A SIMPL Model of Phage-Bacteria Interactions Accounting for Mutation and Competition

Carli Peterson[1], Darsh Gandhi[1], Austin Carlson[1], Emma Richardson[1], Aaron Lubkemann[1], John E. Serralta[2], Michael S. Allen[2], Souvik Roy[1], Christopher M. Kribs[1], Hristo V. Kojouharov[1]

[1]The University of Texas at Arlington, [2]The University of North Texas Health Science Center at Fort Worth

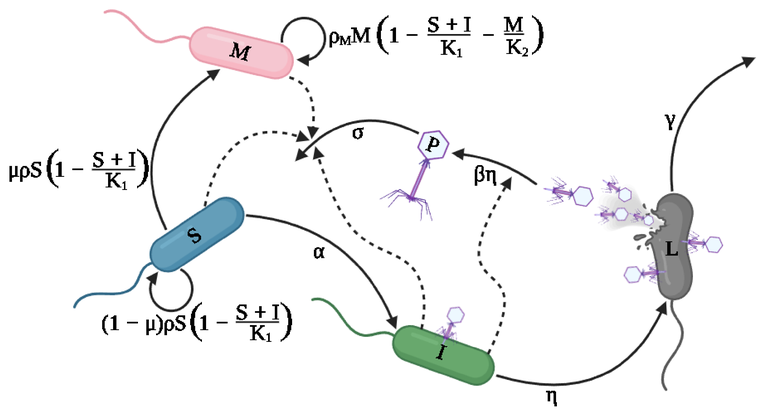
Background and Motivation

- *Pseudomonas aeruginosa* is an opportunistically pathogenic bacterium that causes $51,000$ infections per year in the United States.
- *P. aeruginosa* is quickly becoming antibiotic-resistant, rendering current treatments impractical.
- Bacteriophage (viruses that selectively infect and kill bacteria) could be an alternative.
- **Research Question:** What assumptions are necessary to accurately capture the interaction between phages and bacterial cells in a controlled environment?

Experimental Setup

- We considered optical density (OD) measurements of a strain of P. aeruginosa over 18 hours.
- Optical density is a quantitative, unitless measure that indicates the degree of light scattering through a sample.
- Six experiments were conducted, in each of which varying amounts of a novel P. aeruginosa phage were added, while the initial amounts of bacterial cells remained constant between tests.
- **Research Question:** How significantly does bacterial debris contribute to optical density readings?

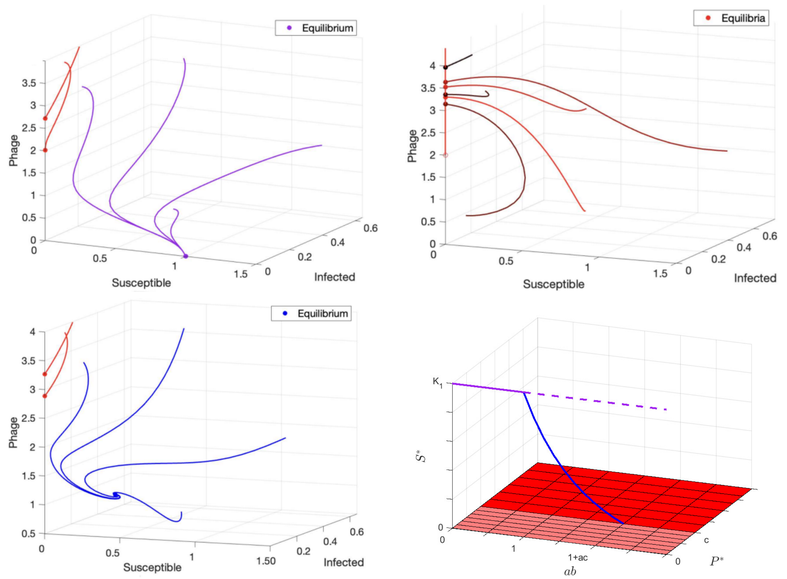
Model Development



The SIMPL Model:

$$
\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \underbrace{(1-\mu)\rho S\left(1-\frac{S+I}{K_1}\right)}_{\text{reproduction without mutation}} - \underbrace{\alpha SP}_{\text{infection}},\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \underbrace{\alpha SP}_{\text{infection}} - \underbrace{\eta I}_{\text{burst}},\\
\frac{\mathrm{d}M}{\mathrm{d}t} &= \underbrace{\rho_M M\left(1-\frac{S+I}{K_1}-\frac{M}{K_2}\right)}_{\text{reproduction}} + \underbrace{\mu\rho S\left(1-\frac{S+I}{K_1}\right)}_{\text{reproduction with mutation}},\\
\frac{\mathrm{d}P}{\mathrm{d}t} &= \underbrace{\beta\eta I}_{\text{burst}} - \underbrace{\sigma SP - \sigma IP}_{\text{attachment}},\\
\frac{\mathrm{d}L}{\mathrm{d}t} &= \underbrace{\eta I}_{\text{burst}} - \underbrace{\gamma L}_{\text{decay}}
\end{aligned}
\qquad (1)
$$

Qualitative Analysis



- The system has three equilibria: (1) bacteria-free, (2) phage-free, (3) coexistence.
- In the SIP subsystem, two transcritical bifurcations occur at $ab = 1$ and $ab = 1 + ac$, where $ab = \dfrac{\alpha\beta}{\sigma}$ and $ac = \dfrac{(1-\mu)\rho}{\eta}$.
- No steady-state is globally stable; depending on the initial amount of bacteriophage, there are scenarios where phage win out despite a parameter combination where bacteria can survive.
- By a theorem of Thieme, the long-term behavior of the SIMPL system is asymptotic to the SIP subsystem.

Parameter Estimation and Optimization Problem

- Take the total bacterial contribution to optical density, $B = S + I + M + \epsilon L$,

$$\frac{dB}{dt} = (\rho S + \rho_M M)\left(1 - \frac{S+I}{K_1}\right) - \rho_M\left(\frac{M}{K_2}\right) - (1-\epsilon)\eta I - \epsilon\gamma L, \qquad (2)$$

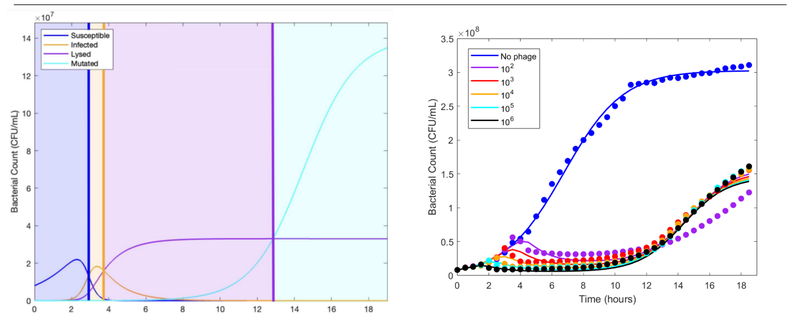
  where $0 \le \epsilon < 1$.
- Optimization problem:

$$\min_{\boldsymbol{\theta}\in\mathcal{T}_{ad}} J(B,\boldsymbol{\theta}) := \frac{\omega}{2}\sum_{i=1}^{6}\sum_{j=1}^{N_t}(B_i(t^j) - B_i^j)^2 + \frac{\nu}{2}\|\boldsymbol{\theta}\|_2^2, \text{ subject to (1).}$$

- We numerically solved the optimization problem in MATLAB using `fmincon`, `MultiStart`, `ode15s`.
- We assessed the accuracy of our parameter estimates using the relative l^2 error percentage:

$$EP = \sqrt{\frac{\sum_{i=1}^{6}\sum_{j=1}^{N_t}(B_i(t^j) - B_i^j)^2}{\sum_{i=1}^{6}\sum_{j=1}^{N_t}(B_i^j)^2}} \times 100$$

Results



- Our model fit the observed optical density data with an error of 8.5%.
- Lysed bacterial cells contribute to optical density measurements about 31% as much as live cells.
- Observed four distinct phases in phage-bacteria interaction: (1) susceptible, (2) infection, (3) lysis, (4) mutation.

Conclusions

- *Pseudomonas aeruginosa* is a deadly bacterium that is mutating to become largely resistant to antibiotic treatments.
- Though bacteriophage therapy is a promising alternative treatment method, we need a solid understanding of the dynamics between bacterial and phage populations to successfully implement this therapy.
- Mathematical models like the one developed in this project provide important insight into this interaction and can be made simple while keeping results accurate.
- We concluded that bacterial debris contributes roughly 31% as much as live bacterial cells to optical density measurements.
- A cocktail of multiple strains of bacteriophage will likely be needed for effective clinical use.

Future Work

- Investigate the effect of bacterial debris on bacterial carrying capacity.
- Extend our model to an in vivo setting by incorporating the removal of bacterial cells due to a patient's immune response.
- Consider a combination treatment of bacteriophage and antibiotics to develop an optimized treatment strategy.
- Explore new methods to convert optical density to bacterial counts.

References & Acknowledgements

References:

1. C Peterson, *et al*. A SIMPL Model of Phage-Bacteria Interactions Accounting for Mutation and Competition. *Submitted Aug 2024, Revised Jan 2025*.
2. J Serralta. Isolation and Characterization of a Novel Bacteriophage for Pseudomonas aeruginosa. *MS thesis*. University of North Texas Health Science Center at Fort Worth, 2023.

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