Tuning Spatial Profiles of Selection Pressure to Modulate the Evolution of Resistance

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***Short Abstract* — Spatial heterogeneity plays an important role in the evolution of drug resistance. While recent studies have indicated that spatial gradients of selection pressure can accelerate resistance evolution, much less is known about evolution in more complex spatial profiles. Here we use a stochastic toy model of drug resistance to investigate how different spatial profiles of selection pressure impact the time to fixation of a resistant allele. Using mean first passage time calculations, we show that spatial heterogeneity accelerates resistance evolution when the rate of spatial migration far exceeds that of mutation but slows fixation when mutation dominates. Interestingly, there exists an intermediate regime — characterized by comparable rates of migration and mutation — in which the rate of fixation can be either accelerated or decelerated depending on the spatial profile, even when spatially averaged selection pressure remains constant. Finally, we demonstrate that optimal tuning of the spatial profile can dramatically slow the spread and fixation of resistant subpopulations, which may lay the groundwork for optimized, spatially-resolved drug dosing strategies for mitigating the effects of drug resistance.**

***Keywords* — antibiotic resistance, spatial heterogeneity, evolution, modeling, mean first passage time, master equation**

I. Background

ANTIBIOTIC resistance is a central impediment to the treatment of microbial infections. While most of the work on understanding resistance has been performed at the molecular level, resistance is a fundamentally stochastic process governed by the complex interplay between microbial evolution and evolutionary selection. Evolution in natural settings takes place in heterogeneous environments characterized by spatial fluctuations in multiple factors, such as drug concentrations, pH, and host immune responses, all of which potentially affect cellular growth. Recent experimental [1] and theoretical [2] results show that understanding evolution and ecology in such spatially-extended systems is crucial for understanding resistance.

In this work, we use stochastic models of evolution along with a mean first passage time from statistical physics to calculate the mean time required for an initially wild-type population to be composed entirely of mutants. For tractability, we restrict our system to having three connected microhabitats and allow cells to replicate according to a simple Moran process. Our primary interest is calculating the fixation time from an initially wild-type population for a given selection pressure landscape and comparing these fixation times across different selection pressure landscapes with the spatially-averaged selection pressure fixed. In addition to the specific selection pressure landscape, the mutation rate and migration rate of the system will determine the fixation time.

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II. Results

We find that the fixation time for a population of initially wild-type cells varies significantly with the spatial distribution of selection pressure, even when the spatially-averaged selection pressure remains fixed. Interestingly, we observe that resistance can be either accelerated or decelerated by spatial heterogeneities in selection pressure.

We observe that there are three different regimes for our system. In the limit where the mutation rate is much smaller than the migration rate, spatial heterogeneity speeds fixation for the system. In the limit where the mutation rate is much larger than the migration rate, any spatial heterogeneity slows fixation. And between these two limits exists an intermediate regime, in which heterogeneity can either speed or slow fixation. While the mutation rate and migration rate are often inherent to the specific system of interest, the selection pressure landscape can potentially be modulated to speed or slow the evolution of resistance in the system.

We also use this method to look at fixation starting with an initial mutant subpopulation. We demonstrate that tuning the spatial distribution of selection pressure can dramatically slow fixation when the resistant subpopulation is not uniformly distributed in space.

III. Conclusion

Using a simple toy model to investigate the evolution of antibiotic resistance in a spatially-extended system, we demonstrate that the selection pressure landscape can be tuned to slow or speed the emergence of antibiotic resistance.

References

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