Development of deterministic and stochastic models for a T7 phage-*E. coli* system with vaccination strategy implementation

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Objective

The goal of this project **is to develop an experiment to explore disease dynamics under various vaccination policies**.

We can generalize our results from an experimental bench system (*E. coli* bacteria and T7 phage[virus]) by **developing a deterministic compartmental model, and then factoring in noise to form a stochastic one**. Additional classes were added to track phage populations and experiment with vaccination strategy.

Introduction

- Vaccination is widely considered the most effective method of preventing the spread of infectious disease.
- Pulse vaccination strategy, the repeated application of a vaccine over a defined population at a set time interval is gaining prominence as a strategy for the elimination of diseases such as measles, hepatitis, and smallpox.
- In order to study the effectiveness of this strategy, a bench experiment will be designed using ***E. coli bacteria*** **and T7 bacteriophage**, and studying the interactions and mechanisms in a chemostat. Bacteria, the most abundant organisms on Earth, are outnumbered 10 to 1 by the bacteriophage that infect them. Bacteria have developed various mechanisms to evade phage infection as phage have simultaneously developed new strategies to infect the host.
- Using this system allows us to study the spread of infectious disease in laboratory setting.
- To test vaccination in system, the rcsA gene (immunity) in *E. coli* will be chemically induced. Preliminary experiments were conducted to determine the best concentration of IPTG to give immunity to the host cells when phage is at a given concentration.
- Elimination and emergence of infectious disease both involve system that is pushed over a critical point. Preliminary studies regarding early warning signs for approaching a bifurcation point and critical slowing down (examining the phage being driven to extinction by vaccination) were also conducted.

Key Assumptions

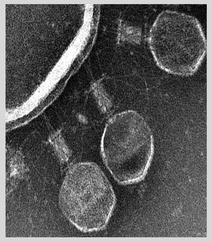


Figure 1. Multiple bacteriophage binding to a host [4]

- No immigration.
- Parameter values do not change over time.
- Population sizes for the simulations started at 10^5 naive hosts and 10^5 phage.
- Burst size is independent of number of phage that infect the bacteria.
- All transmission occurs environmentally, and is density-dependent.
- Full immunity when vaccinated.
- Vaccination will be implemented using the pulse vaccination strategy, which consists of discrete periodical repetitions of vaccinations.

Deterministic Model

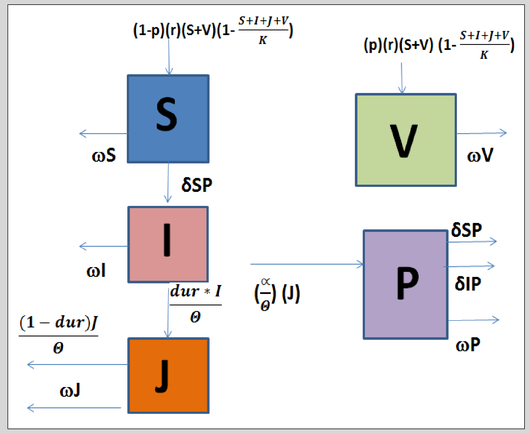


Figure 2. Transitions in the SVIJP compartmental model

Parameter	Value Used	Meaning
δ	6.24 mL/hr	Adsorption rate. Measures how easily phage bind to bacteria
α	98 phage	Burst size; number of phage produced by each infected host
r	.738 cfu/hr	Doubling time of the bacteria
ω	0.25 turnovers/hr	Natural mortality (washout rate)
p	Varies	Proportion of hosts vaccinated at birth
Θ	0.5 hours	Latent period (lysis time)
dur	.0025 hours	Subset of latent period where the host can only be infected by multiple phage
K	10^8 mL	Assumed carrying capacity

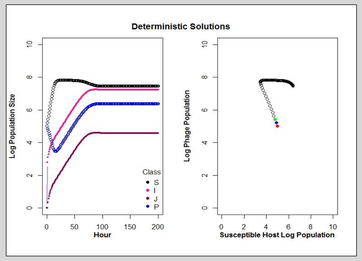
Table 1 . Parameter Values. Many were taken from Lenski 1985.
From the next generation matrix method, the calculated R_0=9.475

With the standard single-adsorption SIP model, there was no coexistence with the bacteria and phage. If the washout rate was too high, phage would extinct; when it was too low both the host and phage would go extinct. Although biologically justified, the simple SIP model did not capture the true dynamics of the system. The infected class of the was divided into 2 main classes I and J to create stability and manage phage removal in the mathematical model.

Figure 3.
No vaccination.

Left The time series. solutions to the ordinary differential equations.

Right Phase plot for the log populations of Phage vs. Susceptible. The red, blue, and green points are the first, second, and third populations (respectively) to indicate a cyclic pattern.



Stochastic Model

The **adaptive tau leaping** method is used to simulate the model stochastically. This code was modified from Tad Dallas's stochastic R code. The code is based off the formation of a "transition matrix" where each row represents a change to the S, V, I, J, or P classes. This matrix is taken in as an argument to the ssradaptivetau function in the AdaptiveTau R package.

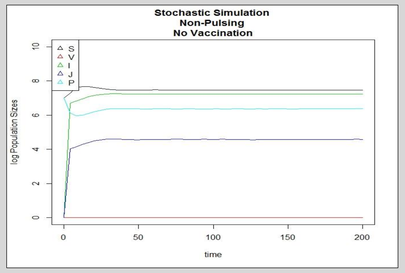
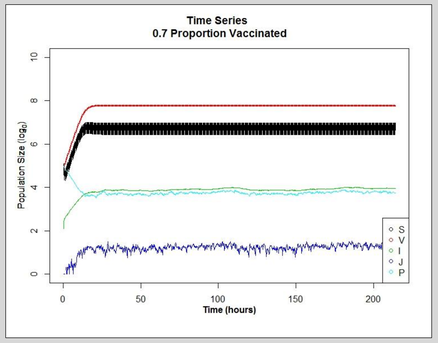


Figure 4.
Time in hours.

Stable point for one stochastic simulation with zero proportion of hosts vaccinated.

Pulse Vaccination Strategy

- A set proportion of the population is vaccinated every 0.5 hours, which is roughly every generation of host.
- Increasing the time in between vaccination pulses did not result in phage extinction
- The infected population and phage populations follow a similar trend in their respective sizes
- Not much residual contamination
- Initial start values at equilibrium increases length of time needed for phage extinction (not shown below)



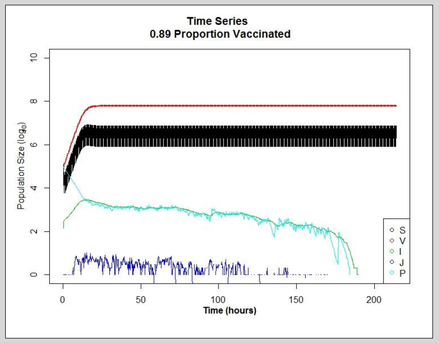


Figure 5 . Time series plots for a single stochastic simulation with pulse vaccination, indicating how increasing the proportion vaccinated can drive the virus from endemic equilibrium (where 70% of hosts are vaccinated) to extinction (where 89% of hosts are vaccinated).

Future Work : Critical Slowing Down

- **Critical slowing down** is the decline in the resilience of the system to perturbations. [5]
- The simplest way to measure the approach to a potential tipping point is directly measure the recovery time (or rate) of the state of the system back to its initial equilibrium state following a perturbation. [5]
- In the case that the system is close to a tipping (**bifurcation**) point the recovery time should *increase* (or the recovery rate should decrease). [5]

Next Steps: CSD

1. *Determine the bifurcation point from multiple simulations.*
2. *Calculate Early Warning Signals.*
   - *Autocorrelation*
   - *Skewness*
   - *Variance.*
3. *Experiment with other vaccination strategies such as non-regular pulse vaccination.* [6]

These together will study how vaccination strategy influences Critical Slowing Down.

Conclusions

- The deterministic and stochastic models behave similarly and produce coexistence and stability when there is no vaccination
- An additional component to the I class, called the J class was added to manage phage removal from the system to create this stability
- Equilibrium was reached with the current parameters for both the deterministic and stochastic models at around 25-30 hours.
- Without vaccination, there is a stable equilibrium. The stability with vaccination is dependent on the proportion vaccinated. Above a certain threshold, the phage is driven to extinction. The duration can make the equilibrium a stable cycle, stable point, or disease-free equilibrium.
- The bifurcation point of where extinction is ensured is at a vaccination rate of nearly 0.98, which in a practical real-world context can be equated to vaccinated nearly an entire population.

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