

# Impact of a periodic presence of antimicrobial on resistance evolution

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**Short Abstract** — Antimicrobial resistance is a major public health issue. It is crucial to determine which conditions accelerate or slow down its evolution. We study theoretically the impact of a periodic alternation of phases of absence and presence of antimicrobial on the time necessary for resistance to take over. We demonstrate that alternations strongly accelerate the evolution of resistance, especially for fast alternations and large microbial populations. For antisymmetric alternations, the time taken by the population to fully evolve resistance features a striking minimum. The corresponding parameters should preferably be avoided in clinical situations, while they could be harnessed in evolution experiments.

**Keywords** — Antimicrobial resistance, evolution, population, stochastic model, fitness landscape, fitness cost, analytical results, numerical simulations

## I. INTRODUCTION

THE discovery of antimicrobials is one of the greatest medical advances of the twentieth century, allowing many major infectious diseases to be treated. However, with the increasing use of antimicrobials, pathogenic microorganisms become resistant to these drugs. Antimicrobial resistance has become a major and urgent problem of public health worldwide [1].

Mutations that confer antimicrobial resistance are often associated with a fitness cost, i.e. a slower reproduction [2]. Indeed, resistance acquisition generally involves either a modification of the molecular target of the antimicrobial, which often alters its biological function, or the production of specific proteins, which entails a metabolic cost. However, resistant microorganisms frequently acquire subsequent mutations that compensate for the initial cost of resistance. These microorganisms are called “resistant-compensated” [3]. Resistance acquisition is therefore often irreversible, even upon removal of the antimicrobial from the environment [2].

In the absence of antimicrobial, the adaptive landscape of the microorganism, which represents its fitness (i.e. its reproduction rate) as a function of its genotype, involves a valley, since the first resistance mutation decreases fitness. However, this fitness valley disappears above a certain concentration of antimicrobial, as the growth of the antimicrobial-sensitive microorganism is impaired. Thus, the adaptive landscape of the microorganism depends drastically on whether the antimicrobial is present or absent. Taking into account these effects constitutes a fundamental problem, which has been little studied so far, in particular because experimental works have traditionally focused on comparing

different mutants in a unique environment.

## II. QUESTIONS AND MODEL

How do the time scales of the evolution and of the variation of the adaptive landscape couple together? What is the impact of the time variability of the adaptive landscape on antimicrobial resistance evolution ?

To answer these questions, we construct a minimal model retaining the fundamental aspects of antimicrobial resistance evolution. Focusing on the case of a homogeneous microbial population of fixed size, which is described in the framework of the Moran model, we perform a complete stochastic study of *de novo* resistance acquisition in the presence of binary alternations of phases of presence and absence of antimicrobial, which may represent, for example, a treatment where the concentration within the patient falls under the Minimum Inhibitory Concentration (MIC) between drug intakes [4].

## III. RESULTS

Combining analytical and numerical approaches, we show that alternations of phases of antimicrobial absence and presence substantially accelerate the evolution of resistance, especially for larger populations. We fully quantify this effect and shed light on the different regimes at play. We also compare the alternation-driven acquisition of resistance to the spontaneous evolution of resistance by fitness valley crossing, and extend previous results on valley crossing [5]. We then generalize our study to the case of asymmetric alternations, featuring a different duration of the phases with and without antimicrobial. We demonstrate the existence of a broad minimum of the time taken by the population to fully evolve resistance, occurring when both phases have durations of the same order. This situation dramatically accelerates the evolution of resistance. We show that this worst-case scenario may unfortunately be quite realistic in clinical settings, and argue for a modification of antimicrobial dosage strategy. We also show how our results could be exploited to accelerate evolution experiments investigating resistance.

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