Antibiotic-mediated altruistic bacterial death and dynamics of collective drug tolerance

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***Short Abstract* — With the number of antibiotic resistant bacteria increasing and no effective treatment available, new approaches for handling bacterial infections are needed. Besides genetic resistance, bacteria can exhibit collective drug tolerance. One phenomenon, the Eagle effect, occurs when higher antibiotic concentrations promote bacterial growth. A possible, but poorly understood, mechanism of the Eagle effect is altruistic cell death. We examined the dynamics of altruistic-death-mediated Eagle effect by mathematical modeling. Our simulations show a strong negative feedback is critical for a strong Eagle effect. This mechanistic understanding allows us to develop a more effective treatment that can overcome the Eagle effect.**

***Keywords* —antibiotic resistance, Eagle effect, altruistic death**

I. Introduction

Less than a century after the deployment of the first antibiotic, there has yet to be an antibiotic that bacteria do not eventually evolve to resist [1]. As a result, bacterial infections are becoming just as life threatening as they were in the pre-antibiotics era [2].

In addition to antibiotic resistance due to genetic alterations in individual cells, bacteria can also collectively tolerate an antibiotic as a population, even though individual cells are sensitive. Such population-level tolerance could lead to counter-intuitive outcomes during antibiotic treatment. One such phenomenon is the Eagle effect, in which bacteria grow better under higher initial antibiotic concentrations [3]. Through the analysis of a synthetic gene circuit, our lab discovered that a possible mechanism for the Eagle effect is altruistic death [4]. Here, a subset of the bacteria lyses in response to an antibiotic. The lysed cells release an enzyme into the environment where it degrades the antibiotic, thus allowing the surviving cells to grow.

This mechanism is consistent with experimental tests of many clinically relevant bacterial pathogens that express extended-spectrum β-lactamases, when treated with β-lactam antibiotics. However, a quantitative understanding of how various factors determine the extent of the Eagle effect is lacking. To address this issue, we modeled the collective drug response and designed an effective dosing regimen that can overcome the Eagle effect.

Acknowledgements: National Science Foundation (NSF) CAREER Award (CBET-0953202), a DuPont Young Professorship (L.Y.), a David and Lucile Packard Fellowship (L.Y.), National Institutes of Health (1RO1GM098642), and Office of Naval Research (N00014-12-1-0631). H.M. acknowledges the support of an NSF graduate fellowship

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II. Methods and Results

A. Modeling the Eagle Effect

Based on the altruistic death mechanism, we used an ordinary-differential-equation model to simulate population responses to antibiotics, by accounting for the key reactions involved in this process, including cell growth and lysis, release of the enzyme, and antibiotic degradation. Using the model, we varied parameters that controlled how sensitive a population is to growth inhibition by antibiotics, lysis by antibiotic degradation of the cell wall, and activation of β-lactamase production. Interestingly, we found that the single most important determinant of the Eagle effect is the strength of the overall negative feedback due to the β-lactamase degrading the antibiotics. Parametric perturbations that result in a stronger negative feedback led to an enhanced Eagle effect. The stronger the population responded to the presence of antibiotics, the more β-lactamase was produced, and the stronger the resulting Eagle effect.

B. Modeling Dose Responses

We further used the model to examine the efficacy of different dosing regimens in which the antibiotic concentration, antibiotic dosing frequency, and initial cell density were varied. The most effective antibiotic regimen had a concentration high enough to reduce the cell density, but low enough to not induce the Eagle effect, and an application frequency that was high enough to prevent cells from growing back between doses, but low enough to not induce the Eagle effect.

III. Conclusion

By modeling the population response to antibiotics, we have identified the aspects that characterize a bacterial infection capable of generating the Eagle effect and determined an antibiotic regimen that overcomes the Eagle effect.

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