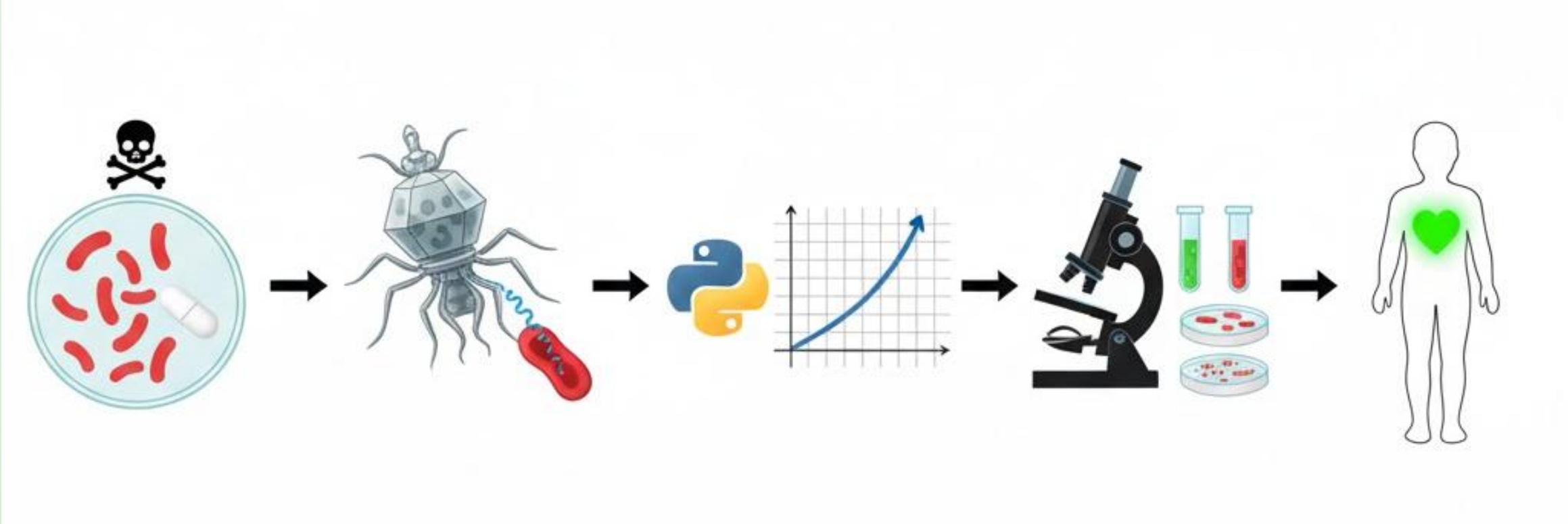
Using a Math Model to Study the Effects of Bacteriophages on the Spread of Antibiotic Resistance

Richard Yan
Advisor: Kevin Crowthers, PhD

Abstract

Antibiotic resistance remains a major challenge in infection control. This study uses a Python-based deterministic and stochastic model to examine how bacteriophages influence resistant and susceptible bacterial populations under antibiotic pressure. Simulations to optimize initial phage concentrations reveal large variability in population outcomes under similar initial conditions and suggest that moderate phage concentrations can balance bacterial clearance while limiting antibiotic resistance gene spread. In vitro experiments are in process to validate these predictions.

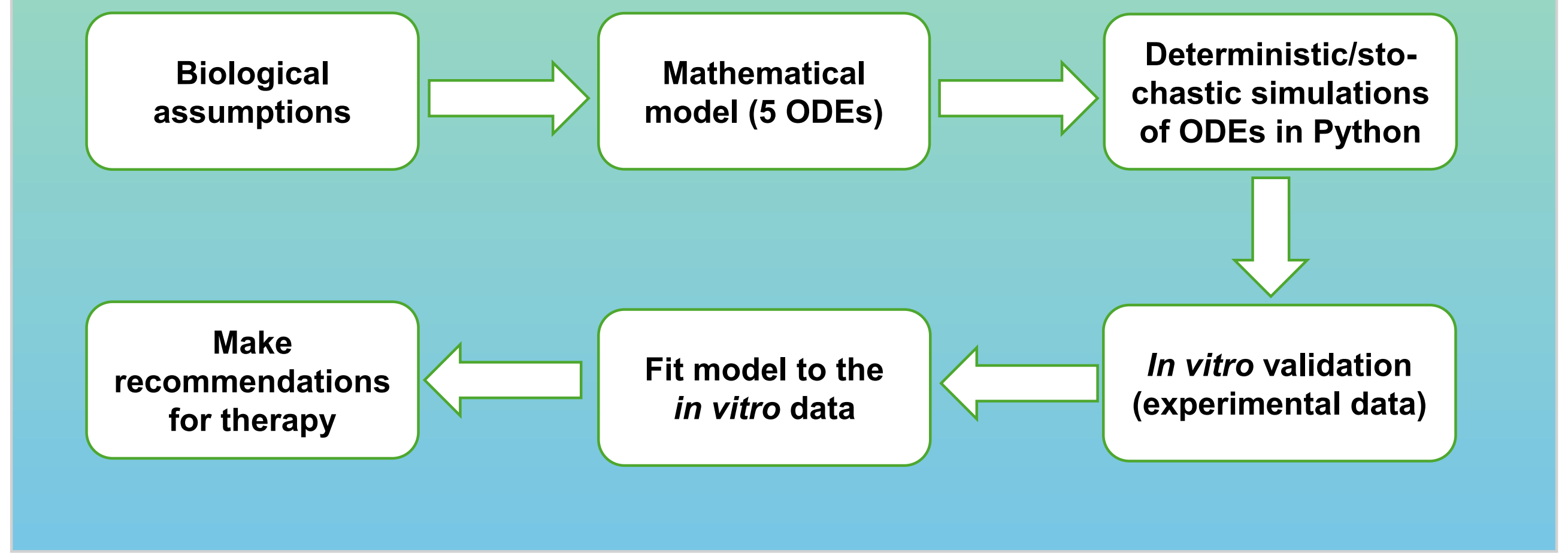


Introduction

- Antibiotic resistance is a primary global health threat, directly linked to **1.27 million deaths** in 2019 (WHO, 2023).
- Resistance is driven mainly by antibiotic misuse, but many other factors can contribute to its spread.
- Bacteriophages can kill resistant bacteria, but they can inadvertently transfer antibiotic resistance genes (ARGs) between bacterial hosts (Calero-Caceres et al., 2019).
- **Math Modeling:** Math models are vital for predicting these interactions over time. There are two major types of models used to study antibiotic resistance.
  - **Deterministic Models:** Assumes no randomness and ideal conditions. They are used if a system doesn't have any noise or unwanted outside factors.
  - **Stochastic Models:** Essential for capturing environmental randomness. Stochastic effects can cause deviations of up to **22.9%** from deterministic averages (Merdan et al., 2017).

Methods

Math Modeling: Biological assumptions were defined to construct a system of five ordinary differential equations modeling susceptible, resistant, and infected bacteria, phages, and antibiotics. The system was simulated in Python, with in-vitro data used for model validation and refinement.



Biological assumptions → Mathematical model (5 ODEs) → Deterministic/stochastic simulations of ODEs in Python → *In vitro* validation (experimental data) → Fit model to the *in vitro* data → Make recommendations for therapy

Research Question

How do bacteriophages influence bacterial populations under antibiotic pressure?

Hypothesis

Phages will reduce the overall bacterial concentration but may increase the proportion of resistant bacteria by spreading antibiotic resistance genes through transduction.

Population Model

$$\frac{dS}{dt} = r_S S\left(1 - \frac{S+R+I}{K}\right) - \beta SP - k_A AS - \mu(A)S - d_S S$$

$$\frac{dI}{dt} = \beta SP - \frac{1}{\tau}I - d_I I$$

$$\frac{dR}{dt} = r_R R\left(1 - \frac{S+R+I}{K}\right) + \mu(A)S - d_R R$$

$$\frac{dP}{dt} = \frac{B}{\tau}I - \beta SP - \delta_P P$$

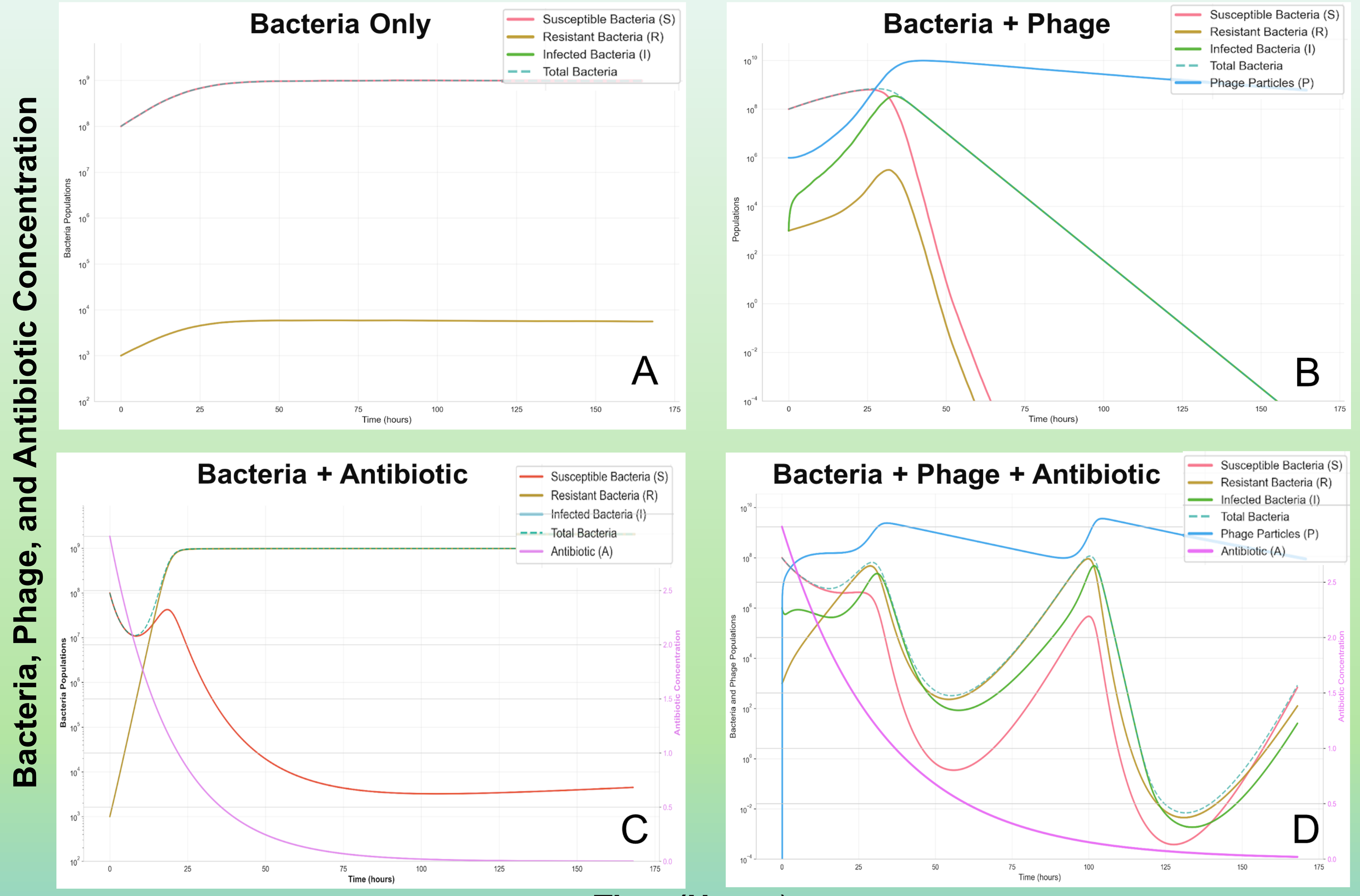
$$\frac{dA}{dt} = -\delta_A A$$

Parameters

Parameter	Description
r_s	Growth rate of susceptible bacteria (per hour)
r_r	Growth rate of resistant bacteria (per hour)
K	Environmental carrying capacity for total bacteria (cells)
beta	Phage adsorption/infection rate (mL per phage per hour)
phi	Reduction factor for phage infection of resistant bacteria (dimensionless)
b	Phage burst size (number of phages released per lysed cell)
tau_L	Phage latent period (hours between infection and lysis)
δp	Natural decay rate of free phage particles (per hour)
k_a	Antibiotic killing rate of susceptible bacteria (per concentration per hour)
k_a_r	Antibiotic killing rate of resistant bacteria (per concentration per hour)
δa	Antibiotic decay or clearance rate (per hour)
mu_0	Baseline mutation rate from susceptible to resistant bacteria (per hour)
alpha	Stress-induced mutation amplification factor due to antibiotics (dimensionless)
K_mu	Antibiotic concentration at which mutation rate is half-maximal
eta	Phage-mediated transduction rate converting susceptible to resistant bacteria (per phage per hour)
d_s	Natural death rate of susceptible bacteria (per hour)
d_r	Natural death rate of resistant bacteria (per hour)
d_I	Natural death rate of infected bacteria prior to lysis (per hour)

Results

Bacteria, Phage and Antibiotic Dynamics (168h)



Time (Hours)

Figure 1: **A:** Control simulation of bacteria alone. Bacterial concentrations initially increases, then plateaus as the growth rate approaches zero near the carrying capacity. **B:** Simulation of bacteria and phage dynamics. Bacteriophages wipe out bacterial populations, then decay due to the absence of bacterial hosts. **C:** Simulation of bacteria and antibiotic dynamics. Susceptible populations decline while resistant populations rise initially, then both stabilize as antibiotic concentration decreases. **D:** Simulation with bacteria, phages, and antibiotic. Bacteria populations initially decrease, but as antibiotics decay, phage and bacteria concentrations oscillate.

Results

Bacteria vs Initial Phage Level

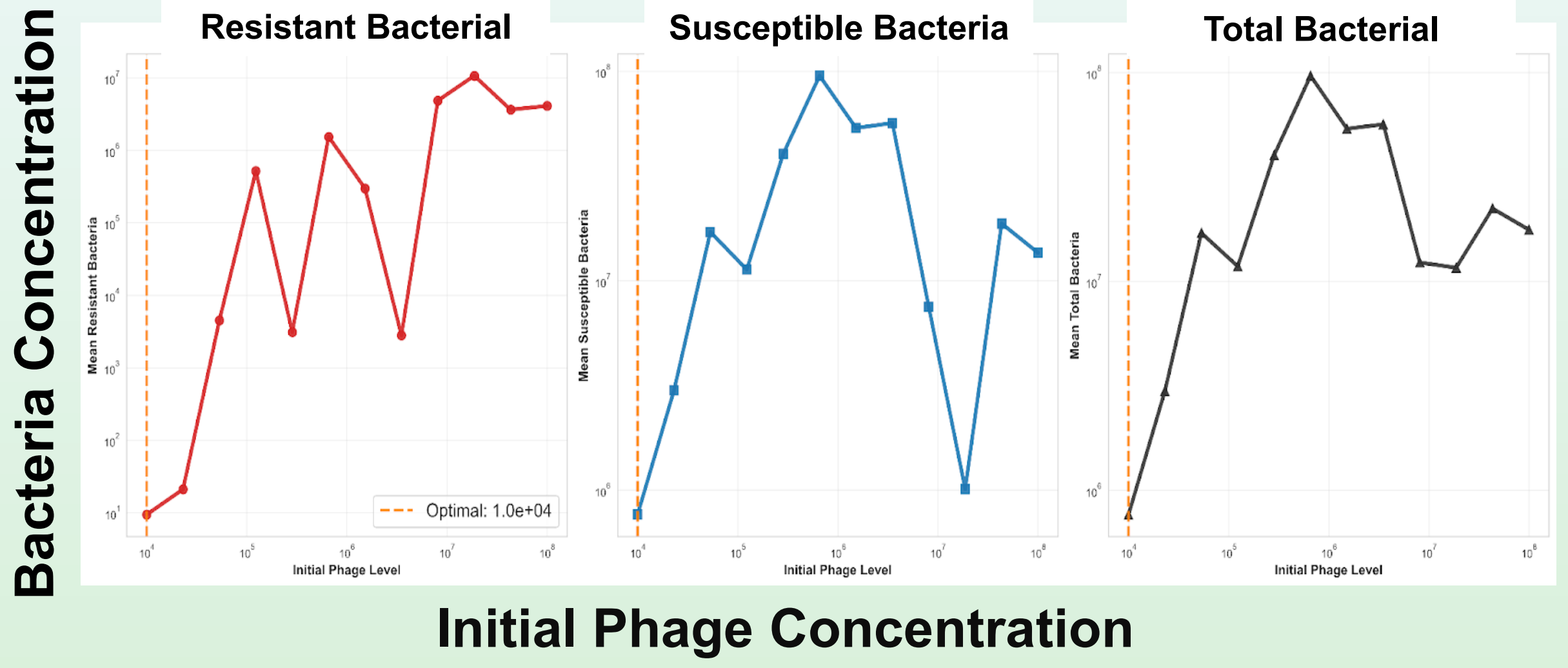


Figure 2: The goal is to minimize resistance first, then total bacterial concentration. A phage concentration of around 10,000 PFU/mL achieves both.

Conclusions

- Without treatment, bacterial populations grow and stabilize, with resistant bacteria remaining present at low levels.
- Phages reduce bacterial populations more effectively than antibiotics alone, and completely eliminate bacteria (likely due to a lack of phage resistance).
- Antibiotics strongly select for resistant bacteria, leading to bacterial rebound as the drug concentration decreases.
- Combining phages and antibiotics suppresses bacterial populations more than using just antibiotics, but oscillations in bacteria populations still occur.
- Resistant bacteria persist in all treatment scenarios, indicating that reducing bacterial load does not necessarily eliminate resistance.
- Model simulations suggest that moderate phage levels provide the best balance between lowering total bacteria and limiting resistant bacteria.

Next Steps

- Validate model predictions and refine parameters with *in vitro* experiments
- Expand the model to include spatial dynamics, immune system interactions, periodic antibiotic dosing, or bacteriophage immunity
- Simulate multiple antibiotic or phage types in the same system
- Use this model to recommend optimal dosing for combination therapy

References

Calero-Caceres, W., Ye, M., & Balcázar, J. L. (2019). Bacteriophages as Environmental Reservoirs of Antibiotic Resistance. *Trends in Microbiology*,27(7), 570–577. https://doi.org/10.1016/j.tim.2019.02.008

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