. (2025). Founders predict trait evolution and population performance after evolutionary rescue in the red flour beetle. *Proceedings of the National Academy of Sciences*, 122(36):e2506244122.

Raynes, Y., Halstead, A. L., and Sniegowski, P. D. (2014). The effect of population bottlenecks on mutation rate evolution in asexual populations. *Journal of Evolutionary Biology*, 27(1):161–169.

Razgour, O., Forester, B., Taggart, J. B., Bekaert, M., Juste, J., Ibáñez, C., Puechmaille, S. J., Novella-Fernandez, R., Alberdi, A., and Manel, S. (2019). Considering adaptive genetic variation in climate change vulnerability assessment reduces species range loss projections. *Proceedings of the National Academy of Sciences*, 116(21):10418–10423.

Reed, T. E., Gienapp, P., and Visser, M. E. (2015). Density dependence and microevolution interactively determine effects of phenology mismatch on population dynamics. *Oikos*, 124(1):81–91.

Rees, M. and Ellner, S. P. (2016). Evolving integral projection models: evolutionary demography meets eco-evolutionary dynamics. *Methods in Ecology and Evolution*, 7(2):157–170.

Regoes, R. R., Wiuff, C., Zappala, R. M., Garner, K. N., Baquero, F., and Levin, B. R. (2004). Pharmacodynamic functions: a multiparameter approach to the design of antibiotic treatment regimens. *Antimicrobial Agents and Chemotherapy*, 48(10):3670–3676.

Renton, M., Busi, R., Neve, P., Thornby, D., and Vila-Aiub, M. (2014). Herbicide resistance modelling: past, present and future. *Pest Management Science*, 70(9):1394–1404.

Restif, O. and Grenfell, B. T. (2007). Vaccination and the dynamics of immune evasion. *Journal of the Royal Society Interface*, 4(12):143–153.

Rex Consortium (2010). The skill and style to model the evolution of resistance to pesticides and drugs. *Evolutionary Applications*, 3(4):375–390.

Rex Consortium and others (2013). Heterogeneity of selection and the evolution of resistance. *Trends in Ecology & Evolution*, 28(2):110–118.

Ribeiro, R. M. and Bonhoeffer, S. (2000). Production of resistant HIV mutants during antiretroviral therapy. *Proceedings of the National Academy of Sciences*, 97(14):7681–7686.

Rousset, F. (1999). Reproductive value vs sources and sinks. *Oikos*, 86(3):591–596.

Roux, F. and Reboud, X. (2007). Herbicide resistance dynamics in a spatially heterogeneous environment. *Crop Protection*, 26(3):335–341.

Russo, M., Pompei, S., Sogari, A., Corigliano, M., Crisafulli, G., Puliafito, A., Lamba, S., Erriquez, J., Bertotti, A., Gherardi, M., et al. (2022). A modified fluctuation-test framework characterizes the population dynamics and mutation rate of colorectal cancer persister cells. *Nature Genetics*, 54(7):976–984.

Salamon, M., St-Martin, M., Barrett, R., and Derry, A. (2025). Evolutionary rescue and adaptive reversal allowed the persistence of freshwater copepods during historical lake acidification and ph recovery. *bioRxiv*, pages 2025–02.

Samani, P. and Bell, G. (2010). Adaptation of experimental yeast populations to stressful conditions in relation to population size. *Journal of Evolutionary Biology*, 23(4):791–796.

Samani, P. and Bell, G. (2016). The ghosts of selection past reduces the probability of plastic rescue but increases the likelihood of evolutionary rescue to novel stressors in experimental populations of wild yeast. *Ecology Letters*, 19(3):289–298.

Santer, M. and Uecker, H. (2020). Evolutionary rescue and drug resistance on multicopy plasmids. *Genetics*, 215(3):847–868.

Scheiner, S. M., Barfield, M., and Holt, R. D. (2017). The genetics of phenotypic plasticity. XV. Genetic assimilation, the Baldwin effect, and evolutionary rescue. *Ecology and Evolution*, 7(21):8788–8803.

Scheiner, S. M., Barfield, M., and Holt, R. D. (2020). The genetics of phenotypic plasticity. XVII. Response to climate change. *Evolutionary Applications*, 13(2):388–399.

Schiffers, K., Bourne, E. C., Lavergne, S., Thuiller, W., and Travis, J. M. (2013). Limited evolutionary rescue of locally adapted populations facing climate change. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120083.

Schmid, M., Paniw, M., Postuma, M., Ozgul, A., and Guillaume, F. (2022). A trade-off between robustness to environmental fluctuations and speed of evolution. *The American Naturalist*, 200(1):E16–E35.

Scibilia, K. R., Gallagher, K., Masud, M., Robertson-Tessi, M., Gatenbee, C. D., West, J., Llamas, P., Prabhakaran, S., Gallaher, J., and Anderson, A. R. (2025). Mathematical oncology: How modeling is transforming clinical decision-making. *Cancer research*, 85(24):4866–4879.

Scire, J., Hozé, N., and Uecker, H. (2019). Aggressive or moderate drug therapy for infectious diseases? Trade-offs between different treatment goals at the individual and population levels. *PLoS Computational Biology*, 15(8):e1007223.

Searle, C. L. and Christie, M. R. (2021). Evolutionary rescue in host-pathogen systems. *Evolution*, 75(11):2948–2958.

Serra, M. C. and Haccou, P. (2007). Dynamics of escape mutants. *Theoretical Population Biology*, 72(1):167–178.

Shang, Y., Kasada, M., and Kondoh, M. (2024). Rescue or murder? The effect of prey adaptation to the predator subjected to fisheries. *Ecology and Evolution*, 14(12):e70336.

Sharma, A., Hill, A., Kurbatova, E., van der Walt, M., Kvasnovsky, C., Tupasi, T. E., Caoili, J. C., Gler, M. T., Volchenkov, G. V., Kazennyy, B. Y., et al. (2017). Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. *The Lancet Infectious Diseases*, 17(7):707–715.

Shaw, M. (1989). Independent action of fungicides and its consequences for strategies to retard the evolution of fungicide resistance. *Crop Protection*, 8(6):405–411.

Shibasaki, S. and Yamamichi, M. (2024). The double-edged effect of environmental fluctuations on evolutionary rescue. *bioRxiv*.

Siedentop, B., Kachalov, V. N., Witzany, C., Egger, M., Kouyos, R. D., and Bonhoeffer, S. (2024). The effect of combining antibiotics on resistance: A systematic review and meta-analysis. *eLife*, 13:RP93740.

Siska, V., Eriksson, A., Mehlig, B., and Manica, A. (2018). A metapopulation model of the spread of the devil facial tumour disease predicts the long term collapse of its host but not its extinction. *bioRxiv*.

Smalley, I., Kim, E., Li, J., Spence, P., Wyatt, C. J., Eroglu, Z., Sondak, V. K., Messina, J. L., Babacan, N. A., Maria-Engler, S. S., et al. (2019). Leveraging transcriptional dynamics to improve BRAF inhibitor responses in melanoma. *EBioMedicine*, 48:178–190.

Smart, A. S. and Phillips, B. L. (2023). Optimizing targeted gene flow to maximize local genetic diversity: when and how to act under various scenarios of environmental change. *Conservation Genetics*, 24(6):869–882.

Sokurenko, E. V., Gomulkiewicz, R., and Dykhuizen, D. E. (2006). Source–sink dynamics of virulence evolution. *Nature Reviews Microbiology*, 4(7):548–555.

Souza, K. S., Fortunato, D. S., Jardim, L., Terribile, L. C., Lima-Ribeiro, M. S., Mariano, C. Á., Pinto-Ledezma, J. N., Loyola, R., Dobrovolski, R., Rangel, T. F., et al. (2023). Evolutionary rescue and geographic range shifts under climate change for global amphibians. *Frontiers in Ecology and Evolution*, 11:1038018.

Souza, K. S., Jardim, L., Rodrigues, F., Batista, M. C., Rangel, T. F., Gouveia, S., Terribile, L. C., Ribeiro, M. S., Fortunato, D. S., and Diniz Filho, J. A. F. (2019). How likely are adaptive responses to mitigate the threats of climate change for amphibians globally? *Frontiers of Biogeography*, 11(3).

Stahlke, A. R., Epstein, B., Barbosa, S., Margres, M. J., Patton, A. H., Hendricks, S. A., Veillet, A., Fraik, A. K., Schönfeld, B., McCallum, H. I., Hamede, R. K., Jones, M. E., Storfer, A., and Hohenlohe, P. A. (2021). Contemporary and historical selection in Tasmanian devils (*Sarcophilus harrisii*) support novel, polygenic response to transmissible cancer. *Proceedings of the Royal Society B: Biological Sciences*, 288(1951):20210577.

Stammnitz, M. R., Gori, K., Kwon, Y. M., Harry, E., Martin, F. J., Billis, K., Cheng, Y., Baez-Ortega, A., Chow, W., Comte, S., Eggertsson, H., Fox, S., Hamede, R. K., Jones, M., Lazenby, B., Peck, S., Pye, R., Quail, M. A., Swift, K., Wang, J., Wood, J., Howe, K., Stratton, M. R., Ning, Z., and Murchison, E. P. (2023). The evolution of two transmissible cancers in Tasmanian devils. *Science*, 380(6642):283–293.

Stana, R., Ben-David, U., Weissman, D. B., and Ram, Y. (2025). Evolutionary rescue by aneuploidy in tumors exposed to anti-cancer drugs. *Genetics*, 230:iyaf098.

Stelkens, R. B., Brockhurst, M. A., Hurst, G. D., and Greig, D. (2014). Hybridization facilitates evolutionary rescue. *Evolutionary Applications*, 7(10):1209–1217.

Storfer, A., Beer, M. A., Gallinson, D., Jones, M. E., Hamede, R., McCallum, H., and Margres, M. J. (2025). The devil in more detail: Eco-evolutionary genomics of tasmanian devil persistence despite range-wide spread of a fatal, transmissible cancer. *Plos Pathogens*, 21(9):e1013523.

Strickland, K., Jones, M. E., Storfer, A., Hamede, R. K., Hohenlohe, P. A., Margres, M. J., McCallum, H. I., Comte, S., Lachish, S., and Kruuk, L. E. B. (2024). Adaptive potential in the face of a transmissible cancer in Tasmanian devils. *Molecular Ecology*, 33(21):e17531. e17531 MEC-24-0363.R1.

Sudo, M., Takahashi, D., Andow, D. A., Suzuki, Y., and Yamanaka, T. (2018). Optimal management strategy of insecticide resistance under various insect life histories: Heterogeneous timing of selection and interpatch dispersal. *Evolutionary Applications*, 11(2):271–283.

Svara, F. and Rankin, D. J. (2011). The evolution of plasmid-carried antibiotic resistance. *BMC Evolutionary Biology*, 11(1):130.

Svensson, E. I. and Connallon, T. (2019). How frequency-dependent selection affects population fitness, maladaptation and evolutionary rescue. *Evolutionary Applications*, 12(7):1243–1258.

Tabashnik, B. E. (1990). Modeling and evaluation of resistance management tactics. In *Pesticide resistance in arthropods*, pages 153–182. Springer.

Tabashnik, B. E., Brévault, T., and Carrière, Y. (2013). Insect resistance to Bt crops: lessons from the first billion acres. *Nature biotechnology*, 31(6):510–521.

Tabashnik, B. E., Gassmann, A. J., Crowder, D. W., and Carrière, Y. (2008). Insect resistance to Bt crops: evidence versus theory. *Nature biotechnology*, 26(2):199–202.

Takahashi, D., Yamanaka, T., Sudo, M., and Andow, D. A. (2017). Is a larger refuge always better? Dispersal and dose in pesticide resistance evolution. *Evolution*, 71(6):1494–1503.

Tanaka, M. M. and Wahl, L. M. (2022). Surviving environmental change: when increasing population size can increase extinction risk. *Proceedings of the Royal Society B: Biological Sciences*, 289(1976):20220439.

Taylor, C. E. (1983). Evolution of resistance to insecticides: the role of mathematical models and computer simulations. In *Pest resistance to pesticides*, pages 163–173. Springer.

Taylor, C. E. and Georghiou, G. P. (1979). Suppression of insecticide resistance by alteration of gene dominance and migration. *Journal of Economic Entomology*, 72(1):105–109.

Taylor, N. P. and Cunniffe, N. J. (2023a). Modelling quantitative fungicide resistance and breakdown of resistant cultivars: designing integrated disease management strategies for septoria of winter wheat. *PLOS Computational Biology*, 19(3):e1010969.

Taylor, N. P. and Cunniffe, N. J. (2023b). Optimal resistance management for mixtures of high-risk fungicides: robustness to the initial frequency of resistance and pathogen sexual reproduction. *Phytopathology*, 113(1):55–69.

Tazzyman, S. and Bonhoeffer, S. (2014). Plasmids and evolutionary rescue by drug resistance. *Evolution*, 68(7):2066–2078.

Thompson, P. L. and Fronhofer, E. A. (2019). The conflict between adaptation and dispersal for maintaining biodiversity in changing environments. *Proceedings of the National Academy of Sciences of the United States of America*, 116(42):21061–21067.

Toll-Riera, M., Olombrada, M., Castro-Giner, F., and Wagner, A. (2022). A limit on the evolutionary rescue of an antarctic bacterium from rising temperatures. *Science Advances*, 8(28):eabk3511.

Tomasini, M. and Peischl, S. (2020). When does gene flow facilitate evolutionary rescue? *Evolution*, 74(8):1640–1653.

Tomasini, M. and Peischl, S. (2022). The role of spatial structure in multi-deme models of evolutionary rescue. *Journal of Evolutionary Biology*, 35(7):986–1001.

Traulsen, A., Gokhale, C. S., Shah, S., and Uecker, H. (2022). The Covid-19 pandemic: basic insights from basic mathematical models version 1.0. *NAL-live*, 2022(3):01000.

Travis, J. M., Smith, H. S., and Ranwala, S. M. (2010). Towards a mechanistic understanding of dispersal evolution in plants: conservation implications. *Diversity and Distributions*, 16(4):690–702.

Trubenova, B., Krejca, M. S., Lehre, P. K., and Koetzing, T. (2019). Surfing on the seascape: Adaptation in a changing environment. *Evolution*, 73(7):1356–1374.

Trubenová, B., Roizman, D., Rolff, J., and Regoes, R. R. (2022). Modeling polygenic antibiotic resistance evolution in biofilms. *Frontiers in Microbiology*, 13:916035.

Uecker, H. (2017). Evolutionary rescue in randomly mating, selfing, and clonal populations. *Evolution*, 71(4):845–858.

Uecker, H. (2025). Meeting report on the Symposium "Evolutionary Applications" at the 3rd Joint Congress on Evolutionary Biology.

Uecker, H. and Bonhoeffer, S. (2021). Antibiotic treatment protocols revisited: the challenges of a conclusive assessment by mathematical modelling. *Journal of The Royal Society Interface*, 18(181):20210308.

Uecker, H. and Hermisson, J. (2011). On the fixation process of a beneficial mutation in a variable environment. *Genetics*, 188(4):915–930.

Uecker, H. and Hermisson, J. (2016). The role of recombination in evolutionary rescue. *Genetics*, 202(2):721–732.

Uecker, H., Otto, S., and Hermisson, J. (2014). Evolutionary rescue in structured populations. *The American Naturalist*, 183(1):E17–E35.

Unckless, R. L. and Orr, H. A. (2020). The population genetics of evolutionary rescue in diploids: X chromosomal versus autosomal rescue. *The American Naturalist*, 195(3):561–568.

United States Environmental Protection Agency (2 Jan 2026). Introduction to biotechnology regulation for pesticides: Insect resistance management in Bt crops (Bt Crop IRM). `https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/introduction-biotechnology-regulation-pesticides#resistance`. Accessed: 2026-01-02.

van den Bosch, F., Fraaije, B., Oliver, R., van den Berg, F., and Paveley, N. (2015). The use of mathematical models to guide fungicide resistance management decisions. In *Fungicide Resistance in Plant Pathogens: Principles and a Guide to Practical Management*, pages 49–62. Springer.

van den Bosch, F. and Gilligan, C. A. (2008). Models of fungicide resistance dynamics. *Annu. Rev. Phytopathol.*, 46(1):123–147.

Van Den Elzen, C. L., Kleynhans, E. J., and Otto, S. P. (2017). Asymmetric competition impacts evolutionary rescue in a changing environment. *Proceedings of the Royal Society B: Biological Sciences*, 284(1857):20170374.

Van Dyken, J. D. (2020). Evolutionary rescue from a wave of biological invasion. *The American Naturalist*, 195(1):115–128.

Van Eldijk, T. J. B., Bisschop, K., and Etienne, R. S. (2020). Uniting community ecology and evolutionary rescue theory: community-wide rescue leads to a rapid loss of rare species. *Frontiers in Ecology and Evolution*, 8:552268.

van Velzen, E. (2023). High importance of indirect evolutionary rescue in a small food web. *Ecology Letters*, 26(12):2110–2121.

Vander Wal, E., Garant, D., Festa-Bianchet, M., and Pelletier, F. (2013). Evolutionary rescue in vertebrates: evidence, applications and uncertainty. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 368(1610):20120090.

Vanselow, A., Halekotte, L., and Feudel, U. (2022). Evolutionary rescue can prevent rate-induced tipping. *Theoretical Ecology*, 15(1):29–50.

Varah, A., Ahodo, K., Coutts, S. R., Hicks, H. L., Comont, D., Crook, L., Hull, R., Neve, P., Childs, D. Z., Freckleton, R. P., and Norris, K. (2020). The costs of human-induced evolution in an agricultural system. *Nature Sustainability*, 3(1):63–71.

Vedder, D., Lens, L., Martin, C. A., Pellikka, P., Adhikari, H., Heiskanen, J., Engler, J. O., and Sarmento Cabral, J. (2022). Hybridization may aid evolutionary rescue of an endangered East African passerine. *Evolutionary Applications*, 15(7):1177–1188.

Vinton, A. C. and Vasseur, D. A. (2020). Evolutionary tracking is determined by differential selection on demographic rates and density dependence. *Ecology and Evolution*, 10(12):5725–5736.

Wahl, L. and Campos, P. R. (2023). Evolutionary rescue on genotypic fitness landscapes. *Journal of the Royal Society Interface*, 20(208):20230424.

Wahl, L. and Zhu, A. (2015). Survival probability of beneficial mutations in bacterial batch culture. *Genetics*, 200(1):309–320.

Wahl, L. M., Gerrish, P. J., and Saika-Voivod, I. (2002). Evaluating the impact of population bottlenecks in experimental evolution. *Genetics*, 162(2):961–971.

Wahl, L. M. and Tanaka, M. M. (2022). Hazardous loss of genetic diversity through selective sweeps in asexual populations. *The American Naturalist*, 199(3):313–329.

Walsworth, T. E., Schindler, D. E., Colton, M. A., Webster, M. S., Palumbi, S. R., Mumby, P. J., Essington, T. E., and Pinsky, M. L. (2019). Management for network diversity speeds evolutionary adaptation to climate change. *Nature Climate Change*, 9(8):632–636.

Walters, R. J. and Berger, D. (2019). Implications of existing local (mal)adaptations for ecological forecasting under environmental change. *Evolutionary Applications*, 12(7):1487–1502.

Wang, X., Fan, M., and Hao, L. (2017). Adaptive evolution of body size subject to indirect effect in trophic cascade system. *Biosystems*, 159:23–35.

Wei, X., Ghosh, S. K., Taylor, M. E., Johnson, V. A., Emini, E. A., Deutsch, P., Lifson, J. D., Bonhoeffer, S., Nowak, M. A., Hahn, B. H., et al. (1995). Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*, 373(6510):117–122.

Wells, K., Hamede, R. K., Jones, M. E., Hohenlohe, P. A., Storfer, A., and McCallum, H. I. (2019). Individual and temporal variation in pathogen load predicts long-term impacts of an emerging infectious disease. *Ecology*, 100(3):e02613.

Wells, K., Hamede, R. K., Kerlin, D. H., Storfer, A., Hohenlohe, P. A., Jones, M. E., and McCallum, H. I. (2017). Infection of the fittest: devil facial tumour disease has greatest effect on individuals with highest reproductive output. *Ecology Letters*, 20(6):770–778.

West, J., Adler, F., Gallaher, J., Strobl, M., Brady-Nicholls, R., Brown, J., Roberson-Tessi, M., Kim, E., Noble, R., Viossat, Y., et al. (2023). A survey of open questions in adaptive therapy: Bridging mathematics and clinical translation. *eLife*, 12:e84263.

Weyerer, F., Weinbach, A., Zarfl, C., and Allhoff, K. T. (2023). Eco-evolutionary dynamics in two-species mutualistic systems: One-sided population decline triggers joint interaction disinvestment. *Evolutionary Ecology*, 37(6):981–999.

WHO (2024). *WHO guideline for malaria*. World Health Organization, Geneva.

Wilson, B. A., Pennings, P. S., and Petrov, D. A. (2017). Soft selective sweeps in evolutionary rescue. *Genetics*, 205(4):1573–1586.

Wu, Y., Saddler, C. A., Valckenborgh, F., and Tanaka, M. M. (2014). Dynamics of evolutionary rescue in changing environments and the emergence of antibiotic resistance. *Journal of Theoretical Biology*, 340:222–231.

Xu, C. C., Fugère, V., da Costa, N. B., Beisner, B. E., Bell, G., Cristescu, M. E., Fussmann, G. F., Gonzalez, A., Shapiro, B. J., and Barrett, R. D. (2025). Pre-exposure to stress reduces loss of community and genetic diversity following severe environmental disturbance. *Current Biology*, 35(5):1061–1073.

Xu, K. (2022). The genetic basis of selfing rate evolution. *Evolution*, 76(5):883–898.

Xu, K. (2023a). The effects of selfing on multi-step adaptation. *Evolution*, 77(2):482–495.

Xu, K. (2023b). Population rescue through an increase in selfing rate under pollen limitation: Plasticity vs. evolution. *The American Naturalist*, 202(3):337–350.

Xu, K., Vision, T. J., and Servedio, M. R. (2023). Evolutionary rescue under demographic and environmental stochasticity. *Journal of Evolutionary Biology*, 36(10):1525–1538.

Yacine, Y., Allhoff, K. T., Weinbach, A., and Loeuille, N. (2021). Collapse and rescue of evolutionary food webs under global warming. *Journal of Animal Ecology*, 90(3):710–722.

Yagoobi, S. and Traulsen, A. (2021). Fixation probabilities in network structured meta-populations. *Scientific Reports*, 11(1):17979.

Yamaguchi, R., Wiley, B., and Otto, S. P. (2022). The phoenix hypothesis of speciation. *Proceedings of the Royal Society B: Biological Sciences*, 289(1987):20221186.

Yamamichi, M. and Miner, B. E. (2015). Indirect evolutionary rescue: prey adapts, predator avoids extinction. *Evolutionary Applications*, 8(8):787–795.

Zeineddine, M. and Jansen, V. A. (2009). To age, to die: parity, evolutionary tracking and Cole's paradox. *Evolution*, 63(6):1498–1507.

Zhang, G. M. and Baucom, R. S. (2025). Herbicidal interference: glyphosate drives both the ecology and evolution of plant–herbivore interactions. *New Phytologist*, 245(2):807–817.

Zhang, J., Cunningham, J., Brown, J., and Gatenby, R. (2022). Evolution-based mathematical models significantly prolong response to abiraterone in metastatic castrate-resistant prostate cancer and identify strategies to further improve outcomes. *eLife*, 11:e76284.

Zhang, J., Cunningham, J. J., Brown, J. S., and Gatenby, R. A. (2017). Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. *Nature Communications*, 8(1):1816.

Zhang, Q.-G. and Buckling, A. (2011). Antagonistic coevolution limits population persistence of a virus in a thermally deteriorating environment. *Ecology Letters*, 14(3):282–288.

Zheng, Q. (1999). Progress of a half century in the study of the Luria–Delbrück distribution. *Mathematical Biosciences*, 162(1-2):1–32.

Zhou, D.-H. and Zhang, Q.-G. (2023). Loss and recovery of ecological diversity associated with evolutionary rescue in abruptly and gradually deteriorating environments. *Evolution*, 78(4):768–777.

Zur Wiesch, P. A., Kouyos, R., Engelstädter, J., Regoes, R. R., and Bonhoeffer, S. (2011). Population biological principles of drug-resistance evolution in infectious diseases. *The Lancet Infectious Diseases*, 11(3):236–247.

Modeling evolutionary rescue

Supplementary File S1

S1 Building and partitioning the citation network

We built a matrix of citations from the list of articles cited in Sections 4 and Section 5 that contain rescue models (i.e. we exclude reviews, experimental papers, non-rescue studies etc.). The (ith, jth) entry of this matrix corresponds to 1 if the ith article cites the jth article, 0 otherwise. This matrix of citations was built using the list of cited references of the articles as found on Web of Science on the 27th of January 2026 (214 articles) or 30th of January 2026 (12 articles) researched under their titles. The matrix contains 127 out of the 156 papers from our filtered list of papers from the initial literature search on Web of Science (the remaining 29 are cited elsewhere in the review) and 99 additional papers. Eight relevant papers from Sections 4 and Section 5 are not included as they are not on Web of Science, presumably because they are a book chapter (Holt and Gomulkiewicz, 1997), too recent (Patil et al., 2025; Stana et al., 2025), pre-prints (Shibasaki and Yamamichi, 2024; Deraje and Osmond, 2025; Deraje and Uecker, 2025), or for unknown reasons (Kanarek et al., 2015; Christie and Searle, 2018). These articles are therefore not represented in the network.

Once the matrix of citations had been built, we applied the Louvain community detection algorithm (Blondel et al., 2008) of the NetworkX Python package to partition the citation network into clusters. The Louvain method is a two-phase recursive algorithm that maximises the modularity coefficient. The modularity coefficient associated to a given partition is a number between 0 and 1 quantifying the degree to which the edges of the network fall within communities rather than at random. The Louvain algorithm starts by considering each node of the network as its own community and shifts nodes between communities whenever this increases the modularity coefficient. When this is no longer possible, it initiates a second phase by considering each community as a node and tries merging communities to increase the modularity coefficient. Note that the final partition is only ensured to locally maximize the modularity coefficient. We chose the community structure that maximized the modularity coefficient across a range of resolution parameter values (21 values uniformly distributed in $[0.8, 1.2]$; 1 is the default value for this parameter). To account for the stochasticity in the merging order of the algorithm, for each parameter value, 1000 independent searches were seeded. The highest modularity coefficient $Q = 0.40834$ was found at a resolution parameter of 1.14. This value of modularity coefficient indicates a reasonably modular network (Fortunato and Barthelemy, 2007).

The code is available as part of Supplementary Material File S2.

S2 The distribution of persistence times and the excess and the rescue probability

We here provide the equations underlying Figure 4 in the main text. The calculations are equivalent to Holt and Gomulkiewicz (1997), just considering a continuous-time process here.

For a birth-death process with birth rate λ and death rate μ, the probability generating function for the number of individuals at time t, $n(t)$, given $n(0) = 1$, is given by

$$P(z,t) = \left(1 + \frac{1}{\frac{e^{-(\lambda-\mu)t}}{z-1} - \frac{\lambda}{\lambda-\mu}\left(1 - e^{-(\lambda-\mu)t}\right)}\right) \tag{S1}$$

(Allen, 2011), and for $n(0) = n_0$, we have

$$P_{n_0}(z,t) = P(z,t)^{n_0}. \tag{S2}$$

From this, we obtain the distribution of extinction times, T_{ext}, as

$$\begin{aligned} P(T_{\text{ext}} \leq t) = P_{n_0}(0,t) &= \left(1 + \frac{1}{-e^{-(\lambda-\mu)t} - \frac{\lambda}{\lambda-\mu}\left(1 - e^{-(\lambda-\mu)t}\right)}\right)^{n_0} \\ &= \left(\frac{e^{-(\lambda-\mu)t} - 1}{e^{-(\lambda-\mu)t} - \frac{\lambda}{\mu}}\right)^{n_0}. \end{aligned} \tag{S3}$$

Let us now turn to a population that consists of m_0 mutant individuals with birth rates λ_m and death rates μ_m and $N_0 - m_0$ wild-type individuals with birth rates λ_w and μ_w. We ignore new mutations. From general branching process theory, we know that the probability generating function for the total number of individuals at time t is given by

$$P_{\text{total}}(z,t) = \left(P_{\text{mutant}}(z,t)\right)^{m_0} \times \left(P_{\text{wildtype}}(z,t)\right)^{N_0 - m_0}, \tag{S4}$$

where $P_{\text{mutant}}(z,t)$ and $P_{\text{wildtype}}(z,t)$ are given by Eq. (S1) with the appropriate birth and death rates.

The distribution of extinction times is thus given by

$$\begin{aligned} P(T_{\text{ext}} \leq t \,|\, \text{evolution}) &= P_{\text{total}}(0,t) \\ &= \left(\frac{e^{-(\lambda_w-\mu_w)t} - 1}{e^{-(\lambda_w-\mu_w)t} - \frac{\lambda_w}{\mu_w}}\right)^{N_0-m_0} \times \left(\frac{e^{-(\lambda_m-\mu_m)t} - 1}{e^{-(\lambda_m-\mu_m)t} - \frac{\lambda_m}{\mu_m}}\right)^{m_0}. \end{aligned} \tag{S5}$$

For comparison, we consider a purely wild-type population, for which we have

$$P(T_{\text{ext}} \leq t \,|\, \text{no evolution}) = \left(\frac{e^{-(\lambda_w-\mu_w)t} - 1}{e^{-(\lambda_w-\mu_w)t} - \frac{\lambda_w}{\mu_w}}\right)^{N_0}. \tag{S6}$$

The probability of persistence up to at least time t with and without evolution (denoted by A_t and B_t) is given by

$$P(A_t) = P(T_{\text{ext}} > t \,|\, \text{evolution}) = 1 - P(T_{\text{ext}} \leq t \,|\, \text{evolution}) \quad \text{and} \tag{S7}$$

$$P(B_t) = P(T_{\text{ext}} > t \,|\, \text{no evolution}) = 1 - P(T_{\text{ext}} \leq t \,|\, \text{no evolution}), \tag{S8}$$

respectively.

Panel a of Figure 4 shows $P(A_t)$ (for two different values of λ_m) and $P(B_t)$. The excess probability, generalized to time-dependent probability, shown in Panel b, is given by

$$P_{\text{excess}}(t) = P(A_t) - P(B_t) = 1 - P(T_{\text{ext}} \leq t|\text{evolution}) - (1 - P(T_{\text{ext}} \leq t|\text{no evolution}). \tag{S9}$$

Plugging both distributions into the generalization of Eq. (1) in the main text yields

$$\begin{aligned} P_{\text{cond}}(t) &= \frac{P(A_t) - P(B_t)}{1 - P(B_t)} \\ &= \frac{1 - P(T_{\text{ext}} \leq t|\text{evolution}) - (1 - P(T_{\text{ext}} \leq t|\text{no evolution}))}{P(T_{\text{ext}} \leq t|\text{no evolution})} \\ &= 1 - \frac{P(T_{\text{ext}} \leq t|\text{evolution})}{P(T_{\text{ext}} \leq t|\text{no evolution})} \\ &= 1 - \left(\frac{\left(e^{-(\lambda_m - \mu_m)t} - 1\right) \cdot \left(e^{-(\lambda_w - \mu_w)t} - \frac{\lambda_w}{\mu_w}\right)}{\left(e^{-(\lambda_m - \mu_m)t} - \frac{\lambda_m}{\mu_m}\right) \cdot \left(e^{-(\lambda_w - \mu_w)t} - 1\right)} \right)^{m_0}, \end{aligned} \tag{S10}$$

which is plotted in Panel c.

The probability of ultimate survival of the process, given $\lambda_m > \mu_m$, denoted by P_{rescue} in the figure, is given by

$$P_{\text{rescue}} = \lim_{t \to \infty} P(A_t) = \left(\frac{\mu_m}{\lambda_m} \right)^{m_0}. \tag{S11}$$

Since $\lim_{t \to \infty} P(B_t) = 0$, $P_{\text{excess}}(t)$ and $P_{\text{cond}}(t)$ both converge to this value.

References

Allen, L. J. (2011). *An introduction to stochastic processes with applications to biology* (2 ed.). Pearson Education.

Blondel, V. D., J.-L. Guillaume, R. Lambiotte, and E. Lefebvre (2008). Fast unfolding of communities in large networks. *Journal of Statistical Mechanics: Theory and Experiment 2008*(10), P10008.

Christie, M. R. and C. L. Searle (2018). Evolutionary rescue in a host–pathogen system results in coexistence not clearance. *Evolutionary Applications 11*(5), 681–693.

Deraje, P. and M. M. Osmond (2025). Quasi epigenetic equilibrium: the implications of plasticity and variability on evolution and extinction. *bioRxiv*, 2025.08.27.672696.

Deraje, P. and H. Uecker (2025). How do mate-finding Allee effects affect evolutionary rescue? *bioRxiv*, 2025–09.

Fortunato, S. and M. Barthelemy (2007). Resolution limit in community detection. *Proceedings of the National Academy of Sciences 104*(1), 36–41.

Holt, R. D. and R. Gomulkiewicz (1997). The evolution of species' niches: a population dynamic perspective. In H. G. Othmer, F. R. Adler, M. A. Lewis, , and J. C. Dallon (Eds.), *Case Studies in Mathematical Modelling: Ecology, Physiology, and Cell Biology*, pp. 25–50. Prentice Hall Englewood Cliffs, NJ.

Kanarek, A. R., C. T. Webb, M. Barfield, and R. D. Holt (2015). Overcoming Allee effects through evolutionary, genetic, and demographic rescue. *Journal of Biological Dynamics 9*(1), 15–33.

Patil, S., A. Ahmed, Y. Viossat, and R. Noble (2025). Preventing evolutionary rescue in cancer using two-strike therapy. *Genetics*, iyaf255.

Shibasaki, S. and M. Yamamichi (2024). The double-edged effect of environmental fluctuations on evolutionary rescue. *bioRxiv*.

Stana, R., U. Ben-David, D. B. Weissman, and Y. Ram (2025). Evolutionary rescue by aneuploidy in tumors exposed to anti-cancer drugs. *Genetics 230*, iyaf098.