Population dynamics of cooperative antibiotic resistance in a *C. elegans* model

Nicole M. Vega[1], Eugene A. Yurtsev[1,2], and Jeff Gore[1,3]

***Short Abstract* — Resistance to β-lactam antibiotics can occur through expression of β-lactamase enzymes, which hydrolytically inactivate the antibiotic. This inactivation can make β-lactam resistance a cooperative behavior. However, the effects of cooperation on the outcomes of antibiotic treatment are not yet well understood, particularly in the host environment. Here we use a combination of experiment and modeling to provide novel insight into the population dynamics of cooperative antibiotic resistance in the host, using the nematode *C. elegans* as a model system.**

***Keywords* — Caenorhabditis elegans, cooperative resistance, population dynamics.**

I. Background

Enzymatic inactivation of antibiotics by resistant bacteria can be "cooperative" when this inactivation lowers the extracellular concentration of drug and thereby allows a sensitive fraction within the population to survive treatment [1]. Recent *in vitro* studies of cooperative antibiotic resistance have revealed surprisingly complex dynamics [1, 2]. However, the host environment differs fundamentally in physical and pharmacokinetic aspects from conditions encountered *in vitro*, and the effects of cooperative resistance in host-associated populations are not well understood.

The nematode C*aenorhabditis elegans* has been proposed as a relevant model organism for tests of antimicrobial efficacy, with improved pharmacokinetics as compared with traditional *in vitro* assays [3]. This system can therefore be used to assess antibiotic treatment-driven dynamics of bacterial communities in a tractable eukaryotic host.

Here, we describe cooperative antibiotic resistance in a host-associated bacterial community using C. *elegans* as a model system. We combine quantitative experimentation with mathematical modeling to characterize the effects of antibiotic treatment and host immune capacity on resistance allele frequency and stability of cooperative interactions. To understand the effects of the host environment on cooperative resistance, we compare the dynamics of the host-associated system with those observed *in vitro*.

II. Summary

A. Cooperative resistance in a synthetic microbial ecosystem

We observe cooperative resistance in host-associated populations, where β-lactam sensitive "cheater" cells of *E. coli* DH5α coexist in the worm intestine with bacteria carrying a plasmid-bound β-lactam resistance allele, even in the presence of bactericidal levels of piperacillin.

B. Antibiotic-induced dynamics in the host

We characterize the effects of β-lactam treatment from observed changes in resistance allele frequency and population size over time. An immune-deficient mutant strain of *C. elegans* is used to assess the effect of host immunity on the dynamics of associated populations. Using a combination of experimental data and modeling, we identify and characterize the stability of equilibria within the system, and we explore hidden factors underlying differences in cooperative dynamics between the host intestine and the *in vitro* environment.

III. Conclusion

Using the tractable model organism *C. elegans*, we quantify the effects of the host environment on bacterial population dynamics during antibiotic treatment and on selective pressure in cooperative communities. Our results demonstrate the importance of the host environment in the dynamics of microbial populations under antibiotic treatment and suggest considerations for translation of *in vitro* studies into the host environment.

References

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[1]Department of Physics, MIT, Cambridge, MA. E-mail: nvega@mit.edu

[2]E-mail: eyurtsev@mit.edu

[3]E-mail: gore@mit.edu