Tuning the Mean Time to Extinction in Bacteria by the Rates of Phenotypic Switching or the Environmental Conditions

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Bacterial populations are often subjected to various unpredictable and adverse environmental conditions. To cope with such stresses, bacteria have developed some evolutionary strategies to survive and thrive. One such strategy is switching between its different phenotypes [1,2]. For example, it has been found that a subpopulation of bacteria, called *persisters*, can survive high antibiotic concentrations [1] and the *persister*-state is fully reversible under growth stimulating conditions [2].

We consider a population with two phenotypes consisting of the *normals* who multiply fast but are vulnerable to stress and the *persisters* who hardly multiply but are resilient to stress. We pursue two questions. From the perspective of bacteria who want to survive as long as possible we ask what optimal strategy of switching between its phenotypes (*normals* and *persisters*) the bacteria must employ to maximize its chances of survival when an environment switches between favorable and adverse conditions with given frequency and amplitudes. On the other hand, persisters are not the only way to allow survival under antimicrobial attacks, but at least one way to improve antibiotic resistance. In view of antibiotic resistance, we ask how to optimally tune the environmental changes in terms of doses and intervals of adverse conditions such as to minimize the time to extinction of the bacterial population, given a fixed set of parameters that characterize the population of *normals* and persisters. Developing tactics for successfully eradicating antimicrobial population and preventing antimicrobial resistance is of much relevance nowadays, it is in the main focus of many recent studies [3].

Our model is based on work of Lohmar and Meerson [4] where they also consider a population of *persisters* and *normal*s. They subjected the bacterial population to a constant environment and an environment with a single catastrophic phase and found that the presence of *persisters* reduces the extinction risk of the population and are most beneficial when the phenotypic switching is not very frequent. Instead of a single catastrophic phase, here we consider our environmental conditions to be frequently or even continually switching between favorable and adverse conditions. Such population dynamics in a changing environment has been previously studied in [5,6] in a population of two strains, one growing slightly faster than the other, and their fixation (one strain takes over the population) properties have been studied under different environmental conditions. However, these studies do not consider any switching between the strains and their final fates.

We consider the environmental variability to be either random (implemented as dichotomous Markov noise, characterized by rates and amplitudes), or given as a periodic variation (either a square or sine wave). The effect of unfavorable environmental conditions is simulated either by reducing the birth rate of the *normals* or by reducing the carrying capacity of the system. Thus, the birth rate or carrying capacity become time dependent. Concerning the methodology, we use a modified Gillespie algorithm which accounts for explicitly time-dependent propensities. The extinction risk is quantified by finding the mean time to extinction τ of the population. Under a perturbation it is more conclusive to determine the change of τ due to the perturbation, which turns out to possibly have both signs, that is, increasing or decreasing τ.

Our numerical results so far show that τ always increases with an increase in the carrying capacity which is expected as a larger carrying capacity means that the environment has larger resources and can sustain larger population size, thus reducing the extinction risk. This result is consistent with the result of previous studies [4]. When the birth rate switches between a high and a low value, mimicking the favorable and adverse conditions respectively, τ is found to be maximum for an intermediate frequency of switching. This holds for periodic as well as random environmental variations. It indicates an answer to the second question which frequency of environmental change to avoid in order to enforce a fast extinction of the bacterial population. The result is easily understood in case of periodic switching. For low frequencies, the population can be wiped out completely during the encounter with the unfavorable conditions if these conditions are adverse enough to reduce the birth rate below a certain value. Therefore, how catastrophic the catastrophic phase is in terms of reducing the birth rate is an important factor in deciding the fate of the population. For intermediate frequencies, the loss during the adverse phases can be compensated by the population gain during the favorable phases and hence a finite population can be sustained for a longer time. For high frequencies of switching, the population does not get enough time to recover from the population loss during the adverse phase and gradually goes extinct. In view of

the first question, given the fluctuating environment with fixed parameters, we find τ to generally increase with an increase in the switching rate from *normals* to *persisters* and to decrease with an increase in the switching rate from *persisters* to *normals*. So, it seems that in most cases a good survival strategy for the bacteria is to increase their switching rate from *normals* to *persisters* and reduce the switching to *normals* to survive as long as possible. We also explore the cases where this might not be true. Along with the mean time to extinction we also study and compare the characteristics such as the modality and shape of the population size distribution for various system parameters.

On the analytical side, we apply the WKB method for calculating the mean time to extinction and its change due to perturbations of the environment in several regimes: (i) the linear regime of small amplitude periodic oscillations, (ii) the adiabatic regime of slow oscillations, slow enough that the system can adapt to the environment, and (iii) the regime of fast oscillations. In the figure we show the normalized mean time to extinction τ/τ_0 with τ_0 referring to the unperturbed system, obtained in the linear regime as a function of the frequency of the environmental change, realized via the birth rate of *normals* ($B = B_0 + \epsilon \sin \omega t$), where ϵ is the small amplitude of the perturbation.
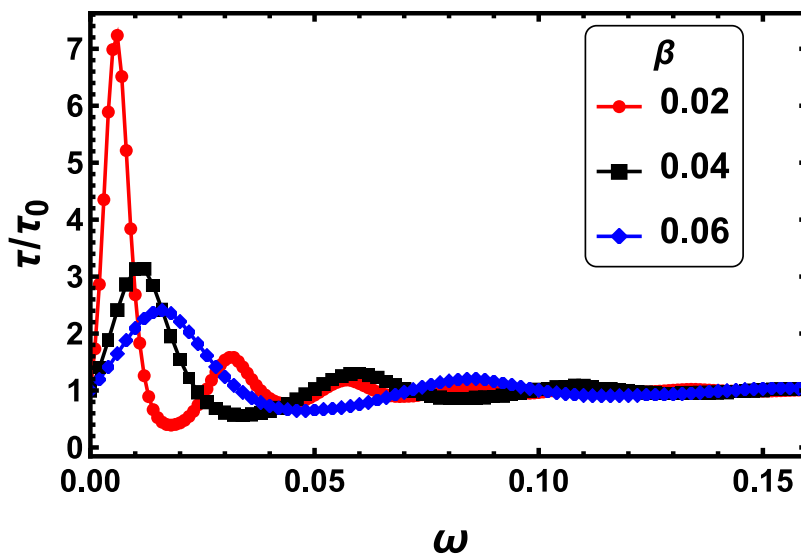
Obviously, the perturbation can modulate τ/τ_0 with both signs: an increase or decrease of $\tau/\tau0$, shown for three values of β (switching from *persisters* to *normals*), while α (switching from *normals* to *persisters*) is taken as 0.06, and the carrying capacity is chosen to be 300. The value of the frequency ω for which τ/τ_0 is maximum (or minimum) for a given β is found to increase as we increase β. So, by tuning the frequency of the external perturbation (for example, the frequency at which antibiotics are introduced into the system in the context of antimicrobial treatment), we can tune the survival of the bacterial population to be as short as possible. In this linear regime, the mean time to extinction is found by calculating the action of the WKB approach along the unperturbed instanton using the Chernykh- Stepanov iteration method [7] and adding to it the minimal additional action due to a small external (sinusoidal) perturbation.

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