Community interactions drive the evolution of antibiotic tolerance in bacteria

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***Short Abstract* —Bacteria are known to evolve to evade antibiotic stress. As most bacteria reside in multi-species communities, we thrive to understand how ecological interactions shape evolution under antibiotic exposure. Studying a community composed of susceptible strain that is protected by a resistant strain under antibiotic stress, we found the susceptible strain evolved tolerance by slow growth. We developed a mathematical model that showed such tolerance can be beneficial when the protective interactions are weak and successfully predicted it would be detrimental when interactions are strong, highlighting the importance of ecological interactions in the evolution of antibiotic tolerance.**

***Keywords* — antibiotics; tolerance; evolution; community interactions; cross-protection.**

I. Introduction

THE extensive use of antibiotics over the decades has brought with it a growing concern of the ever-evolving ability of bacteria to evade them. A plethora of studies have revealed the many mechanisms by which bacteria can evolve both resistance and tolerance, in clinical as well as laboratory conditions [1-3]. Most laboratory studies have focused on a single bacterial population, though bacterial interactions are abundant and known to impact the community response to antiboitic. One setting in which bacterial interactions play a significant role in the face of antibiotics is where an antibiotic-resistant strains can protect susceptible strains against antibiotics, allowing the two to coexist even under large antibiotic concentrations, far exceeding the minimum inhibitory concentration (MIC) of the susceptible cells [4-5]. We experimentally evolved such a community to understand how community context shapes bacterial response to antibiotics.

II. Results

We studied the evolutionary dynamics of a simple synthetic two-strain bacterial community exposed to the antibiotic ampicillin, where an auxothroph resistant strain degraded ampicillin thus protecting a susceptible strain. Surprisingly, we observed that the susceptible strain repeatedly evolved tolerance in multiple parallel lines of this community, typified by a reduced death rate and a concomitant decrease in growth rate.

To understand when a decreased death rate is beneficial despite an accompanying decreased growth rate, we calculated the relative fitness of tolerant isolates in different conditions. Briefly, our model simulated the growth of a community with three distinct strains: resistant auxotroph which grew at a fixed growth rate regardless of the antibiotic; susceptible ancestor which grew at a faster rate at antibiotic concentrations below the MIC, and died when antibiotic concentrations are above the MIC; and a tolerant descendant of the susceptible strain, with reduced growth and death rates. Simulations suggested that tolerance is beneficial when the population size of the resistant auxotroph is small, resulting in slow antibiotic degradation leading to a long death phase of the susceptible strains. Thus, tolerant isolates, which have a lower death rate, are fitter, even at the cost of a lower growth rate. Interestingly, our model predicted that increasing the resistant population carrying capacity thereby speeding up antibiotic degradation will abolish the benefits of tolerance by slow growth.

To test this surprising prediction, we repeated our evolution experiment in conditions where the resistant strain capacity is larger. In agreement with our prediction, in this setting tolerance was much less likely to evolve.

Using whole genome sequencing we identified 3 genetic hotspots were mutated multiple times in our evolved lines, suggesting a genetic basis for tolerance by slow growth.

III. Conclusion

An antibiotic resistant strain is able not only to rescue a susceptible strain but, depending of the protection strength, can also drive the evolution of tolerance or restrict it. This experimental and theoretical framework exemplifies the role ecology plays in shaping evolution.

IV. References

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