Gene Networks and Drug Resistance: Breakthroughs Using Novel Model Systems

Antimicrobial (drug) resistance is a global health threat due to the emergence of multidrug-resistant microorganisms and the rapid onset of resistance to common antibiotic and antifugal treatments. My research combines mathematical modeling based in fundamental physics with synthetic biology to study gene regulatory networks and drug resistance. This novel approach has led to several important discoveries, including: 1) nongenetic variability in gene expression promotes drug resistance by enabling a fraction of the cell population to survive initial drug treatment, 2) gene network structure facilitates resistance evolution by increasing the timescale of nongenetic drug-resistant states (phenotypes) and the probability of acquiring drug-resistance mutations, and 3) temperature significally alters the function of gene networks in ways that can be predicted by multiscale biophysical models incorporating population dynamics, Arrhenius scaling of reaction rates, and protein structure changes. This research advances our knowledge of gene networks, enables more robust cellular engineering for real-world applications, and opens new lines of investigation for developing more effective and “evolution proof” antimicrobial therapies.