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Dynamics of evolutionary rescue in changing environments and the emergence of antibiotic resistance

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HIGHLIGHTS

- Antibiotic resistance evolution is an example of evolutionary rescue.
- We model resistance evolution as evolutionary rescue in changing environments.
- Fitness trade-offs are important in decaying but not periodic environments.
- Dosage is a more important factor than dose frequency in controlling infections.
- Niche construction can have a strong effect on evolutionary rescue.

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ABSTRACT

Populations can go extinct when their environments deteriorate, but evolutionary rescue occurs when a shrinking population adapts to the new environmental conditions. The emergence of resistance from a drug sensitive bacterial population under treatment can be regarded as an instance of evolutionary rescue. Understanding evolutionary rescue in a particular context such as drug resistance requires knowledge of how the environment changes and how selection coefficients change as a result. In this study, we propose a model for evolutionary rescue under three different scenarios of environmental change: abrupt change, periodic fluctuation and gradual decay. The model makes use of the notion of reaction norms to describe fitness values that depend on both genotype and environmental state. We find that although drug sensitive bacterial populations may be large, allowing them to generate resistant mutants frequently, a harsh abrupt change due to the drug usually drives them extinct. Evolutionary rescue occurs far more frequently under the milder forms of environmental change we investigated. Rescue is favoured when the absolute fitnesses of individuals remain sufficiently high over the range of environment qualities experienced by the population. The minimum environment quality, which is inversely related to drug dose in the antibiotic context, is thus an important factor. Interestingly, in the periodic fluctuation model, the inter-dose period is less influential in promoting rescue through resistance unless the minimum environment quality is in a particular range. We also investigated fitness trade-offs across environments including the case of a resistant allele not subject to any trade-off (a “superbug”). This fitness trade-off affects the probability of rescue in decaying environments, but surprisingly has only a weak effect in the periodic fluctuation scenario. Finally, we use the model to show how niche construction, whereby organisms are the source of environmental change, produces more complex dynamics.

1. Introduction

All populations are at some risk of extinction in a given time interval, even if that risk is very small for a given population. Sudden environmental change due to biotic or abiotic factors may lead to declines in population size and to extinction (Maynard Smith, 1989). A population facing environmental change may survive if there is appropriate standing genetic variation that allows organisms to overcome the new conditions (Bürger and Lynch, 1995). This situation can be viewed as a race between ecological processes leading to extinction and evolutionary processes leading to adaptation (Gomulkiewicz and Holt, 1995; Maynard Smith, 1989), and the event of population survival is called *evolutionary rescue* (Gomulkiewicz and Holt, 1995; Holt and

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Gomulkiewicz, 1997; Bell and Gonzalez, 2009, 2011; Zhang and Buckling, 2011). Rescue is known to be favoured by large initial population sizes, a high (adaptive) mutation rate, and a low initial level of maladaptation due to the environmental change (Gomulkiewicz and Holt, 1995; Orr and Unckless, 2008). Generally, evolutionary rescue does not occur easily because environmental changes afford little time for new beneficial mutations to appear before a population declines to unsustainable numbers (Orr and Unckless, 2008). Rescue is uncertain and may fail even in very large populations (Bell, 2013) such as *Escherichia coli* exposed to high temperatures (Riehle et al., 2003) and phytoplankton communities exposed to acidification and elevated metal concentration (Kwiatkowski and Roff, 1976).

The emergence of drug resistance when bacterial populations experience antibiotics constitutes an example of evolutionary rescue, as noted by Orr and Unckless (2008). Here, the environment of bacteria undergoes sudden damage by the presence of antibiotics. Current understanding of evolutionary rescue is based on the consequences of a single abrupt environmental change leading to a steady decline in population size (Gomulkiewicz and Holt, 1995; Orr and Unckless, 2008; Martin et al., 2013). However, environmental change can be more complex (Collins, 2011). To study the dynamics of evolutionary rescue in the context of antibiotic resistance requires models that capture environmental fluctuation during the treatment of bacterial infections. Specifically, the concentration of drugs would fluctuate periodically as a dose is taken, the drug is gradually removed from the local environment, the next dose is taken, and so on. Although bacterial pathogens usually face lethal drug concentrations in clinical settings, they may be exposed to a wider range of antibiotic concentrations in natural environments (Hughes and Andersson, 2012). In gradually deteriorating environments, there may be enough time for resistant alleles to grow to sustainable sizes. Environmental change can be even more complex: an organism alters its environment and those changes alter selective pressures on the organism, leading to a feedback process known as niche construction (Odling-Smee et al., 2003). Each of these environmental changes may affect evolutionary rescue differently.

Mathematical models have been developed to understand the dynamics of drug concentrations within patients and the effect of drugs on bacterial populations (Garrett, 1971; Austin et al., 1998; Regoes et al., 2004; Udekwu et al., 2009; Levin and Udekwu, 2010). These models establish the baseline dynamical behaviour of drug concentration within patients under treatment. The evolution of antibiotic resistance resulting from drug presence has also been studied mathematically to determine treatment conditions minimising the rise of resistance (Lipsitch and Levin, 1997; Bonhoeffer et al., 1997; D'Agata et al., 2008; Gullberg et al., 2011). Resistance often comes at a cost to fitness in the absence of the drug (Schrag and Perrot, 1996; Lenski, 1998; Andersson and Hughes, 2011; Hughes and Andersson, 2012). This cost, however, can be reduced or eliminated by compensatory mutation (Lenski, 1998; Bergstrom and Feldgarden, 2008; Andersson and Hughes, 2010). The dynamical consequences of resistance-cost compensation under simple environmental change between drug presence and absence have been modelled (Tanaka and Valckenborgh, 2011; zur Wiesch et al., 2011). There is a need, however, to integrate complex fitness landscapes including a resistance cost and its compensation with more realistic forms of environmental change due to changing drug concentrations.

As the environment changes, selection coefficients also change, rather than remaining constant after the change as in existing models of evolutionary rescue (Gomulkiewicz and Holt, 1995; Orr and Unckless, 2008). It is thus important to consider fitness values as a function of both genotype and environmental state (Via and Lande, 1985; Gomulkiewicz and Kirkpatrick, 1992; Schlichting and Pigliucci, 1995; Schulz zur Wiesch et al., 2010). Thermal reaction norms, for instance, have been shown to evolve under changing environmental conditions (Mongold et al., 1996; Knies et al., 2006). Metabolic efficiency, which can evolve (Le Gac et al., 2008), can also be viewed as a reaction norm in which the environment is the concentration of a nutrient. In the case of antibiotic resistance, the growth rates of sensitive and resistant bacteria under a range of drug concentrations (Andersson and Hughes, 2010) constitute the norms of reaction that influence the emergence of resistance.

Viewing fitness values as a function of both genotype and environment allows us to consider the role of trade-offs between fitnesses in different environmental states. A resistance cost in the absence of the drug represents a fitness trade off that results in a crossing over of the sensitive and resistant reaction norms (Andersson and Hughes, 2011; Hughes and Andersson, 2012). Conceivably, a resistant allele with compensated cost can appear with the highest fitness across all environmental conditions. The possibility of such types, which we shall call *superbugs*, raises the question of whether they could enhance the probability of evolutionary rescue.

In this paper, we ask whether evolutionary rescue can occur readily in the case of antibiotic treatment of sensitive bacteria given the conditions of this system. Specifically, how is rescue by resistant lineages affected by the balance between a large population size and the large drop in fitness from a high drug concentration? And how is rescue affected by alternative forms of environmental change? To what extent do superbugs – which are not subject to fitness trade-offs – contribute to evolutionary rescue? We study this problem by developing a model of the evolution and extinction of populations facing environmental change, and we apply it to the particular problem of antimicrobial resistance. This model provides a new framework for simultaneously considering environmental change and fitness values of alternative genetic states. This is achieved by defining norms of reaction for the fitnesses of sensitive and resistant alleles over varying drug concentrations.

2. Models

Here we introduce the model and its underlying assumptions. We begin with a description of how the quality of the environment changes because of changes in drug concentration. We then describe the norms of reaction which relate genotype and environment to the various fitness parameters. Next, we show how these features combine to produce our dynamical model. We then describe an extension in which the bacteria themselves alter the environment (niche construction), and finally we give details of how our model is implemented through simulations.

We apply the model of evolutionary rescue to the evolution of antimicrobial drug resistance. Here, we envisage a within-host bacterial population initially made up of only drug sensitive cells; resistance can evolve and rescue the bacterial population following the introduction of the antimicrobial compound.

2.1. The environment

Let q be a variable tracking the quality of the environment; the range of q will be the closed unit interval. The case $q=1$ corresponds to the best possible environment and q_0 (where $0 \le q_0 < 1$) is the minimum environmental quality in the model. The environment function $q(t)$ can accommodate different forms of environmental change. Here, we consider three scenarios of environmental change, namely *abrupt change*, *gradual decay* and *periodic fluctuation* (see Fig. 1). We measure time discretely in generations. In each case, the environment starts to change after the 50th generation, after some standing genetic variation has