1 Introduction

1.1 Antibiotics, the Resistance Crisis, and Pharmacodynamic Selection

This section introduces antibiotics as the foundation of modern medicine and outlines the growing global threat of antimicrobial resistance, citing recent burden estimates. It describes the evolutionary origins of resistance, including chromosomal mutations and horizontal gene transfer via plasmids, and introduces pharmacodynamic (PD) functions as the link between antibiotic concentration and bacterial population dynamics.

1.2 Treatment Strategies and Combination Therapy

This section presents empirical treatment strategies such as combination, cycling, and mixing, with a focus on the theoretical advantages of combination therapy (as shown in the work of Bonhoeffer, Angst, and others). It discusses clinical success in diseases like HIV, malaria, and tuberculosis, but contrasts this with inconclusive outcomes in bacterial infections, summarizing findings from clinical studies and a recent meta-analysis by Siedentop.

1.3 Drug-Interaction Models below the MIC: Loewe and Bliss

This section explains the two main models for assessing drug interactions—Bliss independence and Loewe additivity—highlighting their assumptions and differences. It references large-scale sub-MIC interaction screens by Pamela Yeh and others, and emphasizes that these methods are typically limited to the sub-MIC range due to methodological constraints.

1.4 High-Throughput Luminescence in the Super-MIC Range

This section introduces bioluminescence as a high-throughput proxy for bacterial population size, based on expression of the lux operon from Vibrio fischeri. It describes how luminescence scales linearly with cell number ("10 bacteria emit 10× the light") and highlights precedent from studies by Kishony, Bollenbach, and Yeh that successfully employed this method for large-scale screening.

1.5 Toward Full-Range Combination Pharmacodynamics

This section motivates the use of luminescence to estimate net growth and killing across the full concentration range, enabling drug-interaction studies beyond the MIC. It introduces a polar-coordinate formalism for visualizing and quantifying pharmacodynamic surfaces for drug combinations, and raises the question of whether interaction types remain consistent between sub- and super-MIC conditions.