ANNUAL REVIEWS

Annual Review of Ecology, Evolution, and Systematics

Evolutionary Rescue

Graham Bell

Biology Department, McGill University, Montreal, Quebec H3A 1B1, Canada;
email: graham.bell@mcgill.ca

Annu. Rev. Ecol. Evol. Syst. 2017. 48:605–27

First published online as a Review in Advance on September 15, 2017

The *Annual Review of Ecology, Evolution, and Systematics* is online at ecolsys.annualreviews.org

https://doi.org/10.1146/annurev-ecolsys-110316-023011

Keywords

evolutionary rescue, natural selection, eco-evolutionary dynamics, extinction, antibiotic resistance, rapid evolution

Abstract

Populations that experience severe stress may avoid extinction through adaptation by natural selection. This process is called evolutionary rescue and has been studied under different names in medicine, agriculture, and conservation biology. It is a component of the emerging field of eco-evolutionary dynamics, which investigates how the ecological attributes of species may evolve rapidly under strong selection. Its distinguishing feature is to combine the evolutionary concept of relative fitness with the ecological concept of absolute fitness in a synthetic theory of persistent adaptation. The likelihood of rescue will depend both on attributes of the population, particularly abundance and variation, and on properties of the environment, particularly the rate and severity of deterioration. Medical interventions (e.g., the administration of antibiotics), agricultural practices (e.g., the application of pesticides), and population ecology (e.g., the effects of species introductions) provide numerous examples of evolutionary rescue. The general theory of rescue has been tested in laboratory experiments with microbes, in which experimental evolution shows how different treatments affect the frequency of rescue. Overall, these experiments have supported the predictions of general theory: In particular, abundance, variation, and dispersal have pronounced and repeatable effects on the rescue of populations and communities. Extending these laboratory results to the field is a major task for future research.

INTRODUCTION

Ecology and evolution have developed independently, isolated from one another, for most of their history; they have been studied by different sets of scientists who have published in different journals and attended different conferences. Conscious efforts were occasionally made to link the two; perhaps the strongest was ecological genetics, which championed the observation of natural populations to identify the agents of selection. However, even this had its limits: E.B. Ford, the author of *Ecological Genetics* (1964), once remarked that ecology "seems to be what animals do when they are doing *nothing interesting*" (quoted in Cain & Provine 1992, p. 3). It was established in the 1950s that the range of phenotypes in natural populations could be rapidly modified by natural selection, showing that evolution could be molded in the short term by ecology. It was not until much later that it became widely appreciated that the converse is also true: The ecological attributes of species can evolve in the short term, altering patterns of distribution and abundance. This realization has given rise in recent years to the growing field of eco-evolutionary dynamics (reviewed in Hendry 2016).

The foundations of ecology and evolution rest on two different metrics. In ecology, the fundamental parameter is the rate of increase of a population, which governs its abundance. In evolution, this is replaced by the rate of increase of a type within a population relative to the weighted average of all types, which governs the change in composition. This amounts to a distinction between absolute fitness, as used in ecology, and relative fitness, as used in evolution. The basic innovation of eco-evolutionary dynamics is to incorporate both absolute and relative fitness within the same framework: Heritable variation in relative fitness will necessarily tend to alter the mean phenotype of a population, but this will lead to permanent adaptation only if the absolute fitness of the type with the greatest relative fitness is positive.

This distinction is particularly important when the environment deteriorates to such an extent that a population, as presently constituted, is unable to replace itself and must therefore dwindle over time until it becomes extinct. Natural selection will continue to act with full force in a declining population, but if the most successful types are unable to grow at replacement rate, then it will nevertheless become extinct, although it may persist for longer than a population unable to evolve. In contrast, if at least one of the types that spread has positive absolute fitness, the decline may be halted and eventually reversed, so that the evolved population recovers in abundance and is able to persist indefinitely in the new conditions of growth. The recovery and persistence of a population through natural selection acting on heritable variation is termed evolutionary rescue to distinguish it from other processes, such as dispersal or plasticity, which may also prevent extinction.

Evolutionary rescue has been studied intensively in two fields, conservation biology and medicine. Conservation biology, broadly defined, is concerned with natural populations exposed to a novel stress, usually imposed by human activities, which subsequently decline and become at risk of extinction. Evolutionary rescue is viewed as a beneficial process that will restore the abundance of a threatened species. Medical research is concerned with the evolution of resistance by viruses, bacteria, and cancer cells to the agents used to exterminate them. Evolutionary rescue is viewed as a malevolent process that propagates disease. Although the underlying eco-evolutionary dynamics are similar in the two fields, they are currently quite isolated from one another, with very few cross-citations (Alexander et al. 2014) (**Figure 1**). I suspect that the evolution of resistance to herbicides and pesticides is a third research focus, based in agriculture and poorly connected with the other two, although this has not yet been investigated by citation analysis. A unified treatment of evolutionary rescue extending across disciplinary boundaries is an important goal for future research.

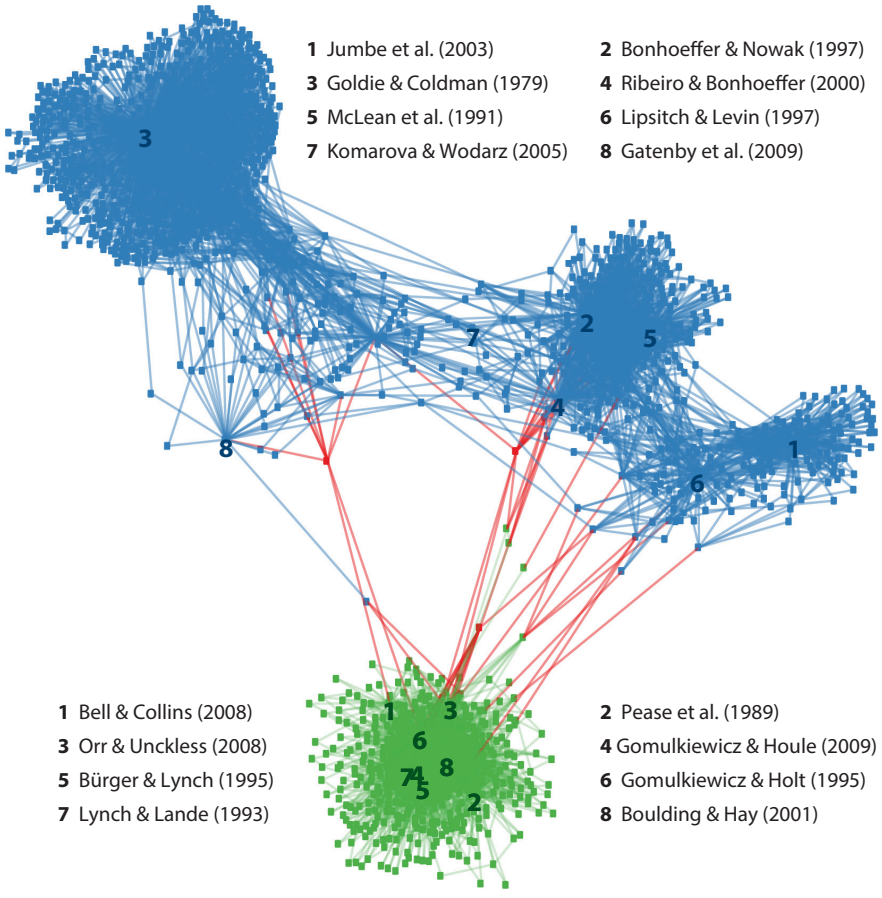

Figure 1

Citation network of evolutionary rescue. Blue lines are citations within the medical literature (addressing viruses, bacteria, and cancer), green lines within the conservation literature, and red lines between the two. Figure adapted from Alexander et al. (2014). This figure is available for reuse under the Creative Commons Attribution 3.0 Unported license (**https://creativecommons.org/licenses/by/3.0/**).

GENERAL PRINCIPLES OF EVOLUTIONARY RESCUE

General Theory: Abrupt Stress

The simplest relevant situation arises when a population is exposed to an abrupt stress that causes it to decline toward extinction unless this is prevented by the spread of a single allele conferring resistance to the stress. The overall population dynamics are the outcome of two processes, the exponential decline of sensitive types and the initially nearly exponential spread of resistant types, resulting in an overall U-shaped trajectory of abundance. This case was first analyzed by Gomulkiewicz & Holt (1995), whose treatment has been revised and extended by Orr & Unckless (2014). The probability of rescue depends on the origin of resistant types, which might already be present in the original population, before the stress is applied, or might arise subsequently by novel mutations. Resistance is more likely to evolve from the standing variation if the number of copies of the resistant allele present before the stress is applied exceeds those likely to arise afterward

through mutation, and vice versa. Resistance tends to evolve more slowly when it is based on novel mutations, because some time must elapse before the first successful mutation starts to spread, so that the minimal population size, in the trough of the U, is lower and recovery is delayed.

A broadly similar theory has been developed for the evolution of antibiotic resistance within infected hosts (the mutant selection window hypothesis; reviewed in Drlica 2003). If no antibiotic has been administered, susceptible types have greater fitness, so that resistant types are rare or absent. At successively higher tissue concentrations of antibiotic, the advantage of the susceptible types is first diminished and then reversed, so that any resistant types that have arisen by mutation or horizontal gene transfer have greater fitness and tend to increase in frequency above some threshold concentration. The advantage of these resistant types increases with dose up to the point at which the growth of resistant types begins to be impaired, and at very high doses, neither type can grow and selection ceases.

Rather similar theories, then, have been developed in population biology and in medicine, although in population biology the U-shaped trajectory of rescue is emphasized, whereas in medicine the relationship of relative fitness to dose has received the most attention. In both cases, rescue is more likely to occur in large populations, because larger populations have both more standing variation and a greater mutation supply rate, and when resistant types have a greater advantage over susceptible types.

The two bodies of theory differ in their treatment of fitness. Population biology theory has consistently used positive absolute fitness as an essential condition for rescue, whereas the medical account of within-host evolution has invoked only the relative fitness of resistant and susceptible types. A radically different interpretation of antibiotic resistance supposes that the dose administered is sufficient to kill all susceptible bacteria immediately. Any resistant types that are already present can now invade the host, because their competitors have been eliminated, provided that their absolute fitness is positive. This is an ecological process of expansion through competitive release, however, rather than an evolutionary process of modification through natural selection (Day et al. 2015).

General Theory: Deteriorating Environment

Natural environments are continually changing, and any change is likely to be for the worse, because populations have become adapted to past conditions but cannot anticipate future conditions. A prolonged episode of directional change in the environment may put a population at risk of extinction if conditions eventually deteriorate to the point at which the current population cannot sustain itself. Natural selection may rescue the population if it drives a change in the mean phenotype that does not lag too far behind the optimal phenotype at any given time. A viable population will therefore become modified at the same rate that the environment deteriorates. Because there is a limit to the rate of modification, set by the genetic variance of fitness, there is necessarily also a limit to the maximum rate of sustained environmental deterioration that a population can tolerate. Quantitative genetic models in which genetic variance is assumed to be replenished by mutation show that rescue is more likely when conditions change slowly and when there is abundant genetic variation (Lynch & Lande 1993). Bürger & Lynch (1995) showed that the maximal rate of environmental change that can be sustained indefinitely is equivalent to approximately 0.1 phenotypic standard deviations per generation. This might be much less in very small populations, however, because demographic stochasticity is more pronounced (Gabriel & Bürger 1992). It may also be unreasonable to assume that there is no limit to the degree of tolerance that can be attained, so that long-continued deterioration may eventually lead to conditions that cannot be tolerated by any phenotype within the potential range of variation of the population.

A mutation that confers resistance to the current level of stress is unlikely to be highly specific and may also confer a degree of resistance to somewhat higher levels of stress. The genetic correlation between viability at different levels of stress may then enable a population to persist for sufficiently long in a deteriorating environment that a second mutation, extending the level of stress that can be tolerated, has an opportunity to arise and spread. The population can then adapt through the fixation of a series of mutations conferring successively higher levels of resistance (Samani & Bell 2010). The effectiveness of this process clearly depends on population size, mutation rate, and the pattern of genetic correlation but has not yet been investigated using a formal population genetics model.

Fluctuating Environments

After one episode of rescue, the environment may again deteriorate, gradually or abruptly, through the imposition of a qualitatively different kind of stress. Any surviving populations will now have undergone two successive rescues, and this sequence of stressors could be extended further. It is not clear whether rescue from a prior stressor will increase, reduce, or leave unchanged the likelihood of surviving a different subsequent stressor. It might be imagined that a rescued population had demonstrated an enhanced evolvability (e.g., because of an elevated mutation rate) and was thereby more likely to survive a subsequent period of severe stress. Conversely, a rescued population is likely to have experienced loss of abundance and genetic variation, rendering it less likely to survive a subsequent stress. There has been little theoretical exploration of these possibilities.

Heterogeneous Environments

The environment may consist of a number of sites each occupied by a local population. Conditions may or may not differ among sites, and the average condition of sites may or may not deteriorate over time. If offspring are able to disperse from one site to another, alleles that spread in one local population may be transmitted to other populations within the metapopulation. Immigrants increase population size and are a source of variation. In principle, directional selection in one population, causing adaptation to local conditions, might be obstructed by the immigration of differently adapted individuals from other sites (see Bourne et al. 2014). In the context of evolutionary rescue, this would require very high rates of dispersal, because the strong selection imposed by severe stress is likely to exceed a modest rate of immigration from unstressed populations. Dispersal might also obstruct adaptation because all the individuals of a rare locally adapted type might be moved to other sites (Kirkpatrick & Peischl 2013). Furthermore, sites with high levels of stress may be colonized by immigrants from sites in which adaptation to somewhat lower levels of stress has evolved, if there is a genetic correlation between growth at somewhat different levels of stress. Hence, dispersal is likely to facilitate evolutionary rescue in metapopulations unless the dispersal amounts to something like complete exchange, with little or no continuity of populations from one generation to the next.

Many sites within the geographical range of a species might be occupied by sink populations that would decline to extinction if they were not frequently restocked by immigrants from more favorable sites. Sink populations can be rescued if types with positive rates of increase are present among the immigrants (Holt & Gomulkiewicz 1997).

In bacteria, dispersal is magnified by horizontal gene transfer, following either immigration or contact with noncellular entities such as gene cassettes. Antibiotic resistance genes often spread in this way, especially those carried on plasmids (Ochman et al. 2000, von Wintersdorff et al. 2016). Mutators that are deficient in methyl-mismatch repair are also particularly vulnerable to horizontal gene transfer, and hence more likely to acquire resistance from other strains.

Density Regulation and Competition

A density-regulated population subjected to a severe stress experiences two opposed tendencies: the reduction of abundance caused by the stress and the restoration of abundance caused by an elevated rate of increase at low density. Hence, a density-regulated population is more likely to recover from low abundance caused by stress than a population with a constant rate of increase. Current theory is inconsistent (cf. Boulding & Hay 2001 with Chevin & Lande 2010), perhaps because of differing underlying models of density dependence (Osmond & de Mazancourt 2013).

A population might be sufficiently abundant to be rescued most of the time after an episode of severe stress, because some variant, present initially at low frequency or arising subsequently by mutation, happens to be resistant. If two similar species, with the same combined abundance, experience the same stress, then other things being equal, they will together have the same probability of rescue. The variant responsible, however, may occur in only one of them, in which case the other will become extinct. Competition between species therefore reduces the frequency of rescue for any given species. This simple argument is less convincing when adaptation to stress reduces competition (Osmond & de Mazancourt 2013) or an inferior competitor is able to adapt more rapidly (Fussmann & Gonzalez 2013).

In communities with complex trophic structure, any focal species may interact with competitors, predators, and prey, some or all of which may respond to a stress that would threaten the extinction of the focal species considered in isolation. The incidence of evolutionary rescue in complex communities has not yet been investigated theoretically.

RESCUE IN HUMANIZED ENVIRONMENTS

An evolutionary rescue experiment is launched whenever a patient begins a course of antibiotic treatment or a field is sprayed with a herbicide. The direct and indirect effects of medical therapy, agricultural practice, and industrial activity provided striking examples of adaptation and extinction long before the phrase evolutionary rescue was coined.

Antibiotic Resistance

There are two extensive meta-analyses of the vast literature on the evolution of antibiotic resistance, Costelloe et al. (2010) and Bell et al. (2014); the former deals with bacterial populations within individual patients, whereas the latter surveys a broader range of regional studies. Both conclude that pathogenic bacteria often evolve resistance within infected patients. The main evidence for this conclusion is that resistance is stronger among bacteria isolated from patients who have recently (within 1 month) received antibiotic therapy than from those who have not done so recently (within the last year). To illustrate this point, the effect of administering an antibiotic on the spread of resistant bacteria in a patient is shown in **Figure 2** for the case of urinary infections. Patients who have been prescribed an antibiotic within the last month are very likely to harbor strains resistant to that particular antibiotic; as time goes by, the frequency of resistant strains declines, although they can persist for a year or more. It is worth quoting in full the main conclusions reached by Costelloe et al. (2010, p. 5) from a survey of 24 large-scale studies:

- Antibiotics prescribed to an individual in primary care were consistently found to be associated with resistance of urinary and respiratory bacteria to those antibiotics in that individual.
- Antibiotics prescribed in primary care may impact on bacterial resistance in a patient for up to 12 months.

Figure 2

The effect of recent antibiotic treatment on the frequency of resistant strains of bacteria in urinary tract infections. The odds ratio is equivalent to a standardized difference between treatment and control groups. Abbreviations: NR, not reported; ST, sulfamethoxazole-trimethoprim. Figure adapted from Costelloe et al. (2010). This figure is available for reuse under the Creative Commons Attribution Noncommercial 2.0 Generic License (**https://creativecommons.org/licenses/by-nc/2.0/**).

- The greater the number or duration of antibiotic courses prescribed in the previous 12 months, the greater the likelihood that resistant bacteria would be isolated from that patient.

This is powerful, if sobering, evidence for the effectiveness of evolutionary rescue in microbial populations. The ecological and evolutionary dynamics of antibiotic resistance have been discussed by Drlica (2003), Gandon et al. (2012), and Day et al. (2015).

Vaccination is an extremely effective means of disease control whenever it can be applied, and the absence of vaccine resistance contrasts strongly with the nearly universal evolution of antibiotic resistance. This is likely to be attributable chiefly to population size: The immune system of a vaccinated patient attacks invading pathogens when they are still very rare, whereas antibiotics are administered only when symptoms appear because the pathogens have become very abundant. Large-scale vaccination programs can reduce populations of viral pathogens to very low levels, and have succeeded in making the smallpox virus completely extinct (Henderson & Klepac 2013).

Herbicide Resistance

The evolution of herbicide resistance in agricultural weeds has been reviewed in Délye et al. (2013), who distinguish between two modes of resistance: target-site resistance, involving elevated expression of the target protein or alteration of the herbicide binding site, and nontarget resistance, which includes a variety of other mechanisms related to the general stress response. Target-site resistance appeared soon after the widespread deployment of herbicides, tends to be specific to a particular herbicide, and is usually based on dominant alleles arising by novel mutation. Nontarget resistance has been identified more recently, often confers broad resistance to a range of herbicides, and appears to arise from standing genetic variation at several or many loci. The history of herbicide resistance has been reviewed in Shaner (2014). Neve et al. (2014) have contributed an exceptionally valuable synthesis that relates the evolution of herbicide resistance to the broader field of evolutionary rescue and eco-evolutionary dynamics. Current information on herbicide resistance is collated by the International Survey of Herbicide-Resistant Weeds at **http://www.weedscience.org**.

When a herbicide is applied to a field, the dose will vary somewhat from place to place, causing selection for plants able to survive a sublethal dose. In outcrossing species, alleles that each confer some degree of resistance can be aggregated by recombination, resulting in the evolution of fully resistant strains. Busi & Powles (2009) exposed susceptible strains of *Lolium* to stressful but sublethal doses of glyphosate and found that a third of progeny were able to survive at the recommended field dose after three or four cycles of selection and crossing. Manalil et al. (2011) extended this observation by observing the rapid evolution of resistance to diclofop, a widely used postemergence herbicide, in *Lolium* populations growing in a realistic crop-field setting. Similar observations were reported by Neve & Powles (2005) and Norsworthy et al. (2008). An attempt to select for glyphosate resistance in *Arabidopsis*, which is almost exclusively self-fertilized, was unsuccessful, despite testing a range of ecotypes and using chemical mutagenesis to generate variation (Brotherton et al. 2007).

Fungicide Resistance

A new generation of fungicides replaced older methods such as Bordeaux mixture and sulfur dust during the 1970s, and the percentage of crops sprayed with fungicide increased from almost zero in 1970 to almost 100% in the 1990s. The new antifungal agents introduced in the 1960s and 1970s were designed to target specific sites in the pathogen and thus led rapidly to the evolution

of target-site resistance (Russell 2005); in many cases, resistance evolved within 2–7 years of the introduction of a new class of fungicide (Lucas et al. 2015, table 1). The large populations and prolific spore production of pathogenic fungi can readily lead to the rapid spread of rare resistant types when strong selection is imposed by highly toxic chemicals. Laboratory screens, with or without mutagenesis, have succeeded in isolating resistant genotypes at low frequency (e.g., Hocart et al. 1990, Hollomon et al. 1997, Reijo et al. 1994), so there is no doubt that rescue based on novel mutations is likely to have often occurred.

Powdery mildew is a very common and widespread fungal disease of cereal crops that provides an example of the evolution of resistance to successive generations of fungicide. It was first attacked with 2-aminopyrimidines in the early 1970s. Selection for resistant strains could be demonstrated (Wolfe 1984), but this group of fungicides remained effective for a while because susceptible strains were competitively superior (Hollomon 1978) and therefore remained common as long as large areas of crop were untreated. The 2-aminopyrimidines were superseded by morpholine and azole fungicides. The level of resistance to morpholines was initially very low but had increased by the early 1990s (Godet & Limpert 1998). Azoles were used at the same time but encountered higher levels of resistance, based on a single allele (Wyand & Brown 2005). Within a few years, target-site resistance to both classes had become widespread, and quinone outside inhibitors largely replaced them by the mid-1990s. Resistance evolved within 2 years (Chin et al. 2001) based on a single substitution in mitochondrial cytochrome *b* (Sierotzki et al. 2000). Field trials showed an increase in the resistant allele from 2% to 58% after three fungicide treatments (Fraaije et al. 2002). A new generation of fungicides is now in use to which there is as yet no resistance in the field, although resistant strains have been identified in the laboratory (Hollomon et al. 1997).

Pesticide Resistance

Resistance to insecticides appeared very soon after the widespread use of agents such as dichlorodiphenyltrichloroethane (DDT) in the 1940s and rapidly proliferated: The few cases reported by the mid-1940s had ballooned to approximately 500 species by the mid-1980s (Mallet 1989). Resistance is usually based on single alleles that cause target-site modification and often arise repeatedly in different lineages (Daborn & Le Goff 2004, Roush & McKenzie 1987). Resistance to warfarin in rats is also based on alleles at a single major locus (Bishop et al. 1977, Kohn et al. 2000). Research on insecticide resistance has been almost exclusively concerned with the genetic and physiological mechanisms of resistance and there are few evolutionary studies, although the experimental evolution of pesticide resistance has been studied in model organisms such as *Caenorhabditis* (Lopes et al. 2008) and *Daphnia* (Jansen et al. 2011). Bacterial toxins [*Bacillus thuringiensis* (Bt) toxin] have been very successful control agents, without widespread resistance in the field, although laboratory selection experiments have identified several sources of potential resistance (Griffitts & Aroian 2005).

Industrial Pollution

Industrial pollution often creates toxic sites where most species become extinct, although a few may be rescued. Some of these situations are classics of evolutionary biology and need only the briefest mention here. Mine tailings contaminated by heavy metals create strong selection for resistance (McNeilly & Bradshaw 1968). The species that survive have standing genetic variation for resistance, whether on abandoned mine sites (Bradshaw 1991) or in more restricted sites near galvanized structures (Al-Hiyaly et al. 1993); conversely, populations in which there is little or no detectable standing genetic variation usually fail to evolve resistance. Soot pollution in cities

rendered some species of moth so conspicuous that they were easily detected by predatory birds, leading to the spread of melanic types (Bishop 1972). Acidification by discharges from smelters destroyed most of the plankton community in downwind lakes, leaving only, in the most acid lakes, a remnant population of acid-tolerant algae (Kwiatkowski & Roff 1976). Very acidic (pH < 3) mining lakes in Germany were dominated by species of *Ochromonas* and *Chlamydomonas*, but the extent to which these were locally adapted was not ascertained (Nixdorf et al. 1998). Because fish can evolve the ability to live at pH 3.5 (Hirata et al. 2003), it seems likely that populations of algae and invertebrates can be rescued in acid lakes, but there has been no systematic investigation of this possibility.

Climate change is an indirect consequence of industrial pollution that may alter the distribution and abundance of organisms. Thomas et al. (2004) predicted that 15–20% of animal and plant species will become extinct by 2050 (i.e., approximately 400,000 by the date of publication of this article), given moderate rates of climate change and permitting dispersal. Sekercioglu et al. (2008) predicted that climate change will cause the extinction of 400–550 species of birds by 2100. The mechanisms by which species might avoid extinction under climate change, including evolutionary rescue, have therefore been widely discussed (Bell & Collins 2008, Moritz & Agudo 2013). The current state of knowledge is summarized in the volume edited by Merilä & Hendry (2014), with articles on fish, birds, mammals, and other groups. Studies of land plants are exceptionally reliable because local adaptation can readily be evaluated by reciprocal transplant experiments. Franks et al. (2014) reviewed 35 studies, all of which found some evidence of adaptive response to climate change. In 21 studies, there was evidence that fitness increased in response to climate change, although 8 of 12 studies estimated that the observed rate of adaptation would not be sufficient to balance the rate of environmental change.

Introductions and Invasions

Introduced species such as rats and goats can drive native species to extinction, especially on islands. Other species persist, but I have not found any assessment of whether evolutionary rescue might be responsible. An introduced fungus has eradicated populations of chestnut throughout their range, seemingly with no evolution of resistance, although less virulent strains of the pathogen may have spread in some populations (Anagnostakis 1987). Elm trees have likewise been eliminated from large parts of their range, although some resistant strains have been reported and efforts have been made to use them to reintroduce the species (Schlarbaum et al. 1998). Other forest trees are also threatened by exotic pathogens, with little evidence of the rapid evolution of resistance typical of newly introduced pesticides. This may reasonably be attributed to their very long generation times.

In contrast, there are several cases in which animals challenged by a lethal introduced pathogen have persisted after evolving resistance. Juvenile rainbow trout are badly harmed by an introduced myxozoan parasite that can depress recruitment so much that the population is endangered. Susceptibility to the pathogen declined in a wild population over four or five generations to a level similar to that of resistant domesticated stocks (Miller & Vincent 2008). Crickets introduced in Hawaii are attacked and killed by a parasitoid fly that locates male hosts through their mating call; infested cricket populations may be reduced in abundance to the point at which they are in danger of extinction. Within 20 generations, male crickets had evolved female-like wings through the spread of a loss-of-function allele at a sex-linked locus and were thus resistant to the parasitoid (Tinghitella 2008, Zuk et al. 2006). Bat populations that have survived infection by the fungal pathogen causing white-nose disease seem to have evolved some degree of resistance to an otherwise lethal epidemic (Langwig et al. 2017).

Parasites, parasitoids, and predators have often been deliberately introduced in an effort to control pests. They are often very effective, but there seems to be little or no evidence that target

species evolve resistance to them (Roderick & Navajas 2003) despite evidence for standing genetic variation in some cases (Hufbauer & Roderick 2005). Possible reasons for this are discussed by Holt & Hochberg (1997). Microbes are a different matter: The classical example is the recovery of rabbit populations in Australia after the deliberate introduction of the myxoma virus, in which evolutionary rescue involved adaptation by both pathogen and host (reviewed in Fenner 1983).

The humanized environment provides a wealth of examples in which evolutionary rescue has succeeded or (much more often) failed in permitting populations to persist when they are exposed to a severe stress (Palumbi 2001). Like all unplanned experiments, they are often difficult to interpret in terms of the processes that lead to success or failure. For a more precise analysis, we must turn to the laboratory.

RESCUE IN LABORATORY EXPERIMENTS

The main vehicle for evaluating the predictions made by the theory of evolutionary rescue is experimental evolution in the laboratory using microbial populations. The strength of this approach is that many replicates of large populations can be propagated over many generations to yield robust estimates of the frequency of rescue. The predictions themselves are for the most part intuitively clear and can readily be related to the main body of population genetics theory.

Experimental Design

The simplest design is a pulse experiment in which an experimental population is abruptly exposed to a severe stress. For example, this is routinely used to estimate the rate of mutation to resistance to an antibiotic through a fluctuation test. Alternatively, a grown culture of known density can be serially diluted and the dilution series exposed to a stress to discover the least number of cells capable of regrowth. Pulse experiments provide a direct demonstration of rescue based on standing genetic variation in the form of resistant types already present at low frequency in the population.

A press experiment subjects an experimental population to chronic stress, for example, increasing concentrations of an antibiotic, during long-term culture by serial transfer or in a chemostat. A press experiment that begins with an isogenic population, derived from a single clone growing under benign conditions, records adaptation to severe stress through novel mutations alone. If the founding population is genetically diverse, such as a sample from an outbred sexual stock, rescue may be attributable either to novel mutation or to standing variation. Press experiments are not unique to studies of evolutionary rescue and indeed were commonplace before the term was invented; for example, Saffhill et al. (1970) used this design to evolve populations of RNA sequences resistant to doses of ethidium bromide that completely inhibited the replication of their ancestor.

A press–pulse experiment combines these designs in two phases. During the first phase, the population experiences a deteriorating environment, as in a press experiment; in the second phase it is transferred abruptly to conditions that would be lethal to the ancestor. Press–pulse experiments are used to evaluate the effect of prior exposure to a stressor on the likelihood of rescue.

Experimental Results: Abundance and Variation

The hallmark of evolutionary rescue is the U-shaped trajectory of decline followed by recovery that was first predicted by Gomulkiewicz & Holt (1995). This has now been repeatedly observed in experiments (e.g., Agashe et al. 2011, Bell & Gonzalez 2009, Ramsayer et al. 2013) and provides the means of estimating the frequency of rescue in different circumstances.

Abundance facilitates rescue both because larger populations initially contain a greater range of variation and because they produce a greater number of mutants before becoming extinct. Bell

& Gonzalez (2009) reported a simple pulse experiment using yeast populations exposed to high salt concentrations. These populations contained rare resistant types and the frequency of rescue increased predictably with population size. Ramsayer et al. (2013) found that a larger population of *Pseudomonas* was more likely than a smaller population to evolve resistance to a lethal dose of streptomycin. These were short-term experiments in which standing genetic variation was the basis of adaptation. This can be manipulated directly, if rather crudely, by mixing different numbers of clones; thus, Ramsayer et al. (2013) found that populations comprising a mixture of clones evolved resistance to streptomycin more often than populations founded by a single clone.

The most extensive investigation of the effect of abundance was a press–pulse experiment with yeast, using culture vessels of different sizes to create a broad range of population sizes (Samani & Bell 2010). The experimental populations were transferred at increasing concentrations of salt until resistant types, identified by large colonies formed after plating on to high-salt agar medium, began to appear in substantial numbers. The rate of increase of each population was then measured at a salt concentration that almost completely suppressed growth in the ancestor and was found to increase as a power function of population size. Larger populations also generated larger resistant colonies. As each population was initially isogenic, novel mutations were solely responsible for adaptation: Larger populations produced both more mutations and mutations of larger effect.

There have been few attempts to test the effect of directly elevating the mutation rate. Perron et al. (2006) used both normal and mutator strains of two species of bacteria in a press experiment to investigate the experimental evolution of resistance to an antimicrobial peptide. In one case, the mutator showed a greater quantitative response to selection, but not in the other; almost all replicate lines of both mutator and normal strains were rescued, however, so no qualitative effect of mutation on rescue could be demonstrated. Couce et al. (2015) showed unequivocally that a normal strain of *Escherichia coli* was invariably killed by concentrations of the β-lactam antibiotic cefotaxime that two mutator strains could survive. Mutator alleles are often found, moreover, in antibiotic-resistant strains from natural populations, in which the very large (up to a thousandfold) increase in mutation rate they cause is a plentiful source of novel mutations (Chopra et al. 2003, Eliopoulos & Blázquez 2003, LeClerc et al. 1996, Oliver et al. 2000).

Populations of flour beetles given corn rather than wheat as a food source decline in abundance and eventually become extinct if founded by a single strain. Populations founded by mixtures of strains often follow a U-shaped rescue curve, with more diverse populations being rescued more often and being more abundant after recovery (Agashe 2009, Agashe et al. 2011). Flour beetles are sexual and the strains interbreed freely, so that mixed populations express diversity arising from recombination. Unicellular eukaryotes can be cultured either with or without sexual episodes, allowing clonal diversity and sexuality to be combined in factorial experiments. In a press experiment exposing the unicellular green alga *Chlamydomonas* to increasing concentrations of salt, the few populations surviving at the highest concentration were from the only treatment combination that gave rise to recombinational diversity, the sexual treatment founded from several clones (Lachapelle & Bell 2012). Long-term asexual lines of *Chlamydomonas* almost always become extinct when cultured in the dark, where only genotypes able to use acetate as a carbon source can survive, whereas most populations founded from outcrossed sexual populations survive (Bell 2013).

Experimental Results: Dispersal and Immigration

Resistance to rifampicin evolved more readily in populations that received immigrants from a source population unexposed to the antibiotic (Perron et al. 2008): Populations receiving no immigrants often became extinct, whereas those receiving many (as many or more than were transferred after each growth cycle) were invariably rescued. Bell & Gonzalez (2011) set up yeast

metapopulations on microwell plates, where each well contained a local population and there was a gradient of salt concentration across the plate. The yeast on each plate could extend its geographical range by the evolutionary rescue of local populations at the edge of the range. These rescue events were approximately twice as frequent when dispersal was allowed as when local populations were completely isolated. In this experiment, the dispersal rate was only 5% of the population per growth cycle.

Experimental Results: Environmental Deterioration

Samani & Bell (2010) cultured yeast populations at increasing salt concentrations and found that there was a critical threshold for rescue when they were abruptly exposed to severe salt stress. Gonzalez & Bell (2013) exposed populations of two species of yeast to a range of salt concentrations for eight growth cycles before transferring them to a lethal concentration. Prior exposure to high sublethal concentrations increased the frequency of rescue events in *Saccharomyces cerevisiae* (domesticated baker's yeast) but not in its sister species, the wild yeast *S. paradoxus*. This difference was tentatively attributed to the much greater preexisting tolerance of *S. cerevisiae* to high salt concentrations. The rate of environmental deterioration modulated the effect of beneficial mutations in *Chlamydomonas* populations exposed to phosphate limitation, with rapid change favoring a few mutations of large effect, whereas adaptation to slower deterioration was based on more mutations of smaller effect (Collins & de Meaux 2009).

The frequency of rescue among *E. coli* populations exposed to the antibiotic rifampicin was very sensitive to the rate of environmental deterioration: Very few populations receiving a single pulse of antibiotic were rescued, whereas most populations exposed to a slowly increasing dose survived, with an intermediate rate of deterioration causing an intermediate frequency of rescue (Lindsey et al. 2013) (**Figure 3**). Rifampicin resistance is often based on mutations in the genes encoding RNA polymerase. The rare events of rescue following abrupt exposure to a high concentration of rifampicin were associated with single point mutations in one of these genes. When the concentration was gradually increased, resistance was usually based on two or more mutations, with the earlier mutations spreading because they conferred resistance to sublethal doses; secondary mutations subsequently extended the range of resistance to higher doses, providing concrete evidence for the scenario envisaged by Samani & Bell (2010). Furthermore, the genetic reconstruction of

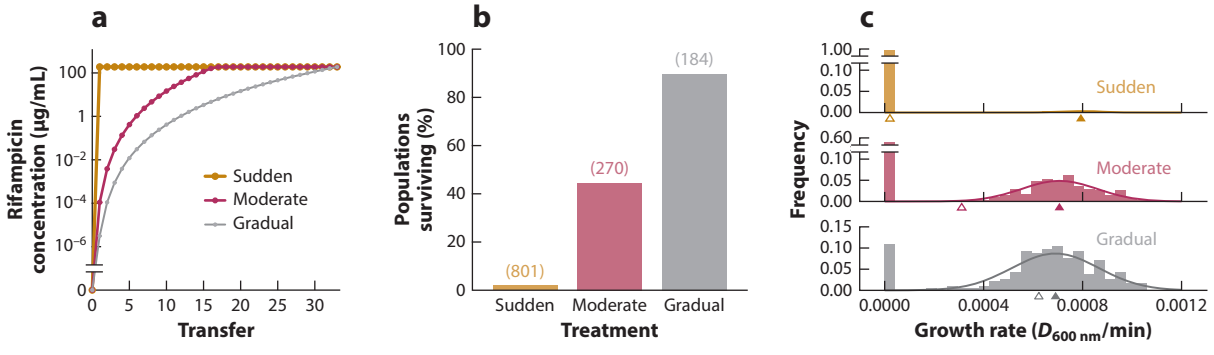

Figure 3

Evolutionary rescue in relation to the rate of environmental deterioration: (*a*) increase of rifampicin concentration, (*b*) frequency of evolutionary rescue, and (*c*) growth rate of populations at the end of the experiment. Figure adapted with permission from Lindsey et al. (2013).

all four combinations of double mutants showed strong epistatic interactions between mutations, so that the final highly resistant genotype could evolve only through a particular succession of less highly resistant genotypes. This result furnishes a clear genetic mechanism for evolutionary rescue in a gradually deteriorating environment.

The experiments by Perron et al. (2008) and Bell & Gonzalez (2011) both evaluated the joint effects of dispersal and the rate of environmental deterioration and found an interaction between them. Rescue was more frequent in *Pseudomonas* populations at low immigration rates when antibiotic concentration increased slowly; at high immigration rates, all populations were rescued regardless of the rate of deterioration. Prior exposure to a deteriorating environment increased the frequency of rescue in yeast metapopulations when they were abruptly transferred to lethal conditions, but dispersal had little effect.

Chlamydomonas populations that had previously undergone rescue in hostile environments were more likely to become extinct when challenged with a qualitatively different stress, relative to populations that had been cultured in permissive conditions (Lachapelle et al. 2017). Populations of yeast that had survived prior starvation through culturing on refractory substrates were more likely to become extinct immediately after exposure to a novel stressor, relative to unstressed controls (Samani & Bell 2016). Those that survived, however, were more likely to be rescued in subsequent generations. Prior rescue, therefore, degraded the plastic response to a novel stressor but enhanced the evolutionary response. An alternative experimental design is to return a population adapting to stress to its benign original environment from time to time; this procedure reduced the frequency of rescue among phage populations exposed to gradually increasing temperature (Hao et al. 2015).

Experimental Results: Community Evolutionary Rescue

The fate of individual species under severe stress in complex communities has not yet been investigated experimentally. The community as a whole may become completely extinct or may recover in some form, with or without change in composition. The recovery of ecological attributes such as productivity, in whole or in part, has been called community evolutionary rescue, or more simply, community rescue. Low-Décarie et al. (2015) extracted microbial communities from natural soils and sediments and set up experimental metacommunities with crossed gradients of a nutrient (glucose) and a stressor (the herbicide dalapon). The metacommunity was first allowed to adapt for several growth cycles before being transferred to uniformly stressful conditions lethal to the original source community. The frequency of community rescue increased with initial diversity (manipulated by dilution), prior exposure (to intermediate levels of stress), and dispersal between local communities (**Figure 4**). The species composition of the community changed in response to the stress, but rescue was attributed to adaptation as well as species sorting, because all species were initially extinguished by severe stress. This press–pulse experiment demonstrated that the main conclusions of similar experiments with single species, including the importance of variation, prior exposure, and dispersal, can be extended to entire communities.

Experimental Results: Limitations

Most of the predictions made by a general theory of evolutionary rescue have been strikingly confirmed by laboratory experiments. To this extent, the theory can be considered one of the most successful in evolutionary biology. These experiments have several weaknesses, however, which may impede a simple interpretation or an extension of the conclusions to natural populations.

The rescue of stressed populations propagated for many generations is usually attributed to standing genetic variation or to novel mutations. In some but by no means all cases, there is

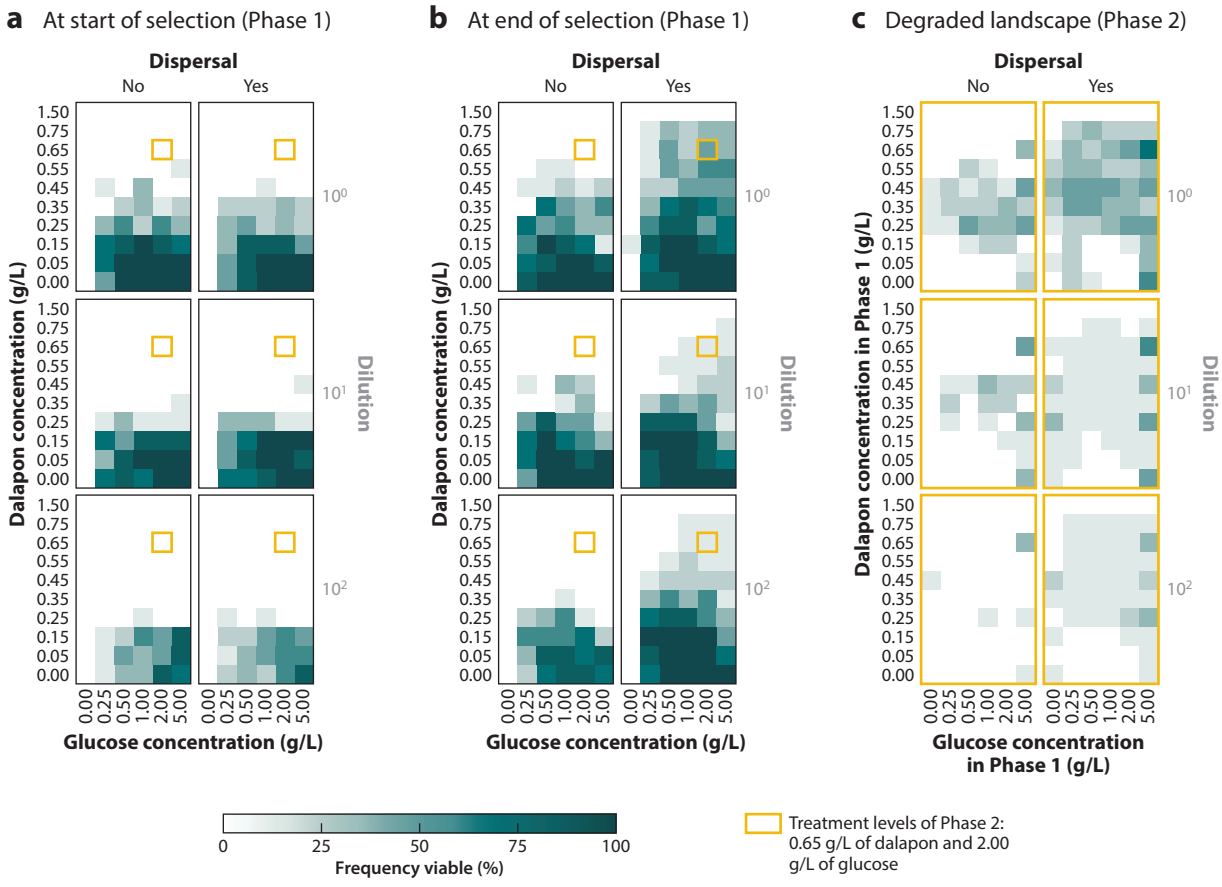

Figure 4

Evolutionary community rescue in a press–pulse experiment using a complex microbial community in a heterogeneous environment. Each rectangle represents a 96-well plate with crossed gradients of glucose and a herbicide, with two levels of dispersal and three levels of initial diversity (dilution). Panels *a* and *b* show occupancy of the landscape at the beginning and end, respectively, of the press phase; the darker teal color indicates more surviving replicate populations. Panel *c* shows the pulse phase when all populations were transferred to lethal conditions (*orange squares* in panels *a* and *b*). Figure adapted with permission from Low-Décarie et al. (2015). Copyright © 2015 National Academy of Sciences.

conclusive evidence for this interpretation (e.g., Lindsey et al. 2013). The populations used in many experiments are asexual cultures of unicellular eukaryotes such as yeasts and algae in which epigenetic marks might be transmitted for many generations. The evolved salt-tolerant lines of *Chlamydomonas* are one example (Lachapelle & Bell 2012) (**Figure 5**). When the evolved lines are transferred directly into new media, they can tolerate concentrations of up to 20 g/L, whereas the ancestors fail at much lower concentrations. If the lines are first acclimated at low concentrations of salt, however, the ancestors can persist at 20 g/L (the same level as the evolved lines tested without prior acclimation), whereas the tolerance of the evolved lines is extended to approximately 40 g/L. The high tolerance of the evolved lines is partly retained in sexual progeny, produced by back-crossing to the ancestor, after any epigenetic marks have been removed during meiosis. Tolerance of intermediate concentrations is thus an originally inducible character that has been fixed and extended in the evolved lines in a fashion resembling the genetic assimilation proposed by

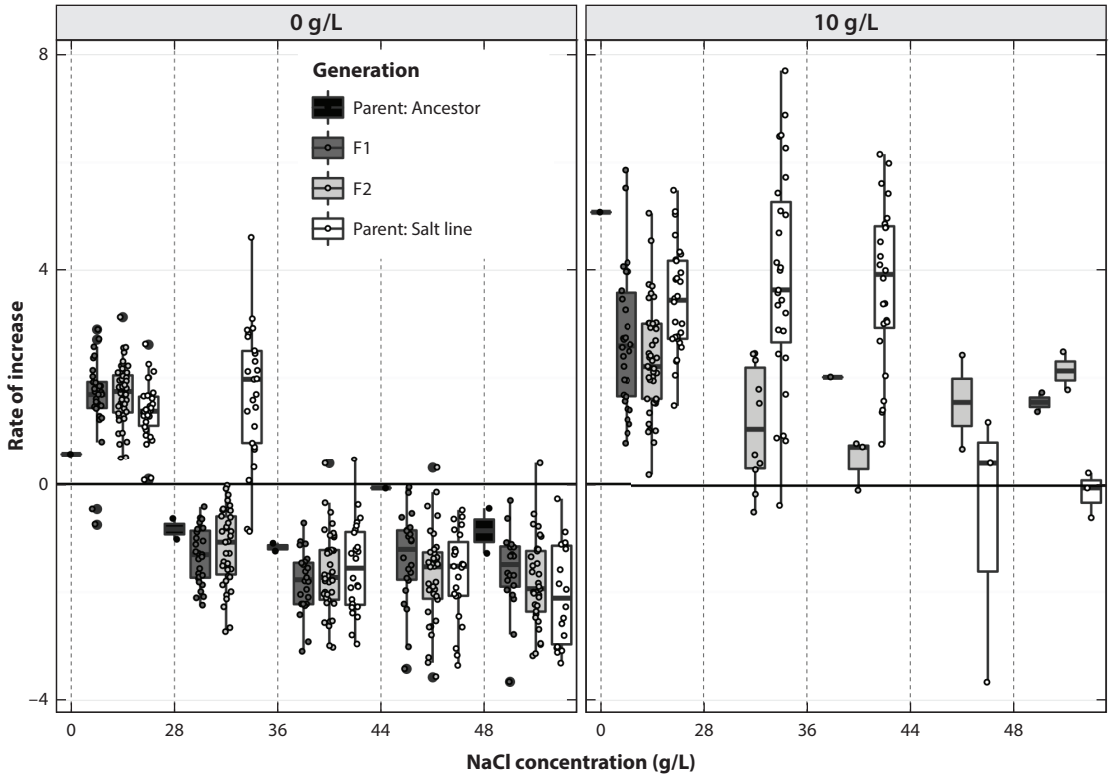

Figure 5

Survival of *Chlamydomonas reinhardtii* in marine conditions. The left panel shows evolved lines, ancestor, and back-crosses when abruptly exposed to a given salt concentration. The right panel shows the same lines when previously acclimated to a 10 g/L salt concentration. Figure adapted with permission from Lachapelle et al. (2015).

Waddington (1953). The assumption that long-continued persistence is based on genetic variation should be checked whenever possible by sequencing or crossing.

Almost all experiments on evolutionary rescue have used microbes to permit evolutionary change to occur within the span of a feasible experiment. The results may well hold in general for antibiotic resistance in pathogenic microbes, but how readily they can be extended to large multicellular organisms is less clear: What we learn from large populations of small organisms may not extend straightforwardly to small populations of large organisms. The most obvious source of disparity is the different balance between novel mutation and standing genetic variation, but plasticity and epigenetic variation may also differ consistently between unicellular and multicellular organisms. Unicellular organisms with large populations and short generations have sometimes been used deliberately as surrogates to anticipate the response of animals and plants to a changing environment; for example, *Chlamydomonas* has been used to investigate both the effect of elevated CO_2 (a permissive treatment; Collins & Bell 2004) and the effect of herbicide (a stressful treatment) (Lagator et al. 2013a,b). Calibrating the response of such model systems will provide the means to predict how populations of large multicellular organisms will respond to severe stress.

Moreover, most experiments have used only a single species of microbe maintained under highly simplified laboratory conditions. The link with diverse communities inhabiting complex

environments might also be fragile; even the link with antibiotic resistance is questionable because the host tissues present a much more hostile and responsive environment than a culture vial or an agar plate. The most serious shortcoming of current research is the lack of field experiments that address the issues of scale and complexity.

FUTURE PROSPECTS

As our understanding of evolutionary rescue matures, it should be possible to apply general principles to particular medical, agricultural, and environmental issues of broad concern. Three conclusions seem particularly clear and robust. First, there is a distinction between large populations of short-lived asexual microbes, in which rescue depends primarily on novel mutation, and small populations of long-lived sexual animals and plants, in which standing genetic variation is likely to be the sole basis of adaptation. Second, rescue is less likely following an abrupt stress than when the environment gradually deteriorates. Third, rescue is facilitated in structured metapopulations by local or limited dispersal. Quantifying these factors for pests and pathogens we wish to eliminate, or for animals and plants we wish to conserve, will be the basis for applying general principles that have been validated in the laboratory to the more complex and less tractable problems presented by natural populations.

This calls for a new research program of highly replicated field experiments to estimate the frequency of rescue for stressed populations. Large arrays of mesocosms, roughly halfway on a logarithmic scale between a microwell and a small lake, could be used to extend laboratory systems to quasi-natural conditions, including a realistic range of trophic interactions. These arrays could also be used to directly address the effect of scale, by showing how the contributions made by different kinds of processes vary with ecosystem volume. Ambitious field experiments are necessary to provide the link between laboratory results and practical solutions to problems of substantial social and economic concern.

Here, I identify two issues that seem especially ripe for investigation as examples of rescue, one from a more applied and the other from a more academic context.

The Dosage Dilemma

A familiar and long-standing controversy in both medicine and agriculture is the dosage dilemma: Should a patient be given the lowest dose of antibiotic that will eliminate susceptible pathogens or a much higher dose that will eliminate even resistant types? Should a field be sprayed with a minimal dose of herbicide or a dose that guarantees elimination of all weeds? This is a dilemma because the two extreme options generate opposed selection pressures. A low dose causes chronic weak selection for low levels of resistance; a high dose eliminates all susceptible or mildly resistant strains, but if a highly resistant strain exists it will expand to exploit the resources freed by the elimination of its competitors. Read et al. (2011) showed that either a low or a high dose may be optimal, with intermediate doses always being suboptimal. The elimination of microbes by low or high levels of stress in different circumstances, such as population size and dispersal, seems to be a clearly defined issue that could readily be decided by experiment.

Ocean Acidification

Elevated atmospheric CO_2 increases the carbonic acid dissolved in seawater and thereby drives down the pH of the world ocean, at present by approximately 0.1 units from its preindustrial value. The further acidification expected to occur during the twenty-first century may have deleterious

effects on marine organisms, especially those with a calcified shell or exoskeleton (Doney et al. 2009, Orr et al. 2005), and fears of widespread extinction have been expressed (Veron 2011). There is considerable uncertainty regarding how marine organisms respond to acidification (Browman 2016, Duarte et al. 2015), however, and the variation among individuals that many studies have reported suggests the potential for adaptation and evolutionary rescue. Laboratory cultures of *Emiliana huxleyi*, an extremely abundant phytoplankton organism with a calcareous test, adapted to elevated CO_2 levels over 700 generations by increasing their calcification rate without any loss of productivity (Benner et al. 2013). Both standing genetic variation and novel mutations can contribute to restoring calcification and growth rates in *Emiliana* populations exposed to elevated CO_2 (Lohbeck et al. 2012, Schlüter et al. 2014). Other organisms failed to evolve specific adaptation after long-term exposure to elevated CO_2 (Crawfurd et al. 2011, Low-Décarie et al. 2013). The potential for marine phytoplankton to evolve in response to ocean acidification has been surveyed by Collins et al. (2014) and Sunday et al. (2014). Further long-term experimental studies of marine organisms exposed to gradual acidification would enable us to judge whether extinction or rescue is more likely in the near future.

Evolutionary rescue stands at the confluence of evolution and ecology, where relative fitness and absolute fitness jointly contribute to the evolution of persistent adaptation in highly stressful environments. I would like to emphasize that evolutionary rescue is about evolutionary mechanisms. So much attention has been given to molecular and genetic mechanisms, especially in medical and agricultural contexts, that the underlying cause for the spread of resistance is often pushed to one side; even in more academic fields the lure of whole-genome sequencing can be too strong to resist (Travisano & Shaw 2012). To understand the fate of populations in danger of extinction, however, it is the evolutionary processes they undergo that must be understood, measured, and used to predict whether or not they are likely to be rescued by natural selection.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

My research program is funded by the Natural Sciences and Engineering Research Council of Canada. I am grateful to A. Gonzalez, R.D. Holt, E. Low-Décarie, and J. Peniston for their comments on an earlier version of this manuscript.

LITERATURE CITED

Agashe D. 2009. The stabilizing effect of intraspecific genetic variation on population dynamics in novel and ancestral habitats. *Am. Nat.* 174(2):255–67

Agashe D, Falk JJ, Bolnick DI. 2011. Effects of founding genetic variation on adaptation to a novel resource. *Evolution* 65(9):2481–91

Alexander HK, Martin G, Martin OY, Bonhoeffer S. 2014. Evolutionary rescue: linking theory for conservation and medicine. *Evol. Appl.* 7(10):1161–79

Al-Hiyaly SAK, McNeilly T, Bradshaw AD, Mortimer AM. 1993. The effect of zinc contamination from electricity pylons. Genetic constraints on selection for zinc tolerance. *Heredity* 70:22–32

Anagnostakis SL. 1987. Chestnut blight: the classical problem of an introduced pathogen. *Mycologia* 79(1):23–37

Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. 2014. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect. Dis.* 14(1):13

Bell G. 2013. Experimental evolution of heterotrophy in a green alga. *Evolution* 67(2):468–76

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

Bell G, Gonzalez A. 2009. Evolutionary rescue can prevent extinction following environmental change. *Ecol. Lett.* 12(9):942–48

Bell G, Gonzalez A. 2011. Adaptation and evolutionary rescue in metapopulations experiencing environmental deterioration. *Science* 332(6035):1327–30

Benner I, Diner RE, Lefebvre SC, Li D, Komada T, et al. 2013. *Emiliania huxleyi* increases calcification but not expression of calcification-related genes in long-term exposure to elevated temperature and pCO_2. *Philos. Trans. R. Soc. B* 368:20130049

Bishop JA. 1972. An experimental study of the cline of industrial melanism in *Biston betularia* (L.) (Lepidoptera) between urban Liverpool and rural North Wales. *J. Anim. Ecol.* 41(1):209–43

Bishop JA, Hartley DJ, Partridge GG. 1977. The population dynamics of genetically determined resistance to warfarin in *Rattus norvegicus* from mid-Wales. *Heredity* 39(3):389–98

Bonhoeffer S, Nowak MA. 1997. Pre-existence and emergence of drug resistance in HIV-1 infection. *Proc. R. Soc. B* 264:631–37

Boulding EG, Hay T. 2001 Genetic and demographic parameters determining population persistence after a discrete change in the environment. *Heredity* 86:313–24

Bourne EC, Bocedi G, Travis JM, Pakeman RJ, Brooker RW, Schiffers K. 2014. Between migration load and evolutionary rescue: dispersal, adaptation and the response of spatially structured populations to environmental change. *Proc. R. Soc. B* 281(1778):20132795

Bradshaw AD. 1991. The Croonian lecture, 1991: genostasis and the limits to evolution. *Philos. Trans. R. Soc. B* 333(1267):289–305

Brotherton JE, Jeschke MR, Tranel PJ, Widholm JM. 2007. Identification of *Arabidopsis thaliana* variants with differential glyphosate responses. *J. Plant Physiol.* 164(10):1337–45

Browman HI. 2016. Applying organized scepticism to ocean acidification research. *ICES J. Mar. Sci.* 73(3):529–36

Bürger R, Lynch M. 1995. Evolution and extinction in a changing environment: a quantitative-genetic analysis. *Evolution* 49(1):151–63

Busi R, Powles S. 2009. Evolution of glyphosate resistance in a *Lolium rigidum* population by glyphosate selection at sublethal doses. *Heredity* 103:318–25

Cain AJ, Provine WB. 1992. Genes and ecology in history. In *Genes in Ecology*, ed. TJ Crawford, GM Hewitt, pp. 3–28. Oxford, UK: Blackwell

Chevin L-M, Lande R. 2010. When do phenotypic plasticity and genetic evolution prevent extinction of a density-regulated population? *Evolution* 64:1143–50

Chin KM, Chavaillaz D, Kaesbohrer M, Staub T, Felsenstein FG. 2001. Characterizing resistance risk of *Erysiphe graminis* f.sp. *tritici* to strobilurins. *Crop Prot.* 20(2):87–96

Chopra I, O'Neill AJ, Miller K. 2003. The role of mutators in the emergence of antibiotic-resistant bacteria. *Drug Resist. Updates* 6(3):137–45

Collins S, Bell G. 2004. Phenotypic consequences of 1,000 generations of selection at elevated CO_2 in a green alga. *Nature* 431(7008):566–69

Collins S, De Meaux J. 2009. Adaptation to different rates of environmental change in *Chlamydomonas*. *Evolution* 63(11):2952–65

Collins S, Rost B, Rynearson TA. 2014. Evolutionary potential of marine phytoplankton under ocean acidification. *Evol. Appl.* 7(1):140–55

Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. 2010. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 340:c2096

Couce A, Rodríguez-Rojas A, Blázquez J. 2015. *Bypass of genetic constraints during mutator evolution to antibiotic resistance. Proc. R. Soc. B* 282(1804):20142698

Crawfurd KJ, Raven JA, Wheeler GL, Baxter EJ, Joint I. 2011. The response of *Thalassiosira pseudonana* to long-term exposure to increased CO_2 and decreased pH. *PLOS ONE* 6(10):e26695

Daborn PJ, Le Goff G. 2004. The genetics and genomics of insecticide resistance. *TRENDS Genet*. 20(3):163–70

Day T, Huijben S, Read AF. 2015. Is selection relevant in the evolutionary emergence of drug resistance? *Trends Microbiol*. 23(3):126–33

Délye C, Jasieniuk M, Le Corre V. 2013. Deciphering the evolution of herbicide resistance in weeds. *Trends Genet*. 29(11):649–58

Doney SC, Fabry VJ, Feely RA, Kleypas JA. 2009. Ocean acidification: the other CO_2 problem. *Annu. Rev. Mar. Sci.* 1:169–92

Donnan PT, Wei L, Steinke DT, Phillips G, Clarke R, et al. 2004. Presence of bacteriuria caused by trimethoprim resistant bacteria in patients prescribed antibiotics: multilevel model with practice and individual patient data. *BMJ* 328:1297–300

Drlica K. 2003. The mutant selection window and antimicrobial resistance. *J. Antimicrob. Chemother.* 52:11–17

Duarte CM, Fulweiler RW, Lovelock CE, Martinetto P, Saunders MI, et al. 2015. Reconsidering ocean calamities. *BioScience* 65(2):130–39

Eliopoulos GM, Blázquez J. 2003. Hypermutation as a factor contributing to the acquisition of antimicrobial resistance. *Clin. Infect. Dis.* 37(9):1201–9

Fenner F. 1983. The Florey lecture, 1983: biological control, as exemplified by smallpox eradication and myxomatosis. *Proc. R. Soc. B* 218(1212):259–85

Fraaije BA, Butters JA, Coelho JM, Jones DR, Hollomon DW. 2002. Following the dynamics of strobilurin resistance in *Blumeria graminis* f.sp. *tritici* using quantitative allele-specific real-time PCR measurements with the fluorescent dye SYBR Green I. *Plant Pathol*. 51(1):45–54

Franks SJ, Weber JJ, Aitken SN. 2014. Evolutionary and plastic responses to climate change in terrestrial plant populations. *Evol. Appl.* 7(1):123–39

Fussmann GF, Gonzalez A. 2013. Evolutionary rescue can maintain an oscillating community undergoing environmental change. *Interface Focus* 3:20130036

Gabriel W, Bürger R. 1992. Survival of small populations under demographic stochasticity. *Theor. Popul. Biol.* 41(1):44–71

Gandon S, Hochberg ME, Holt RD, Day T. 2012. What limits the evolutionary emergence of pathogens? *Philos. Trans. R. Soc. B* 368:20120086

Gatenby RA, Silva AS, Gillies RJ, Frieden BR. 2009. Adaptive therapy. *Cancer Res*. 69:4894–4903

Godet F, Limpert E. 1998. Recent evolution of multiple resistance of *Blumeria* (*Erysiphe*) *graminis* f.sp. *tritici* to selected DMI and morpholine fungicides in France. *Pest Manag. Sci.* 54(3):244–52

Goldie JH, Coldman AJ. 1979. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat. Rep*. 63:1727–31

Gomulkiewicz R, Holt RD. 1995. When does evolution by natural selection prevent extinction? *Evolution* 49(1):201–7

Gomulkiewicz R, Houle D. 2009. Demographic and genetic constraints on evolution. *Am. Nat.* 174:E218–29

Gonzalez A, Bell G. 2013. Evolutionary rescue and adaptation to abrupt environmental change depends upon the history of stress. *Philos. Trans. R. Soc. B* 368(1610):20120079

Griffitts JS, Aroian RV. 2005. Many roads to resistance: how invertebrates adapt to Bt toxins. *Bioessays* 27(6):614–24

Hao YQ, Brockhurst MA, Petchey OL, Zhang QG. 2015. Evolutionary rescue can be impeded by temporary environmental amelioration. *Ecol. Lett.* 18(9):892–98

Hay AD, Thomas M, Montgomery A, Wetherell M, Lovering A, et al. 2005. The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using individual patient data. *J. Antimicrob. Chemother.* 56:146–53

Henderson DA, Klepac P. 2013. Lessons from the eradication of smallpox: an interview with DA Henderson. *Philos. Trans. R. Soc. B* 368(1623):20130113

Hendry AP. 2016. *Eco-Evolutionary Dynamics*. Princeton, NJ: Princeton Univ. Press

Hillier S, Roberts Z, Dunstan F, Butler C, Howard A, Palmer S. 2007. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study. *J. Antimicrob. Chemother.* 60:92–99

Hirata T, Kaneko T, Ono T, Nakazato T, Furukawa N, et al. 2003. Mechanism of acid adaptation of a fish living in a pH 3.5 lake. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 284(5):R1199–212

Hocart MJ, Lucas JA, Peberdy JF. 1990. Resistance to fungicides in field isolates and laboratory-induced mutants of *Pseudocercosporella herpotrichoides*. *Mycol. Res*. 94:9–17

Hollomon DW. 1978. Competitive ability and ethirimol sensitivity in strains of barley powdery mildew. *Ann. Appl. Biol.* 90(2):195–204

Hollomon DW, Wheeler I, Dixon K, Longhurst C, Skylakakis G. 1997. Defining the resistance risk of the new powdery mildew fungicide quinoxyfen. *Pestic. Sci.* 51(3):347–51

Holt RD, Gomulkiewicz R. 1997. How does immigration influence local adaptation? A re-examination of a familiar paradigm. *Am. Nat.* 149:563–72

Holt RD, Hochberg ME. 1997. When is biological control stable (or is it)? *Ecology* 78:1673–83

Hufbauer RA, Roderick GK. 2005. Microevolution in biological control: mechanisms, patterns, and processes. *Biol. Control* 35(3):227–39

Jansen M, Coors A, Stoks R, De Meester L. 2011. Evolutionary ecotoxicology of pesticide resistance: a case study in *Daphnia*. *Ecotoxicology* 20(3):543–51

Jumbe N, Louie A, Leary R, Liu W, Deziel MR, et al. 2003. Application of a mathematical model to prevent in vivo amplification of antibiotic-resistant bacterial populations during therapy. *J. Clin. Investig.* 112:275–85

Kirkpatrick M, Peischl S. 2013. Evolutionary rescue by beneficial mutations in environments that change in space and time. *Philos. Trans. R. Soc. B* 368(1610):20120082

Kohn MH, Pelz HJ, Wayne RK. 2000. Natural selection mapping of the warfarin-resistance gene. *PNAS* 97(14):7911–15

Komarova NL, Wodarz D. 2005. Drug resistance in cancer: principles of emergence and prevention. *PNAS* 102:9714–19

Kwiatkowski RE, Roff JC. 1976. Effects of acidity on the phytoplankton and primary productivity of selected northern Ontario lakes. *Can. J. Bot.* 54(22):2546–61

Lachapelle J, Bell G. 2012. Evolutionary rescue of sexual and asexual populations in a deteriorating environment. *Evolution* 66(11):3508–18

Lachapelle J, Bell G, Colegrave N. 2015. Experimental adaptation to marine conditions by a freshwater alga. *Evolution* 69(10):2662–75

Lachapelle J, Colegrave N, Bell G. 2017. The effect of selection history on extinction risk during severe environmental change. *J. Evol. Biol.* In press. **https://doi.org/10.1111/jeb.13147**

Lagator M, Vogwill T, Colegrave N, Neve P. 2013a. Herbicide cycling has diverse effects on evolution of resistance in *Chlamydomonas reinhardtii*. *Evol. Appl.* 6(2):197–206

Lagator M, Vogwill T, Mead A, Colegrave N, Neve P. 2013b. Herbicide mixtures at high doses slow the evolution of resistance in experimentally evolving populations of *Chlamydomonas reinhardtii*. *New Phytol.* 198(3):938–45

Langwig KE, Hoyt JR, Parise KL, Frick WF, Foster JT, Kilpatrick AM. 2017. Resistance in persisting bat populations after white-nose syndrome invasion. *Philos. Trans. R. Soc. B* 372:20160044

LeClerc JE, Li B, Payne WL, Cebula TA. 1996. High mutation frequencies among *Escherichia coli* and *Salmonella* pathogens. *Science* 274:1208–11

Lindsey HA, Gallie J, Taylor S, Kerr B. 2013. Evolutionary rescue from extinction is contingent on a lower rate of environmental change. *Nature* 494(7438):463–67

Lipsitch M, Levin BR. 1997. The population dynamics of antimicrobial chemotherapy. *Antimicrob. Agents Chemother.* 41:363–73

Lohbeck KT, Riebesell U, Reusch TB. 2012. Adaptive evolution of a key phytoplankton species to ocean acidification. *Nat. Geosci.* 5(5):346–51

Lopes PC, Sucena É, Santos ME, Magalhães S. 2008. Rapid experimental evolution of pesticide resistance in *C. elegans* entails no costs and affects the mating system. *PLOS ONE* 3(11):e3741

Low-Décarie E, Jewell MD, Fussmann GF, Bell G. 2013. Long-term culture at elevated atmospheric CO_2 fails to evoke specific adaptation in seven freshwater phytoplankton species. *Proc. R. Soc. B* 280(1754):20122598

Low-Décarie E, Kolber M, Homme P, Lofano A, Dumbrell A, et al. 2015. Community rescue in experimental metacommunities. *PNAS* 112(46):14307–12

Lucas JA, Hawkins NJ, Fraaije BA. 2015. Chapter two—the evolution of fungicide resistance. *Adv. Appl. Microbiol.* 90:29–92

Lynch M, Lande R. 1993. Evolution and extinction in response to environmental change. *Biot. Interact. Glob. Change* 1993:234–50

Mallet J. 1989. The evolution of insecticide resistance: Have the insects won? *Trends Ecol. Evol.* 4(11):336–40

Manalil S, Busi R, Renton M, Powles SB. 2011. Rapid evolution of herbicide resistance by low herbicide dosages. *Weed Sci.* 59:210–17

McLean AR, Emery VC, Webster A, Griffiths PD. 1991. Population-dynamics of HIV within an individual after treatment with zidovudine. *AIDS* 5:485–89

McNeilly T, Bradshaw AD. 1968. Evolutionary processes in populations of copper tolerant *Agrostis tenuis* Sibth. *Evolution* 22(1):108–18

Merilä J, Hendry AP. 2014. Climate change, adaptation, and phenotypic plasticity: the problem and the evidence. *Evol. Appl.* 7(1):1–14

Metlay JP, Strom BL, Asch DA. 2003. Prior antimicrobial drug exposure: a risk factor for trimethoprim-sulfamethoxazole-resistant urinary tract infections. *J. Antimicrob. Chemother.* 51:963

Miller MP, Vincent ER. 2008. Rapid natural selection for resistance to an introduced parasite of rainbow trout. *Evol. Appl.* 1(2):336–41

Moritz C, Agudo R. 2013. The future of species under climate change: resilience or decline? *Science* 341(6145):504–8

Neve P, Busi R, Renton M, Vila-Aiub MM. 2014. Expanding the eco-evolutionary context of herbicide resistance research. *Pest Manag. Sci.* 70(9):1385–93

Neve P, Powles S. 2005. Recurrent selection with reduced herbicide rates results in the rapid evolution of herbicide resistance in *Lolium rigidum*. *Theor. Appl. Genet.* 110:1154–66

Nixdorf B, Mischke U, Leßmann D. 1998. Chrysophytes and chlamydomonads: pioneer colonists in extremely acidic mining lakes (pH < 3) in Lusatia (Germany). In *Phytoplankton and Trophic Gradients*, ed. M Alvarez-Cobelas, CS Reynolds, P Sánchez-Castillo, J Kristiansen, pp. 315–27. Dordrecht, Neth.: Springer

Norsworthy JK, Scott RC, Smith KL, Oliver LR. 2008. Response of northeastern Arkansas *Palmer amaranth* (*Amaranthus palmeri*) accessions to glyphosate. *Weed Technol.* 22:408–13

Ochman H, Lawrence JG, Groisman EA. 2000. Lateral gene transfer and the nature of bacterial innovation. *Nature* 405(6784):299–304

Oliver A, Cantón R, Campo P, Baquero F, Blázquez J. 2000. High frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection. *Science* 288:1251–53

Orr HA, Unckless RL. 2008. Population extinction and the genetics of adaptation. *Am. Nat.* 172:160–69

Orr HA, Unckless RL. 2014. The population genetics of evolutionary rescue. *PLOS Genet.* 10(8):e1004551

Orr JC, Fabry VJ, Aumont O, Bopp L, Doney SC, et al. 2005. Anthropogenic ocean acidification over the twenty-first century and its impact on calcifying organisms. *Nature* 437(7059):681–86

Osmond MM, de Mazancourt C. 2013. How competition affects evolutionary rescue. *Philos. Trans. R. Soc. B* 368:20120085

Palumbi SR. 2001. Humans as the world's greatest evolutionary force. *Science* 293(5536):1786–90

Pease CM, Lande R, Bull JJ. 1989. A model of population growth, dispersal and evolution in a changing environment. *Ecology* 70:1657–64

Perron GG, Gonzalez A, Buckling A. 2008. The rate of environmental change drives adaptation to an antibiotic sink. *J. Evol. Biol.* 21(6):1724–31

Perron GG, Zasloff M, Bell G. 2006. Experimental evolution of resistance to an antimicrobial peptide. *Proc. R. Soc. B* 273(1583):251–56

Ramsayer J, Kaltz O, Hochberg ME. 2013. Evolutionary rescue in populations of *Pseudomonas fluorescens* across an antibiotic gradient. *Evol. Appl.* 6(4):608–16

Read AF, Day T, Huijben S. 2011. The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy. *PNAS* 108(Suppl. 2):10871–77

Reijo RA, Cooper EM, Beagle GJ, Huffaker TC. 1994. Systematic mutational analysis of the yeast beta-tubulin gene. *Mol. Biol. Cell* 5(1):29–43

Ribeiro RM, Bonhoeffer S. 2000. Production of resistant HIV mutants during antiretroviral therapy. *PNAS* 97:7681–86

Roderick GK, Navajas M. 2003. Genes in new environments: genetics and evolution in biological control. *Nat. Rev. Genet.* 4(11):889–99

Roush RT, McKenzie JA. 1987. Ecological genetics of insecticide and acaricide resistance. *Annu. Rev. Entomol.* 32:361–80

Russell PE. 2005. A century of fungicide evolution. *J. Agric. Sci.* 143(01):11–25

Saffhill R, Schneider-Bernloehr H, Orgel LE, Spiegelman S. 1970. In vitro selection of bacteriophage Qβ RNA variants resistant to ethidium bromide. *J. Mol. Biol.* 51:531–39

Samani P, Bell G. 2010. Adaptation of experimental yeast populations to stressful conditions in relation to population size. *J. Evol. Biol.* 23(4):791–96

Samani P, 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. *Ecol. Lett.* 19(3):289–98

Schlarbaum SE, Hebard F, Spaine PC, Kamalay JC. 1998. Three American tragedies: chestnut blight, butternut canker, and Dutch elm disease. *Exot. Pests East. For. Conf. Proc.*, April 8–10, 1997, Nashville, pp. 45–54. Washington, DC/Nashville, TN: U.S. For. Serv./Tenn. Exot. Pest Plant Counc.

Schlüter L, Lohbeck KT, Gutowska MA, Gröger JP, Riebesell U, Reusch TB. 2014. Adaptation of a globally important coccolithophore to ocean warming and acidification. *Nat. Clim. Change* 4(11):1024–30

Sekercioglu CH, Schneider SH, Fay JP, Loarie SR. 2008. Climate change, elevational range shifts, and bird extinctions. *Conserv. Biol.* 22(1):140–50

Shaner DL. 2014. Lessons learned from the history of herbicide resistance. *Weed Sci.* 62(2):427–31

Sierotzki H, Wullschleger J, Gisi U. 2000. Point mutation in cytochrome *b* gene conferring resistance to strobilurin fungicides in *Erysiphe graminis* f. sp. *tritici* field isolates. *Pestic. Biochem. Physiol.* 68(2):107–12

Steinke DT, Seaton RA, Phillips G, MacDonald TM, Davey PG. 2001. Prior trimethoprim use and trimethoprim-resistant urinary tract infection: a nested case-control study with multivariate analysis for other risk factors. *J. Antimicrob. Chemother.* 47:781–87

Sunday JM, Calosi P, Dupont S, Munday PL, Stillman JH, Reusch TB. 2014. Evolution in an acidifying ocean. *Trends Ecol. Evol.* 29(2):117–25

Thomas CD, Cameron A, Green RE, Bakkenes M, Beaumont LJ, et al. 2004. Extinction risk from climate change. *Nature* 427(6970):145–48

Tinghitella RM. 2008. Rapid evolutionary change in a sexual signal: genetic control of the mutation 'flatwing' that renders male field crickets (*Teleogryllus oceanicus*) mute. *Heredity* 100(3):261–67

Travisano M, Shaw RG. 2012. Lost in the map. *Evolution* 67(2):305–14

Veron JE. 2011. Ocean acidification and coral reefs: an emerging big picture. *Diversity* 3(2):262–74

von Wintersdorff CJ, Penders J, van Niekerk JM, Mills ND, Majumder S, et al. 2016. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. *Front. Microbiol.* 7:173

Waddington CH. 1953. Genetic assimilation of an acquired character. *Evolution* 7(2):118–26

Wolfe MS. 1984. Trying to understand and control powdery mildew. *Plant Pathol.* 33(4):451–66

Wyand RA, Brown JKM. 2005. Sequence variation in the *CYP51* gene of *Blumeria graminis* associated with resistance to sterol demethylase inhibiting fungicides. *Fungal Genet. Biol.* 42(8):726–35

Zuk M, Rotenberry JT, Tinghitella RM. 2006. Silent night: adaptive disappearance of a sexual signal in a parasitized population of field crickets. *Biol. Lett.* 2(4):521–24