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Type	Oral communication
Session	Systems Biology
Title	An ecological perspective on persisters resuscitation
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Motivation

For a long time, antibiotic resistance, tolerance and persistence have been studied from the point of view of one organism and how each drug could affect its genome, metabolism and growth rate. However, in recent years, the study of microbial communities and how their ecological interactions could alter the efficacy of antibiotics has gained ground. In fact, mounting evidence suggests that such interactions play a crucial role in the emergence and maintenance of antibiotic persistence/tolerance and in the actual efficiency of antibacterial treatments. Hence, interactions are important in i) maintaining the stability of the underlying population and ii) affecting the survival of community members during antibiotic exposure. Persister cells are those who survive in the presence of antibiotics without undergoing genetic changes. Recent evidence suggests that one of the mechanisms used by them is to low their ATP levels, this induce protein aggregation and thus non or slow-growing bacterial cells, stochastically favouring persisters formation. It has been estimated that the fraction of persisters within a microbial population may range from about 0.05% to 2%, in relation, among other factors, to the antibiotics used, the growth phase and the taxonomy of the microbes under study. The phenotypic features that allow persister resuscitation are starting to gain attention, since this process may represent an attractive target for antibiotic treatments. Although resuscitation dynamics of a group of persisters has long been considered to be constant over time, a recent work suggested that cells resuscitate exponentially rather than with a fixed rate. The problem of resuscitation and, more in general, pathogens clearance, is strongly connected to the small size of the population of persisters. Indeed, while the dynamics of large populations can be thought of as deterministic processes, the dynamics of small populations may be less predictable and affected by factors that are negligible in the first scenario. The underline probability of these stochastic processes has been described in different ways, although a community-level model that accounts for persisters-resuscitation is missing.

Methods

Here, we argue that microbe-microbe interactions in a microbial community represent an additional factor affecting the mode, tempo and success of persister resuscitation. Since antibiotic exposure drastically reduces the size of sensitive species (virtually to the size of persisters pool), even mildly negative interactions may impede the resuscitation of persisters once their population size has dropped under a certain threshold. At the same time, noise may contribute to this complex scenario, as stochastic fluctuations in cell numbers could interfere with the dynamics of the ecological network and influence the resuscitation of the persister pool. To investigate these issues, we developed a theoretical model of a three-member microbial community. This includes a pathogenic, antibiotic-sensitive and persisters-generating species together with two other interacting community members. We analysed how the interplay among the three players (as well as other model parameters) affect the resuscitation of the persisters. We modelled a system of chemical reactions using the chemical master equation and the Gillespie stochastic simulation algorithm, and implemented them using MATLAB.

Results

First, we developed a deterministic model and studied how its parameters (such as the antibiotic killing rate and exposure time) affected the dynamics of the aforementioned community and, more importantly, the capacity of the persister cells to resuscitate after the antibiotic treatment). In this way we showed that the interactions among the members of such a community had a major role in determining the end-point microbial structure and hence the success of a hypothetical microbial infection. However, as it was explained before, such a model could not take into account stochastic fluctuations in the species abundances and in the rate of persister cells generation, factors that are known to play a role in the resuscitation of persisters. For this reason we conducted stochastic simulations using the same overall community model and found that, in some cases, the pathogen species could resuscitate and eventually dominate the community following antibiotic treatment, a scenario that was never observed using the deterministic model but that is known to occur seldom during real microbial infections eradication. By conducting an extensive array of stochastic simulations we were able to identify key parameters accounting for this phenomenon and that affect the timing of persisters resuscitation. Our findings highlight the role of population size fluctuations (and hence the cellular mechanisms that account for them) in determining the success of microbial infections and, more in general, in the resilience of microbial populations following a stressful perturbation.

Info

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