Phenotypic-dependent variability and the emergence of tolerance in bacterial populations

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Ecological and evolutionary dynamics have been historically regarded as unfolding at broadly separated timescales. However, these two types of processes are nowadays well-documented to intersperse much more tightly than traditionally assumed, especially in communities of microorganisms. Advancing the development of mathematical and computational approaches to shed novel light onto eco-evolutionary problems is a challenge of utmost relevance.

With this motivation in mind, here we scrutinize recent experimental results showing evidence of rapid evolution of tolerance by lag in bacterial populations that are periodically exposed to antibiotic stress in laboratory conditions. In particular, the distribution of single-cell lag timesi.e., the times that individual bacteria from the community remain in a dormant state to cope with stressevolves its average value to approximately fit the antibiotic-exposure time. Moreover, the distribution develops right-skewed heavy tails, revealing the presence of individuals with anomalously large lag times. Here, we develop a Markov individual-based stochastic model for phenotypic adaptation that mimicks the actual demographic processes of the experimental setup. Individuals are characterized by a single phenotypic trait: their intrinsic lag time, which is transmitted with variation to the progeny. The model –in a version in which the amplitude of phenotypic variations grows with the parents lag time– is able to reproduce quite well the key empirical observations

Mathematically models such as our are described by a Master equation ruling the time evolution of the joint probability-distribution functions for the whole set of all particles. However, as it is often the case for such many-particle Master equations, it is hard to handle analytically in an exact way. Thus, in order to gain quantitative understanding beyond purely computational analyses, here we develop an approximationwhich becomes exact in the limit of infinitely large population sizes, that allows us to derive a macroscopic (or mean-field) description of the stochastic model in terms of the probability density of finding an individual at any given phenotypic state, (i.e. the one-particle probability density):

$$\begin{aligned}\partial_t\phi(\tau,t) &= \eta(t)\left[f(\tau,t)-\bar{f}(t)\right]\phi(\tau,t)\\ &- (\eta(t)+1)\Big[\partial_\tau\theta(\tau)f(\tau,t)\phi(\tau,t)\\ &- \frac{1}{2}\partial_\tau^2\sigma^2(\tau)f(\tau,t)\phi(\tau,t)\Big] \qquad (1)\end{aligned}$$

this equation is *a generalization of the celebrated continuous-time Crow-Kimura* equation of population genetics, also called selection-mutation equation. In particular, notice that the dynamics of the probability density is exposed to the combined action of the process of selection (first term in previous equation) and mutation, as specified by the drifts (the second and third line). This type of equations, combining replicator dynamics with Fokker-Planck type of terms.

Even if the model does not account for all the biological mechanisms (e.g., genetic changes) in a detailed wayi.e., it is a phenomenological one it sheds light onto the eco-evolutionary dynamics of the problem and can be helpful to design strategies to hinder the emergence of tolerance in bacterial communities. From a broader perspective, this work represents a benchmark for the mathematical framework designed to tackle much more general eco-evolutionary problems, thus paving the road to further research avenues.

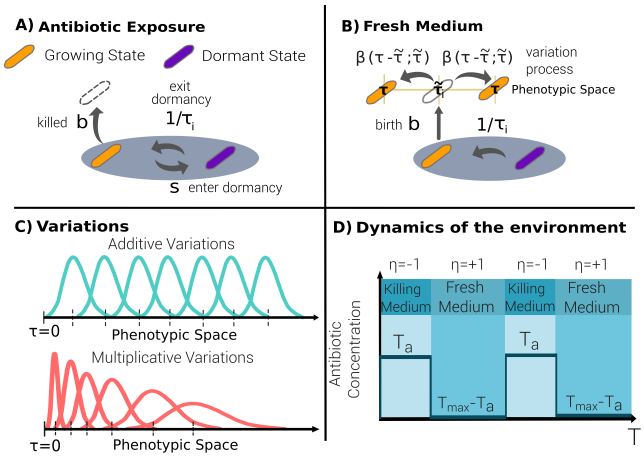

Fig. 1. **Sketch of the main ingredients of the individual-based stochastic model**. Each individual bacterium (i) is characterized by its phenotypic state, lag time τ_i and experiences demographic processes. **(A)** In the presence of antibiotics, bacteria can stochastically switch between the dormant and the growing state (at transition rates s and $1/\tau_i$, respectively); growing individuals can also attempt reproduction (at a "birth" rate b) and be immediately killed by the action of antibiotics (as bactericidal antibiotics usually act during duplication attempts). **(B)** In the fresh medium, dormant bacteria can wake up at a rate $1/\tau_i$, that depends on their intrinsic (phenotypic) lag time; on the other hand, growing cells can reproduce asexually by duplication; the resulting offspring inherit the characteristic time scale with some variation, as specified by a function β. **(C)** Two possible types of variation functions β: in the additive case (top), the standard deviation is constant, i.e. independent of the initial state τ_i, while in the multiplicative case (bottom) the standard deviation is assumed to grow linearly with the parent's lag time τ_i. **(D)** Sketch of the environmental variation, alternating periodically between antibiotic exposure (time T_a) and a fresh medium ($T_{max}-T_a$).