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Modeling Disease Impact of Vibrio-Phage Interactions

Christopher Botelho
University of Central Florida, cbotelho@knights.ucf.edu

MODELING DISEASE IMPACT OF VIBRIO-PHAGE INTERACTIONS

by

CHRISTOPHER BOTELHO
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ABSTRACT

Since the work of John Snow, scientists and medical professionals have understood that individuals develop cholera by means of consuming contaminated water. Despite the knowledgeof cholera's route of infection, many countries have experienced and still experience endemic cholera. Cholera is caused by the *Vibrio cholerae* (*V. cholerae*) bacterium and presents with acute diarrhea and vomiting. If untreated, infected individuals may die due to dehydration. Cholera is a disease that most commonly affects countries with poor infrastructure and water sanitation. Despite efforts to control cholera in such countries, the disease persists. One such example is Haiti which has been experiencing a cholera outbreak since 2010. While there has been much research in the field of microbiology to understand *V. cholerae*, there has been comparably less research in the field of mathematical biology to understand the dynamics of *V. cholerae* in the environment. A mathematical model of *V. cholerae* incorporating a phage population is coupled with a SIRS disease model to examine the impact of vibrio and phage interaction. It is shown that there might exist two endemic equilibria, besides the disease free equilibrium: one in which phage persist in the environment and one in which the phage fail to persist. Existence and stability of these equilibria are established. Disease control strategies based on vibrio and phage interactions are discussed.

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CHAPTER 1: INTRODUCTION

Cholera has devastated many countries throughout history. There have been seven pandemics of cholera, the first of which originated in India in 1817 [1]. It is believed that increases in travel have contributed to the pandemic growth of cholera [1]. Worldwide, it is estimated that there are 1.3 to 4 million cholera cases and 21,000 to 143,000 deaths due to cholera yearly [17]. In 2015, the World Health Organization (WHO) reported that Democratic Republic of the Congo, Kenya, Malawi, Mozambique, Nigeria, Somalia, South Sudan, Tanzania, Dominican Republic, Haiti, Afghanistan and Iraq had been affected by cholera [16]. Despite efforts to control cholera in countries with poor infrastructure and sanitation, cholera persists.

The bacterium *V. cholerae* is the etiologic agent of cholera, specifically the O1 and O139 serogroups. *V. cholerae* may be found in water sources that have not been chemically treated or filtered. Consumption of water from such sources may yield a cholera infection for the consumer. After consumption of *V. cholerae* contaminated water or food, the bacteria rapidly replicate in the gut of the effected individual, producing a cholera infection. Cholera presents with watery diarrhea and vomiting. If left untreated, an infected individual may die within hours due to dehydration, metabolic acidosis, and uremia [17, 5]. In less severe cases of cholera, treatment may include oral or IV re-hydration however, in more severe cases antibiotics may also be used. An infected individual may shed new *V. cholerae* bacteria into the environment by means of defecation, if waste is not disposed of properly. An infected individual may shed up to $10^7 - 10^9$ bacteria per milliliter of fecal waste [12].

V. cholerae is a Gram negative, facultative anaerobe, non-spore forming curved rod bacterium

with a single polar flagellum. *V. cholerae's* flagellum makes the bacterium highly motile. The *V. cholerae* bacteria is found in rivers, lakes, oceans and estuaries [6]. In these environments, bacteria may be found in biofilms or may be found free floating. According to Rodney M. Donlan [4], "A biofilm is an assemblage of surface-associated microbial cells that is enclosed in an extracellular polymeric substance matrix." It is biologically advantageous for *V. cholerae* to exist in biofilms as it helps the bacterium survive harsh environmental conditions [14].

Another mode of survival for *V. cholerae* is its ability to enter a viable but nonculturable (VBNC) state. A bacterium that enters the VBNC state is a living cell that is not able to replicate on routine media [8]. According to Li *et al.* [8], "VBNC cells have higher physical and chemical resistance than culturable cells." Though still viable cells, VBNC bacteria have a reduced metabolic rate [8]. While VBNC *V. cholerae* cells have a reduced metabolic rate, they remain virulent with a reduced rate of adhesion [8, 10]. While bacteria enter a VBNC state when environmental conditions are harsh, they may leave this state and return to a culturable state when environmental conditions are favorable. Leaving the VBNC state and returning to a culturable state is called "resuscitation" [10].

It may seem that *V. cholerae* is the perfect bacterium. With all of its survival mechanisms, a natural question that arises is, what prevents the bacteria from growing so abundant and taking over all water sources. The answer to this question is bacteriophage. A bacteriophage (or phage) is a virus that infects bacteria. These viruses may be lytic or lysogenic. A lytic bacteriophage enters the bacterium and replicates. After the virus replicates, it causes the cell to lyse, or burst, which results in more bacteriophage in the environment. A bacteriophage that is lysogenic, integrates its DNA into the bacterium's genome. This causes the bacterial daughter cells to also have the bacteriophage DNA in their genome.

Bacteriophage may be purely lytic, purely lysogenic or a combination. Some bacteriophages are lysogenic until environmental conditions are unsuitable for bacterial cell survival, at which point they lyse the cell. One such example of a lysogenic bacteriophage is the lysogenic CTXΦ bacteriophage. The CTXΦ bacteriophage is responsible for encoding for production of cholera toxin which induces the cholera illness. According to Solis-Sanchez *et al.* [13], "since 2007, more than 200 vibrio phages have been described." Lytic phage help keep the bacterial populations in check. The relationship between bacteria and bacteriophage exhibits predator-prey-like qualities.

The ability for *V. cholerae* to persist in the environment despite harsh conditions makes cholera a considerable public safety concern. To better understand the relationship between bacteria and bacteriophage, we develop a mathematical model to describe these processes as well as their impact on disease dynamics among a human population. We use mathematical methods to analyze the model to understand these dynamics.

CHAPTER 2: MODEL DEVELOPMENT

We devise a mathematical model to represent the bacteria-bacteriophage dynamics as well as the impact these dynamics have on a human population. Here, we state our assumptions and build the model. We give full biological justification and simplification justification in the section titled "Model Limitations." We use a compartmental model which includes compartments for susceptible individuals (S), infected individuals (I), recovered individuals (R), bacteria (B) and bacteriophage (P). We account for human immunity loss, so recovered individuals may return to the susceptible compartment. We treat the encounters of bacteria and phage in a manner similar to predator-prey dynamics described by Lotka-Volterra equations [9].

We make many simplifications in human compartments of the model in attempt to reserve complication for bacterial and phage compartments as this is the primary interest. In order to simplify model analysis, we assume constant human birth Λ. Individuals who are born, are born directly into the susceptible compartment. We assume that the natural per-capita death rate is constant μ. We also assume no disease-related deaths occur for model simplicity as well as the relatively low cholera related death rate seen biologically.

With the previous model specifications in mind, we begin to construct the human compartments of our model. Humans consume bacteria at a constant rate α. Upon consumption from bacteria infected source, an individual contracts infection with probability $f(B) = \frac{B}{H+B}$. This probability follows a dose response curve similar to the ones used by Codeço [2]. Here, H is the quantity of bacteria that yields fifty percent chance of infection. Humans recover at a constant rate r and lose immunity at constant rate γ.

Now, we begin developing the bacteria and bacteriophage compartments of the model. Here, we attempt to retain as much biological reality in the model while maintaining enough simplicity to perform an effective model analysis. We assume that bacteria (B) grow exponentially in absence of phage and human contribution. That is without phage and human contribution to the culturable reservoir, we have $\dot{B} = KB$ where K is the intrinsic growth rate of bacteria. Here, $K = \nu - \delta$ where ν is the bacterial "birth" rate and δ is the bacterial death rate. Humans shed new bacteria into the environment by means of defecation and vomiting at a rate η. We consider bacteriophage to be predators as in Lotka-Volterra equations with search efficiency b. We assume that the conversion rate for the phage to be given by χ. Phage "die" at a rate m. A comprehensive list of parameters and parameter description is seen in table 2.1.

Table 2.1: Model parameter values, descriptions and associated units

Parameters for Bacteria-Phage Model		
Λ	human birth rate	persons·days^{-1}
μ	human death rate	days^{-1}
α	rate of bacterial consumption	days^{-1}
$f(B)$	probability of infection upon consumption	unitless
r	recovery rate	days^{-1}
γ	rate in which immunity is lost	days^{-1}
η	rate in which infected individuals shed bacteria	bacteria·person^{-1}·days^{-1}
ν	culturable bacteria growth rate	days^{-1}
b	phage attack rate	days^{-1}·phage^{-1}
δ	bacterial death rate	days^{-1}
χ	phage gain from culturable bacteria	days^{-1}·bacteria^{-1}
m	phage death rate	death^{-1}

With the above assumptions in mind, we obtain the system of ordinary differential equations given

by

$$\begin{cases} \dot{S} &= \Lambda + \gamma R - \alpha f(B) S - \mu S \\ \dot{I} &= \alpha f(B) S - (r + \mu) I \\ \dot{R} &= rI - \gamma R - \mu R \\ \dot{B} &= \nu B + \eta I - \delta B - bBP \\ \dot{P} &= \chi bBP - mP. \end{cases} \tag{2.1}$$

This system is seen represented in the following flow diagram:

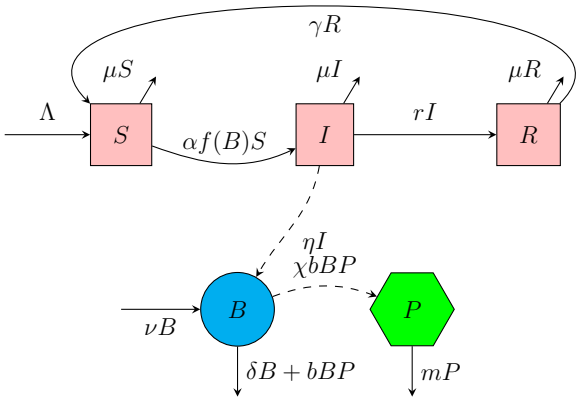

Figure 2.1: Flow diagram for model

Well known theory in ordinary differential equations give that initial value problem $(S(0), I(0), R(0), B(0), P(0))$ and (2.1) has a unique solution.

CHAPTER 3: MODEL ANALYSIS

A unique disease free equilibrium, a phage present endemic equilibrium, and a phage free endemic equilibrium are found and discussed along with stability conditions. The basic reproduction number, $\mathcal{R}_0$, is discussed as well as a new critical value $\mathcal{R}_P$. It will be shown that the disease may be controlled by $\mathcal{R}_P$, even in the case that $\mathcal{R}_0 > 1$.

3.1 Feasible Region and Boundedness of Solutions

The feasible region is given by

$$\Gamma = \{(S, I, R, B, P) \in \mathbb{R}^5_+ : S + I + R \leq \frac{\Lambda}{\mu}\}.$$

In the following lemma, it is shown that $S + I + R \leq \frac{\Lambda}{\mu}$ for all $t \geq 0$. We denote the interior of Γ by Γ^0.

To show that the solutions of the model are bounded, we consider the compartments that make up the human population together and the phage/bacteria compartments separately. That is, we consider $N = S + I + R$ and $E = \chi B + P$.

Lemma 1. *All solutions to (2.1) are bounded whenever $\delta > \nu$.*

Proof. Now, $\dot{N} = \dot{S} + \dot{I} + \dot{R} = \Lambda - \mu N$ which gives the first order problem $\dot{N} + \mu N = \Lambda$. Using the method of integrating factor, we may write this as $\frac{d}{dt}\{e^{\mu t} N\} = \Lambda e^{\mu t}$ which gives $N = \frac{\Lambda}{\mu} + (N_0 - \frac{\Lambda}{\mu})e^{-\mu t}$ where N_0 is the initial human population $N(0)$. It is seen that as $t \to \infty$, $N \to \frac{\Lambda}{\mu}$. If $N_0 < \frac{\Lambda}{\mu}$, N increases monotonically to $\frac{\Lambda}{\mu}$ and if $N_0 > \frac{\Lambda}{\mu}$, N decreases monotonically to $\frac{\Lambda}{\mu}$. So, N is bounded by $\max\{N_0, \frac{\Lambda}{\mu}\}$ for all $t \geq 0$. From here forward, we assume $N_0 < \frac{\Lambda}{\mu}$

without loss of generality.

We now consider $\dot{E} = \chi\dot{B} + \dot{P}$ for the case $\delta > \nu$. Let $\epsilon = \min\{\delta - \nu, m\}$. We have

$$\begin{aligned}
\dot{E} &= \chi\dot{B} + \dot{P} \\
&= -\chi(\delta - \nu)B - mP + \eta\chi P \\
&\leq -\epsilon(\chi B + P) + \eta\chi I \\
&= -\epsilon E + \eta\chi I \\
&\leq -\epsilon E + \eta\chi N \\
&\leq -\epsilon E + \eta\chi\frac{\Lambda}{\mu}
\end{aligned}$$

which gives the first order problem $\dot{E} + \epsilon E \leq \eta\chi\frac{\Lambda}{\mu}$ which may be written as $\frac{d}{dt}\{e^{\epsilon t}E\} \leq e^{\epsilon t}\eta\chi\frac{\Lambda}{\mu}$ using the integrating factor $e^{\epsilon}t$. Now, integrating both sides of the inequality yields

$$E \leq \frac{\eta\chi\Lambda}{\epsilon\mu} + Ce^{-\epsilon t} \leq \frac{\eta\chi\Lambda}{\epsilon\mu} + C$$

where C is some constant. Thus E is bounded for all $t \geq 0$. □

Boundedness of the bacterial and phage components has yet to be shown for the case $\delta < \nu$.

3.2 Disease Free Equilibrium (DFE)

An equilibrium point is a point where the rate of change among all components is zero. That is, an equilibrium point gives $\dot{S} = \dot{I} = \dot{R} = \dot{B} = \dot{P} = 0$. It is seen that letting $I = 0$ in the model (2.1), we obtain the disease free equilibrium (DFE) $Q^0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$.

3.3 Local Stability of DFE

Stability conditions for DFE are explored and a new critical value $\mathcal{R}_B$ is discussed. We begin by examining the Jacobian matrix at DFE (J_{DFE}). We have:

$$J_{DFE} = \begin{bmatrix} -\mu & \gamma & 0 & -\frac{\alpha\Lambda}{H\mu} & 0 \\ 0 & -(\gamma+\mu) & r & 0 & 0 \\ 0 & 0 & -(r+\mu) & \frac{\alpha\Lambda}{H\mu} & 0 \\ 0 & 0 & \eta & \nu-\delta & 0 \\ 0 & 0 & 0 & 0 & -m \end{bmatrix}. \tag{3.1}$$

It is seen that J_{DFE} is a block triangular matrix of the form

$$J_{DFE} = \begin{bmatrix} \mathcal{A} & * & * \\ 0 & \mathcal{B} & * \\ 0 & 0 & \mathcal{C} \end{bmatrix}$$

with

$$\mathcal{A} = \begin{bmatrix} -\mu & \gamma \\ 0 & -(\gamma+\mu) \end{bmatrix}, \quad \mathcal{B} = \begin{bmatrix} -(r+\mu) & \frac{\alpha\Lambda}{H\mu} \\ \eta & \nu-\delta \end{bmatrix}, \quad \mathcal{C} = \begin{bmatrix} -m \end{bmatrix}$$

So, the spectrum of J_{DFE} is $\lambda(J_{DFE}) = \lambda(\mathcal{A}) \cup \lambda(\mathcal{B}) \cup \lambda(\mathcal{C})$ (proof given in appendix). Since $\mathcal{A}$ and $\mathcal{C}$ are upper triangular, their eigenvalues lie on the diagonal. So finding the eigenvalues of J_{DFE} is reduced to finding the eigenvalues of the 2×2 sub-matrix $\mathcal{B}$. We have $\lambda(\mathcal{A}) = \{-\mu, -(\gamma+\mu)\}$ and $\lambda(\mathcal{C}) = \{-m\}$. Now, $\mathrm{Tr}(\mathcal{B}) = -(r+\mu) + \nu - \delta$ and $\mathrm{Det}(\mathcal{B}) = -(r+\mu)(\nu-\delta) - \frac{\Lambda\alpha\eta}{H\mu}$ and so the eigenvalues of $\mathcal{B}$ are both negative provided $\mathrm{Tr}(\mathcal{B}) < 0$ and $\mathrm{Det}(\mathcal{B}) > 0$. $\mathrm{Tr}(\mathcal{B}) < 0$

gives the condition $1 > \frac{\nu}{r+\mu+\delta}$ and $\mathrm{Det}(\mathcal{B}) > 0$ gives the condition $1 > \frac{\Lambda\alpha\eta}{H\mu\delta(r+\mu)} + \frac{\nu}{\delta}$. Note that $\frac{\Lambda\alpha\eta}{H\mu\delta(r+\mu)} + \frac{\nu}{\delta} > \frac{\nu}{\delta} > \frac{\nu}{\delta+r+\mu}$. So $1 > \frac{\Lambda\alpha\eta}{H\mu\delta(r+\mu)} + \frac{\nu}{\delta}$ is necessary and sufficient to conclude that the eigenvalues of $\mathcal{B}$ are negative. Denote

$$\mathcal{R}_B = \frac{\Lambda\alpha\eta}{H\mu\delta(r+\mu)} + \frac{\nu}{\delta}.$$

The eigenvalues $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ are all negative under the condition $\mathcal{R}_B < 1$. This motivates the following theorem.

Theorem 2. *If $\mathcal{R}_B < 1$, then the disease free equilibrium is locally stable.*

3.4 Global Stability of DFE

Theorem 3. *If $\mathcal{R}_B < 1$, then the disease free equilibrium is globally asymptotically stable in Γ.*

Proof. Suppose $\mathcal{R}_B < 1$. We have

$$\begin{aligned}
& \mathcal{R}_B = \frac{\Lambda\alpha\eta}{\mu\delta(r+\mu)H} + \frac{\nu}{\delta} < 1 \\
\implies \quad & \frac{\Lambda\alpha\eta}{\mu\delta(r+\mu)H} + \frac{\nu}{\delta} - 1 < 0 \\
\implies \quad & \frac{\Lambda\alpha\eta}{(r+\mu)\mu H} + \nu - \delta < 0 \\
\implies \quad & \frac{\Lambda\alpha}{\mu H} + \frac{(r+\mu)(\nu-\delta)}{\eta} < 0.
\end{aligned}$$

Consider the function $L = I + \frac{r+\mu}{\eta}B + \frac{r+\mu}{\eta\chi}P$. Clearly $L \geq 0$. Now,

$$
\begin{aligned}
\dot{L} &= \dot{I} + \frac{r+\mu}{\eta}\dot{B} + \frac{r+\mu}{\eta\chi}\dot{P} \\
&= \alpha f(B)S - (r+\mu)I + \frac{r+\mu}{\eta}(\eta I + \nu - \delta B - bBP) + \frac{r+\mu}{\eta\chi}(\chi bBP - mP) \\
&= \alpha\frac{B}{B+H}S + \frac{(r+\mu)(\nu)-\delta}{\eta}B - \frac{m(r+\mu)}{\eta\chi}P \\
&\leq \alpha\frac{\Lambda}{\mu}\cdot\frac{B}{H} + \frac{(r+\mu)(\nu-\delta)}{\eta}B - \frac{m(r+\mu)}{\eta\chi}P \\
&= \big(\frac{\Lambda\alpha}{H\mu} + \frac{(r+\mu)(\nu-\delta)}{\eta}\big)B - \frac{m(r+\mu)}{\eta\chi}P \leq 0.
\end{aligned}
$$

So L is a Lyapunov function.

Now, when $\dot{L} = 0$, it is required that $B = P = 0$. But, from (2.1), it is clear that $I = 0$, $R = 0$, and $S = \frac{\Lambda}{\mu}$. So, $\{Q^0\}$ is the largest invariant subset where $\dot{L} = 0$. Therefore, by LaSalle's invariance principle [7], Q^0 is globally asymptotically stable in Γ.

□

3.5 Basic Reproduction Number

The basic reproduction number, denoted by $\mathcal{R}_0$, is described by the average new infections a single infected host will induce, in an entirely susceptible population, in it's entire infectious life [3]. The procedure of constructing the next generation matrix outlined by O. Diekmann, J.A.P. Heesterbeek and M.G. Roberts [3] is followed to obtain $\mathcal{R}_0$ for the model (2.1). Consider the sub-system consisting of compartments of infection and those that contribute to infection, that is the infectious

compartment I and bacterial compartment B. The sub-system is given by

$$\begin{cases} \dot{B} &= (\nu - \delta)B - bBP + \eta I \\ \dot{I} &= \alpha \frac{B}{H+B} S - (r + \mu)I. \end{cases} \tag{3.2}$$

Now, linearizing at the DFE gives the linearized system

$$\dot{x} = \begin{bmatrix} \nu - \delta & \eta \\ \frac{\alpha\Lambda}{\mu H} & -(r+\mu) \end{bmatrix} x$$

where $x = [B, I]^T$. The linearized system may be written as

$$T - \Sigma = \begin{bmatrix} \nu & \eta \\ \frac{\alpha\Lambda}{\mu H} & 0 \end{bmatrix} + \begin{bmatrix} -\delta & 0 \\ 0 & -(r+\mu) \end{bmatrix}.$$

The transmission matrix consists of all terms that directly contribute to new infections and is given by

$$T = \begin{bmatrix} \nu & \eta \\ \frac{\alpha\Lambda}{\mu H} & 0 \end{bmatrix}.$$

The transition matrix consists of changes in infectious state and is given by

$$\Sigma = \begin{bmatrix} -\delta & 0 \\ 0 & -(r+\mu) \end{bmatrix}.$$

Now, the next generation matrix NGM is given by $K = -T\Sigma^{-1}$. The NGM is therefore

$$K = \begin{bmatrix} \frac{\nu}{\delta} & \frac{\eta}{r+\mu} \\ \frac{\alpha\Lambda}{\mu\delta H} & 0 \end{bmatrix}.$$

The basic reproduction number is then given by

$$\mathcal{R}_0 = \rho(K) = \frac{1}{2}\Big(\frac{\nu}{\delta} + \sqrt{\frac{\nu^2}{\delta^2} + \frac{4\nu\alpha\Lambda\eta}{(r+\mu)\mu\delta H}}\Big).$$

We know that if $\mathcal{R}_0 < 1$, the disease dies out (DFE is stable) and if $\mathcal{R}_0 > 1$, the disease persists (DFE is unstable).

We now prove that the stability conditions of the DFE given by $\mathcal{R}_B$ and $\mathcal{R}_0$ are equivalent.

Lemma 4. $\mathcal{R}_0 < 1$ $(\mathcal{R}_0 > 1)$ $\iff$ $\mathcal{R}_B < 1$ $(\mathcal{R}_B > 1)$.

Proof. We have:

$$\begin{aligned}
\mathcal{R}_0 = \frac{1}{2}\Big(\frac{\nu}{\delta} + \sqrt{\frac{\nu^2}{\delta^2} + \frac{4\nu\alpha\Lambda\eta}{(r+\mu)\mu\delta H}}\Big) &< 1 \\
\iff \quad \frac{\nu}{\delta} + \sqrt{\frac{\nu^2}{\delta^2} + \frac{4\nu\alpha\Lambda\eta}{(r+\mu)\mu\delta H}} &< 2 \\
\iff \quad \frac{\nu^2}{\delta^2} + \frac{4\nu\alpha\Lambda\eta}{\delta(r+\mu)\mu\delta H} &< 4 - 4\frac{\nu}{\delta} + \frac{\nu^2}{\delta^2} \\
\iff \quad \frac{\eta\alpha\Lambda}{(r+\mu)H\mu} &< (1 - \frac{\nu}{\delta}) \\
\iff \quad \mathcal{R}_B = \frac{\Lambda\alpha\eta}{\delta(r+\mu)\mu H} + \frac{\nu}{\delta} &< 1.
\end{aligned}$$

□

3.6 Endemic Equilibria

We determine that there may exist two distinct endemic equilibria. One equilibrium has a zero phage population while the other has a positive phage population. We call the equilibrium with a zero phage population the phage free endemic equilibrium (PFEE) and denote it by $Q_{PFEE} = (S_*, I_*, R_*, B_*, 0)$. We call the equilibrium with a positive phage population the phage persistent endemic equilibrium (PPEE) and denote it by $Q_{PPEE} = (S^*, I^*, R^*, B^*, P^*)$. It is shown that there are two critical values $\mathcal{R}_B$ and $\mathcal{R}_P$ that determine both the existence and stability of Q_{PFEE} and Q_{PPEE}.

3.6.1 Phage Free Endemic Equilibrium (PFEE)

Letting $\dot{S} = \dot{I} = \dot{R} = \dot{B} = \dot{P} = 0$, the system

$$\begin{cases} \dot{S} &= \Lambda + \gamma R - \alpha f(B) S - \mu S = 0 \\ \dot{I} &= \alpha f(B) S - (r + \mu) I = 0 \\ \dot{R} &= rI - \gamma R - \mu R = 0 \\ \dot{B} &= \nu B + \eta I - \delta B - bBP = 0 \\ \dot{P} &= \chi bBP - mP = 0 \end{cases} \tag{3.3}$$

is obtained. Clearly $P = 0$ satisfies $\dot{P} = 0$. So the system becomes

$$\Lambda + \gamma R - \alpha f(B)S - \mu S = 0 \tag{3.4}$$

$$\alpha f(B)S - (r + \mu)I = 0 \tag{3.5}$$

$$rI - (\gamma + \mu)R = 0 \tag{3.6}$$

$$(\nu - \delta)B + \eta I = 0. \tag{3.7}$$

Now, (3.7) gives $B_* = \frac{\eta}{\delta - \nu} I_*$ and so it is required that $\delta > \nu$ to ensure $B_* \geq 0$. It is also seen that (3.6) gives $R_* = \frac{r}{\gamma + \mu} I_*$ and (3.5) gives $S_* = \frac{r+\mu}{\alpha}\big(\frac{\delta - \nu}{\eta} H + I_*\big)$. Clearly R_* is positive whenever I_* is positive and S_* is positive whenever $\delta > \nu$ and I_* is positive. Using B_*, S_* and R_* described above in (3.4),

$$\Lambda + \frac{\gamma r}{\gamma + \mu} I_* - (r + \mu)I_* - \frac{\mu(r + \mu)}{\alpha} \cdot \frac{\delta - \nu}{\eta}\big(H + \frac{\eta}{\delta - \nu} I_*\big) = 0 \tag{3.8}$$

is obtained. Equation (3.8) can be rearranged as

$$\frac{\Lambda\alpha\eta - \mu(r + \mu)(\delta - \nu)H}{\alpha\eta} = I_*\big(\frac{r\mu}{\gamma + \mu} + \mu + \frac{\mu(r + \mu)}{\alpha}\big). \tag{3.9}$$

It is clear that for I_* to be positive, it is required that the left hand side of (3.9) must be positive. That is $\Lambda\alpha\eta - \mu(r + \mu)(\delta - \nu)H > 0$. This gives $\mathcal{R}_B = \frac{\Lambda\alpha\eta}{H\mu\delta(r+\mu)} + \frac{\nu}{\delta} > 1$. Solving for I_* in (3.9) gives

$$I_* = \frac{(\gamma + \mu)[\Lambda\alpha\eta - \mu H\delta(r + \mu) + \mu\nu H(r + \mu)]}{\eta(r\mu\alpha + \mu\alpha(\gamma + \mu) + \mu(r + \mu)(\gamma + \mu))}. \tag{3.10}$$

This motivate the following theorem.

Theorem 5. *There exists an endemic equilibrium point without phage, Q_{PFEE}, under the condition $\mathcal{R}_B > 1$ and $\delta > \nu$.*

3.6.2 Local Stability of PFEE

The stability of Q_{PFEE} is now discussed. Another critical value $\mathcal{R}_P$ is obtained and it is shown that Q_{PFEE} is stable for $\mathcal{R}_P < 1$. The critical value $\mathcal{R}_P$ is defined by

$$\mathcal{R}_P := \frac{b}{\delta}\left(\frac{\nu}{b} + \frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{r\mu\alpha m + \mu\alpha m(\gamma+\mu) + \mu\chi bH(r+\mu)(\gamma+\mu) + m\mu(r+\mu)(\gamma+\mu)}\right).$$

Theorem 6. *The phage free endemic equilibrium Q_{PFEE} is locally stable whenever $\mathcal{R}_P < 1 < \mathcal{R}_B$.*

Proof. Consider the case where $\mathcal{R}_B > 1$ and $\mathcal{R}_P < 1$. It is clear from the definition of $\mathcal{R}_P$ that $\mathcal{R}_P < 1$ implies $\nu < \delta$ and so under these conditions, existence of Q_{PFEE} is guaranteed.

Now, examining the Jacobian matrix at Q_{PFEE} given by

$$J_{PFEE} = \begin{bmatrix} -\alpha f(B_*) - \mu & 0 & \gamma & -\frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} & 0 \\ \alpha f(B_*) & -(r+\mu) & 0 & \frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} & 0 \\ 0 & r & -(\gamma+\mu) & 0 & 0 \\ 0 & \eta & 0 & \nu-\delta & -bB_* \\ 0 & 0 & 0 & 0 & \chi bB_* - m \end{bmatrix},$$

it is seen that $J_{PFEE} = \begin{bmatrix} \bar{C} & * \\ 0 & \chi b B_* - m \end{bmatrix}$ with

$$\bar{C} = \begin{bmatrix} -\alpha f(B_*) - \mu & 0 & \gamma & -\frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} \\ \alpha f(B_*) & -(r+\mu) & 0 & \frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} \\ 0 & r & -(\gamma+\mu) & 0 \\ 0 & \eta & 0 & \nu - \delta \end{bmatrix}.$$

So, the eigenvalues of J_{PFEE} are given by $\lambda_5 = \chi b B_* - m$ and $\lambda(\bar{C}) = \{\lambda_1, \lambda_2, \lambda_3, \lambda_4\}$.

We now consider $\lambda_5 = \chi b B_* - m$. Using the equilibrium equations, we write

$$\begin{aligned} \lambda_5 &= \chi b B_* - m \\ &= \frac{\eta}{\delta - \nu} I_* \chi b - m \\ &= \frac{\chi b}{\delta - \nu} \left(\frac{(\gamma+\mu)[\Lambda\alpha\eta - \mu H\delta(r+\mu) + \mu\nu H(r+\mu)]}{r\mu\alpha + \mu\alpha(\gamma+\mu) + \mu(r+\mu)(\gamma+\mu)} \right) - m. \end{aligned}$$

So, in order for Q_{PFEE} to be stable, it is necessary that $\lambda_5 < 0$. That is

$$\frac{\chi b}{\delta - \nu} \left(\frac{(\gamma+\mu)[\Lambda\alpha\eta - \mu H\delta(r+\mu) + \mu\nu H(r+\mu)]}{r\mu\alpha + \mu\alpha(\gamma+\mu) + \mu(r+\mu)(\gamma+\mu)} \right) - m < 0.$$

We have,

$$\begin{aligned} & \frac{\chi b}{\delta - \nu} \left(\frac{(\gamma+\mu)[\Lambda\alpha\eta - \mu H\delta(r+\mu) + \mu\nu H(r+\mu)]}{r\mu\alpha + \mu\alpha(\gamma+\mu) + \mu(r+\mu)(\gamma+\mu)} \right) - m < 0 \\ \implies \quad & \frac{\chi b(\gamma+\mu)[\Lambda\alpha\eta - \mu H\delta(r+\mu) + \mu\nu H(r+\mu)]}{r\mu\alpha m + \mu\alpha m(\gamma+\mu) + \mu m(r+\mu)(\gamma+\mu)} + \nu < \delta \end{aligned}$$

$$\implies \qquad \Lambda\alpha\eta\chi b(\gamma+\mu)+\mu\nu H\chi b(r+\mu)(\gamma+\mu)+\nu K<\delta[K+\mu\chi bH(r+\mu)(\gamma+\mu)]$$

$$(\text{where } K=r\mu\alpha m+\mu\alpha m(\gamma+\mu)+\mu m(r+\mu)(\gamma+\mu))$$

$$\implies \qquad \frac{1}{\delta}\cdot\frac{b(\Lambda\alpha\eta\chi(\gamma+\mu)+\mu\nu H\chi(r+\mu)(\gamma+\mu))+K\nu}{K+\mu\nu H\chi(r+\mu)(\gamma+\mu)}<1$$

$$\implies \mathcal{R}_P=\frac{b}{\delta}\Big(\frac{\nu}{b}+\frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{r\mu\alpha m+\mu\alpha m(\gamma+\mu)+\mu\chi bH(r+\mu)(\gamma+\mu)+m\mu(r+\mu)(\gamma+\mu)}\Big)<1.$$

Now, it must be shown that under the stated conditions above, $\lambda_1,\lambda_2,\lambda_3,\lambda_4$ have negative real parts. To do this, examine $\det(\bar{C}-tI)$; calculation of $\det(\bar{C}-tI)$ is shown in appendix. We have

$$\begin{aligned}\det(\bar{C}-tI)=(\mu+t)\Big[&t^3+(r+2\mu+\gamma+\delta-\nu+\alpha f(B_*))t^2\\&+\Big(\alpha f(B_*)(\gamma+r+\mu+\delta-\nu)+(\gamma+\mu)(r+\mu)\\&+(r+2\mu+\gamma)(\delta-\nu)-\frac{H(r+\mu)(\delta-\nu)}{H+B_*}\Big)t\\&+(\gamma+\mu)(r+\mu)(\delta-\nu)+\alpha f(B_*)(\gamma+r+\mu)(\delta-\nu)\\&-\frac{H(r+\mu)(\delta-\nu)(\gamma+\mu)}{H+B_*}\Big].\end{aligned}$$

Clearly $t=-\mu$ is a zero of the above polynomial and so we must now determine whether the third degree factor has zeros with negative real parts. To make this determination, we utilize the Routh-Hurwitz criterion. By Routh-Hurwitz criterion, a third degree polynomial $p(t)=a_0t^3+a_1t^2+a_2t+a_3$ with $a_0,a_1,a_2,a_3>0$, and $a_1a_2>a_0a_3$, has roots with negative real parts. We now verify these conditions for

$$
\begin{aligned}
p(t) = t^3 &+ (r + 2\mu + \gamma + \delta - \nu + \alpha f(B_*))t^2 \\
&+ \left(\alpha f(B_*)(\gamma + r + \mu + \delta - \nu) + (\gamma + \mu)(r + \mu) \right. \\
&\left. + (r + 2\mu + \gamma)(\delta - \nu) - \frac{H(r + \mu)(\delta - \nu)}{H + B_*} \right) t \\
&+ (\gamma + \mu)(r + \mu)(\delta - \nu) + \alpha f(B_*)(\gamma + r + \mu)(\delta - \nu) \\
&- \frac{H(r + \mu)(\delta - \nu)(\gamma + \mu)}{H + B_*}.
\end{aligned}
$$

We have

$$
\begin{aligned}
a_0 &= 1 > 0 \\
a_1 &= \gamma + 2\mu + r + \delta - \nu + \alpha f(B_*) > 0 \\
a_2 &= \alpha f(B_*)(\gamma + r + \mu + \delta - \nu) + (\gamma + \mu)(r + \mu) + (r + 2\mu + \gamma)(\delta - \nu) - \frac{H(r + \mu)(\delta - \nu)}{H + B_*} \\
&= \alpha f(B_*)(\gamma + r + \mu + \delta - \nu) + (\gamma + \mu)(r + \mu + \delta - \nu) + \frac{B_*(r + \mu)(\delta - \nu)}{H + B_*} > 0 \\
a_3 &= (\gamma + \mu)(r + \mu)(\delta - \nu) + \alpha f(B_*)(\gamma + r + \mu)(\delta - \nu) - \frac{H(r + \mu)(\delta - \nu)(\gamma + \mu)}{H + B_*} \\
&= \alpha f(B_*)(\gamma + r + \mu)(\delta - \nu) + \frac{B_*(r + \mu)(\delta - \nu)(\gamma + \mu)}{H + B_*} > 0.
\end{aligned}
$$

and

$$
\begin{aligned}
a_1a_2 &= (\gamma+2\mu+r+\delta-\nu+\alpha f(B_*))\big[\alpha f(B_*)(\gamma+r+\mu+\delta-\nu) \\
&\qquad + (\gamma+\mu)(r+\mu+\delta-\nu)+\frac{B_*(r+\mu)(\delta-\nu)}{H+B_*}\big] \\
&= \alpha f(B_*)(\gamma+r+\mu+\delta-\nu)(\gamma+2\mu+r+\delta-\nu+\alpha f(B_*)) \\
&\qquad + (\gamma+\mu)(r+\mu+\delta-\nu)(\gamma+2\mu+r+\delta-\nu+\alpha f(B_*)) \\
&\qquad + \frac{B_*(r+\mu)(\delta-\nu)(\gamma+2\mu+r+\delta-\nu+\alpha f(B_*))}{H+B_*} \\
&> \alpha f(B_*)(\gamma+r+\mu+\delta-\nu)(\gamma+2\mu+r+\delta-\nu+\alpha f(B_*)) \\
&\qquad + \frac{B_*(r+\mu)(\delta-\nu)(\gamma+2\mu+r+\delta-\nu+\alpha f(B_*))}{H+B_*} \\
&> \alpha f(B_*)(\gamma+r+\mu)(\delta-\nu)+\frac{B_*(r+\mu)(\delta-\nu)(\gamma+\mu)}{H+B_*} \\
&= a_0a_3.
\end{aligned}
$$

So, by the Routh-Hurwitz criterion, $\det(\bar{C}-tI)$ has roots with negative real parts. Thus the equilibrium point Q_{PFEE} is stable under the above assumptions. □

From the work above, it is clear that when $\mathcal{R}_{\mathcal{P}}>1$, $\lambda_5>0$ and so under this condition Q_{PFEE} is unstable if it exists.

The following lemma provides a comparison between the two critical values $\mathcal{R}_B$ and $\mathcal{R}_P$.

Lemma 7. $\mathcal{R}_P<\mathcal{R}_B$

Proof.

$$\begin{aligned}\mathcal{R}_P &= \frac{b}{\delta}\left(\frac{\nu}{b} + \frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{r\mu\alpha m + \mu\alpha m(\gamma+\mu) + \mu\chi bH(r+\mu)(\gamma+\mu) + m\mu(r+\mu)(\gamma+\mu)}\right)\\ &< \frac{b}{\delta}\left(\frac{\nu}{b} + \frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{\mu\chi bH(r+\mu)(\gamma+\mu)}\right)\\ &= \frac{b}{\delta}\left(\frac{\nu}{b} + \frac{\Lambda\alpha\eta}{\mu bH(r+\mu)}\right)\\ &= \frac{\Lambda\alpha\eta + \nu\mu(r+\mu)H}{\mu\delta(r+\mu)H} = \mathcal{R}_B\end{aligned}$$

□

3.6.3 Global Stability of PFEE Without Loss of Immunity

We now discuss the global stability of the PFEE for the case where recovered individuals do not become susceptible again ($\gamma = 0$). With the above assumptions in mind, we obtain the system which is given by

$$\begin{cases}\dot{S} &= \Lambda - \alpha f(B)S - \mu S\\ \dot{I} &= \alpha f(B)S - (r+\mu)I\\ \dot{R} &= rI - \mu R\\ \dot{B} &= \nu B + \eta I - \delta B - bBP\\ \dot{P} &= \chi bBP - mP.\end{cases} \tag{3.11}$$

Before stating and proving global stability of the PFEE, recall the comparison of the geometric and arithmetic mean of non-negative numbers $x_1, x_2, ..., x_n$ which is given by $x_1 + x_2 + \cdots + x_n \geq n\cdot\sqrt[n]{x_1x_2\cdots x_n}$. This will be used in the proof of the following theorem.

Lemma 8. *Suppose $x, x_* > 0$. Then $x - x_* - x_* \ln(\frac{x}{x_*}) \geq 0$.*

Proof. Consider the function $g(\theta) = \theta - \ln(\theta)$. Now, $g'(\theta) = \frac{\theta-1}{\theta}$ and $g''(\theta) = \frac{1}{\theta^2}$. We have that $\theta = 1$ is a critical value of g and $g'' > 0$ and so $\theta = 1$ corresponds to a minimum of g. We have $g(1) = 1$ and so we have $g(\theta) = \theta - \ln(\theta) \geq 1$. Letting $\theta = \frac{x}{x_*}$, we obtain $\frac{x}{x_*} - \ln(\frac{x}{x_*}) \geq 1$ which gives $x - x_* - x_* \ln(\frac{x}{x_*}) \geq 0$ as desired. □

Theorem 9. *For the case $\gamma = 0$, the phage free endemic equilibrium Q_{PFEE} is globally asymptotically stable in Γ^0 whenever $\mathcal{R}_P < 1 < \mathcal{R}_B$.*

Proof. The condition $\mathcal{R}_P < 1 < \mathcal{R}_B$ guarantees the existence of Q_{PFEE} by Theorem 6. Now, consider the function

$$L = S - S_* - S_* \ln\big(\frac{S}{S_*}\big) + I - I_* - \ln\big(\frac{I}{I_*}\big) + \frac{r+\mu}{\eta}\left(B - B_* - B_* \ln\big(\frac{B}{B_*}\big)\right) + \frac{r+\mu}{\eta\chi}P$$

We see that $L \geq 0$ by Lemma 8, and $L(Q_{PFEE}) = 0$. Now, using the equilibrium equations

$$\begin{aligned} \alpha f(B_*) S_* - \mu S_* &= \Lambda \\ (r+\mu) I_* &= \alpha f(B_*) S_* \\ (\nu - \delta) B_* &= -\eta I_* \end{aligned}$$

in the derivative of L, we obtain

$$\dot{L} = \dot{S}\frac{\dot{S}}{S} S_* + \dot{I} - \frac{\dot{I}}{I} I_* + \frac{r+\mu}{\eta}\big(\dot{B} - \frac{\dot{B}}{B} B_*\big) + \frac{r+\mu}{\eta\chi}\dot{P}$$

$$
\begin{aligned}
&= \Lambda - \alpha f(B)S - \mu S - \frac{\Lambda S_*}{S} + \alpha f(B)S_* + \mu S_* + \alpha f(B)S - (r+\mu)I \\
&\quad - \frac{\alpha f(B)SI_*}{I} + (r+\mu)I_* + \frac{r+\mu}{\eta}\big((\nu-\delta)B + \eta I - bBP - (\nu-\delta)B_* - \frac{\eta I B_*}{B} + bB_*P\big) \\
&\quad + \frac{r+\mu}{\eta\chi}\big(\chi bBP - mP\big) \\
&= \alpha f(B_*)S_* + \mu S_* - \mu S - \alpha f(B_*)S_*\frac{S_*}{S} - \mu S_*\frac{S_*}{S} + \alpha f(B)S_* + \mu S_* - \frac{\alpha f(B)SI_*}{I} \\
&\quad + \alpha f(B_*)S_* + \frac{r+\mu}{\eta}\big((\nu-\delta)B - bBP - (\nu-\delta)B_* - \frac{\eta I B_*}{B} + bB_*P\big) \\
&\quad + \frac{r+\mu}{\eta\chi}\big(\chi bBP - mP\big) \\
&= \mu S_*\big(2 - \frac{S}{S_*} - \frac{S_*}{S}\big) + \alpha f(B_*)S_*\big(2 - \frac{S_*}{S} - \frac{f(B)SI_*}{f(B_*)S_*I} + \frac{f(B)}{f(B_*)}\big) \\
&\quad + \frac{r+\mu}{\eta}\big((\nu-\delta)B - bBP - (\nu-\delta)B_* - \frac{\eta I B_*}{B} + bB_*P\big) + \frac{r+\mu}{\eta\chi}\big(\chi bBP - mP\big) \\
&= \mu S_*\big(2 - \frac{S}{S_*} - \frac{S_*}{S}\big) + \alpha f(B_*)S_*\big(2 - \frac{S_*}{S} - \frac{f(B)SI_*}{f(B_*)S_*I} + \frac{f(B)}{f(B_*)}\big) \\
&\quad + \frac{r+\mu}{\eta}\big((\nu-\delta)B - (\nu-\delta)B_* + bB_*P\big) - (r+\mu)I\frac{B_*}{B} - \frac{r+\mu}{\eta\chi}mP \\
&= \mu S_*\big(2 - \frac{S}{S_*} - \frac{S_*}{S}\big) + \alpha f(B_*)S_*\big(2 - \frac{S_*}{S} - \frac{f(B)SI_*}{f(B_*)S_*I} + \frac{f(B)}{f(B_*)}\big) \\
&\quad + \frac{r+\mu}{\eta}\big((\nu-\delta)B + bB_*P\big) + \alpha f(B_*)S_* - (r+\mu)I\frac{B_*}{B}\cdot\frac{I_*}{I_*} - \frac{r+\mu}{\eta\chi}mP \\
&= \mu S_*\big(2 - \frac{S}{S_*} - \frac{S_*}{S}\big) + \alpha f(B_*)S_*\big(3 - \frac{S_*}{S} - \frac{f(B)SI_*}{f(B_*)S_*I} + \frac{f(B)}{f(B_*)} - \frac{IB_*}{I_*B}\big) \\
&\quad + \frac{r+\mu}{\eta\chi}\big(\chi(\nu-\delta)B + \chi bB_*P - mP\big) \\
&= \mu S_*\big(2 - \frac{S}{S_*} - \frac{S_*}{S}\big) + \alpha f(B_*)S_*\big(3 - \frac{S_*}{S} - \frac{f(B)SI_*}{f(B_*)S_*I} + \frac{f(B)}{f(B_*)} - \frac{IB_*}{I_*B}\big) \\
&\quad + \frac{r+\mu}{\eta}(\nu-\delta)B_*\frac{B}{B_*} + \frac{r+\mu}{\eta\chi}\big(\chi bB_* - m\big) \\
&= \mu S_*\big(2 - \frac{S_*}{S} - \frac{S}{S_*}\big) + \alpha f(B_*)S_*\big(3 - \frac{S_*}{S} + \frac{f(B)}{f(B_*)} - \frac{B}{B_*} - \frac{f(B)SI_*}{f(B_*)S_*I} - \frac{B_*I}{BI_*}\big) \\
&\quad + \frac{r+\mu}{\eta\chi}\big(\chi bB_* - m\big)P
\end{aligned}
$$

So, we must show

$$\dot{L} = \mu S_*\big(2 - \frac{S_*}{S} - \frac{S}{S_*}\big) + \alpha f(B_*)S_*\big(3 - \frac{S_*}{S} + \frac{f(B)}{f(B_*)} - \frac{B}{B_*} - \frac{f(B)SI_*}{f(B_*)S_*I} - \frac{B_*I}{BI_*}\big) + \frac{r+\mu}{\eta\chi}\big(\chi b B_* - m\big)P \leq 0.$$

From the comparison of the geometric and arithmetic means inequality, we have

$$\frac{S_*}{S} + \frac{S}{S_*} \geq 2\cdot\sqrt{\frac{S_*}{S}\cdot\frac{S}{S_*}} = 2$$

and so $2 - \frac{S_*}{S} - \frac{S}{S_*} \leq 0$. Now consider

$$\begin{aligned} &3 - \frac{S_*}{S} + \frac{f(B)}{f(B_*)} - \frac{B}{B_*} - \frac{f(B)SI_*}{f(B_*)S_*I} - \frac{B_*I}{BI_*} \\ &= -1 + \frac{f(B)}{f(B_*)} - \frac{B}{B_*} + \frac{f(B_*)B}{f(B)B_*} \\ &\quad + 4 - \frac{S_*}{S} - \frac{f(B_*)B}{f(B)B_*} - \frac{f(B)SI_*}{f(B_*)S_*I} - \frac{B_*I}{BI_*}. \end{aligned}$$

Again using the comparison of the geometric and arithmetic means inequality, we see

$$\frac{S_*}{S} + \frac{f(B_*)B}{f(B)B_*} + \frac{f(B)SI_*}{f(B_*)S_*I} + \frac{B_*I}{BI_*} \geq 4\cdot\sqrt[4]{\frac{S_*}{S}\cdot\frac{f(B_*)B}{f(B)B_*}\cdot\frac{f(B)SI_*}{f(B_*)S_*I}\cdot\frac{B_*I}{BI_*}} = 4$$

and so $4 - \frac{S_*}{S} - \frac{f(B_*)B}{f(B)B_*} - \frac{f(B)SI_*}{f(B_*)S_*I} - \frac{B_*I}{BI_*} \leq 0$. Now observe

$$
\begin{aligned}
&-1+\frac{f(B)}{f(B_*)}-\frac{B}{B_*}+\frac{f(B_*)B}{f(B)B_*}\\
&=-1+\frac{B_*+H}{B+H}\cdot\frac{B}{B_*}-\frac{B}{B_*}+\frac{B+H}{B_*+H}\\
&=\frac{1}{B_*(B+H)(B_*+H)}\Big(-B_*(B+H)(B_*+H)+B(B_*+H)(B_*+H)\\
&\quad -B(B+H)(B_*+H)+B_*(B+H)(B+H)\Big)\\
&=\frac{-H}{B_*(B+H)(B_*+H)}\big({B_*}^2-2BB_*+B^2\big)\\
&=\frac{-H(B_*-B)^2}{B_*(B+H)(B_*+H)}\leq 0.
\end{aligned}
$$

With this, we have that $3-\dfrac{S_*}{S}+\dfrac{f(B)}{f(B_*)}-\dfrac{B}{B_*}-\dfrac{f(B)SI_*}{f(B_*)S_*I}-\dfrac{B_*I}{BI_*}\leq 0.$

Now,

$$
\begin{aligned}
\chi bB_*-m&=\frac{\chi b\eta}{\delta-\nu}I_*-m\\
&=\frac{\chi b[\Lambda\alpha\eta-\mu H\delta(r+\mu)+\mu\nu H(r+\mu)]}{(\delta-\nu)\big(r\alpha+\mu\alpha+\mu(r+\mu)\big)}-m\\
&<0
\end{aligned}
$$

$$
\begin{aligned}
\iff\quad & \chi b[\Lambda\alpha\eta-\mu H\delta(r+\mu)+\mu\nu H(r+\mu)]<m(\delta-\nu)\big(r\alpha+\mu\alpha+\mu(r+\mu)\big)\\
\iff\quad & \mathcal{R}_P=\frac{b}{\delta}\Big(\frac{\nu}{b}+\frac{\Lambda\alpha\eta\chi\mu}{r\mu\alpha m+\mu\alpha m\mu+\mu\chi bH(r+\mu)\mu+m\mu(r+\mu)\mu}\Big)<1.
\end{aligned}
$$

Thus, we conclude that under the specified conditions, $\dot{L}\leq 0$. That is L is a Lyapunov function.

Now, $\dot{L}=0$ implies that $S=S_*$, $B=B_*$, $I=I_*$, and $P=0$. From (3.3), it is then seen

that $R = R_*$. So $\{Q_{PFEE}\}$ is the largest invariant subset where $\dot{L} = 0$. Therefore, by LaSalle's invariance principle [7], Q_{PFEE} is globally asymptotically stable in Γ^0.

□

3.6.4 Phage Persistent Endemic Equilibrium (PPEE)

Here, we discuss the existence of a third equilibrium point. The phage persistent endemic equilibrium (PPEE) exists under the condition $\mathcal{R}_P > 1$. We discuss global stability of the PPEE for the case where $\gamma = 0$.

We proceed finding the PPEE by letting $\dot{S} = \dot{I} = \dot{R} = \dot{B} = \dot{P} = 0$. So we obtain the system

$$\dot{S} = \Lambda + \gamma R - \alpha f(B)S - \mu S = 0 \tag{3.12}$$

$$\dot{I} = \alpha f(B)S - (r + \mu)I = 0 \tag{3.13}$$

$$\dot{R} = rI - \gamma R - \mu R = 0 \tag{3.14}$$

$$\dot{B} = \nu B + \eta I - \delta B - bBP = 0 \tag{3.15}$$

$$\dot{P} = \chi bBP - mP = 0. \tag{3.16}$$

Now, instead of letting $P = 0$ for the equation $\chi bB^*P^* - mP^* = 0$, we consider $P^* \neq 0$ and so $B^* = \frac{m}{\chi b}$, which is always feasible. Using this in (3.14) gives the equation $\frac{(\nu-\delta)m}{\chi b} + \eta I^* - \frac{m}{\chi}P^* = 0$ or $P^* = \frac{(\nu-\delta)}{b} + \frac{\eta\chi}{m}I^*$ which is only feasible and distinct from the PFEE when $\frac{(\nu-\delta)}{b} + \frac{\eta\chi}{m}I^* > 0$. Now, using B^* in (3.12), we have obtain $S^* = \frac{r+\mu}{\alpha}\big(\frac{\chi bH}{m} + 1\big)I^*$ which is feasible whenever I^* is feasible. From (3.13), it is clear that $R^* = \frac{r}{\gamma+\mu}I^*$ which is feasible whenever I^* is feasible. Now,

using R^*, B^* and S^* in (3.11), we obtain the equation

$$\Lambda + \frac{\gamma r}{\gamma+\mu} I^* - (r+\mu)I^* - \mu\frac{r+\mu}{\alpha}\big(\frac{\chi bH}{m} + 1\big)I^* = 0$$

which, upon solving for I^*, yields

$$I^* = \frac{\Lambda\alpha m(\gamma+\mu)}{r\mu\alpha m + \mu(\gamma+\mu)\alpha m + \mu(r+\mu)(\gamma+\mu)\chi bH + m\mu(r+\mu)(\gamma+\mu)}.$$

Clearly, $I^* > 0$ and so I^* is always feasible. Thus the only condition on the PPEE comes from the inequality $\frac{(\nu-\delta)}{b} + \frac{\eta\chi}{m} I^* > 0$. Using I^* in this inequality gives the inequality

$$\frac{(\nu-\delta)}{b} + \frac{\eta\chi}{m}\frac{\Lambda\alpha m(\gamma+\mu)}{r\mu\alpha m + \mu(\gamma+\mu)\alpha m + \mu(r+\mu)(\gamma+\mu)\chi bH + m\mu(r+\mu)(\gamma+\mu)} > 0.$$

Upon rearranging terms in this inequality, we obtain the equivalent condition

$$\mathcal{R}_P = \frac{b}{\delta}\big(\frac{\nu}{b} + \frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{r\mu\alpha m + \mu\alpha m(\gamma+\mu) + \mu\chi bH(r+\mu)(\gamma+\mu) + m\mu(r+\mu)(\gamma+\mu)}\big) > 1.$$

This motivates the following theorem.

Theorem 10. *There exists a second endemic equilibrium (PPEE) to the system when $\mathcal{R}_P > 1$.*

Lemma 11. *If $\nu > \delta$, then Q_{PPEE} exists, Q_{PFEE} does not exist and Q^0 is unstable.*

Proof. Clearly when $\nu > \delta$, the conditions for existence of Q_{PFEE} are not satisfied and so it does

not exist. Now,

$$\begin{aligned}\mathcal{R}_P &= \frac{b}{\delta}\Big(\frac{\nu}{b} + \frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{r\mu\alpha m + \mu\alpha m(\gamma+\mu) + \mu\chi bH(r+\mu)(\gamma+\mu) + m\mu(r+\mu)(\gamma+\mu)}\Big)\\ &> 1 + \frac{b}{\delta}\cdot\frac{\Lambda\alpha\eta\chi(\gamma+\mu)}{r\mu\alpha m + \mu\alpha m(\gamma+\mu) + \mu\chi bH(r+\mu)(\gamma+\mu) + m\mu(r+\mu)(\gamma+\mu)}\\ &> 1.\end{aligned}$$

So, Q_{PPEE} exists and by Lemma 7, $1 < \mathcal{R}_P < \mathcal{R}_B$ which gives that the DFE Q^0 is unstable. □

3.6.5 Global Stability of PPEE Without Loss of Immunity

We now discuss the global stability of the $PPEE$ under the condition $\gamma = 0$.

Theorem 12. *For the case where $\gamma = 0$, whenever Q_{PPEE} exists, it is globally asymptotically stable.*

Proof. Suppose $Q_{PPEE} = (S^*, I^*, R^*, B^*, P^*)$ exists. That is, $\mathcal{R}_P > 1$. Now, consider the function

$$\begin{aligned}L = S - S^* - S^*\ln\big(\frac{S}{S^*}\big) + I - I^* - \ln\big(\frac{I}{I^*}\big)\\ + \frac{r+\mu}{\eta}\left(B - B^* - B^*\ln\big(\frac{B}{B^*}\big)\right) + \frac{r+\mu}{\eta\chi}\left(P - P^* - P^*\ln\big(\frac{P}{P^*}\big)\right)\end{aligned}$$

We see that $L \geq 0$ by lemma 8. Now, we use the equilibrium equations

$$\begin{aligned}
\alpha f(B^*)S^* - \mu S^* &= \Lambda \\
(r+\mu)I^* &= \alpha f(B^*)S^* \\
(\nu-\delta)B^* + \eta I^* &= bB^*P^* \\
\chi b B^* P^* &= mP^*
\end{aligned}$$

in the derivative of L to obtain

$$\begin{aligned}
\dot{L} &= \dot{S} - \frac{\dot{S}}{S}S^* + \dot{I} - \frac{\dot{I}}{I}I^* + \frac{r+\mu}{\eta}\big(\dot{B} - \frac{\dot{B}}{B}B^*\big) + \frac{r+\mu}{\eta\chi}\big(\dot{P} - \frac{\dot{P}}{P}P^*\big) \\
&= \Lambda - \alpha f(B)S - \mu S - \frac{\Lambda - \alpha f(B)S - \mu S}{S}S^* + \alpha f(B)S - (r+\mu)I \\
&\quad - \frac{\alpha S - (r_\mu)I}{I}I^* + \frac{r+\mu}{\eta}\big((\nu-\delta)B + \eta I - bBP - \frac{(\nu-\delta)B + \eta I - bBP}{B}B^*\big) \\
&\quad + \frac{r+\mu}{\eta\chi}\big(\chi bBP - mP - \frac{\chi bBP - mP}{P}P^*\big) \\
&= \alpha f(B^*)S^* + \mu S^* - \mu S - \frac{\alpha f(B^*)S^{*2}}{S} - \frac{\mu S^{*2}}{S} + \alpha f(B)S^* + \mu S^* - \frac{\alpha f(B)SI^*}{I} \\
&\quad + (r+\mu)I^* + \frac{r+\mu}{\eta}\big((\nu-\delta)B - (\nu-\delta)B^* - \frac{\eta I B^*}{B} + bB^*P\big) \\
&\quad + \frac{r+\mu}{\eta\chi}\big(-mP - \chi bBP^* + mP^*\big) \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(1 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)}\big) + \alpha f(B^*)S^* - \frac{\alpha f(B)SI^*}{I} \\
&\quad + \frac{r+\mu}{\eta}\big((\nu-\delta)B - (\nu-\delta)B^* - \frac{\eta I B^*}{B} + bB^*P\big) + \frac{r+\mu}{\eta\chi}\big(-mP - \chi bBP^* + mP^*\big) \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(2 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{f(B)SI^*}{f(B^*)S^*I}\big) + \frac{r+\mu}{\eta}(\nu-\delta)B \\
&\quad - \frac{r+\mu}{\eta}(\nu-\delta)B^* - (r+\mu)I\frac{B^*}{B} + \frac{r+\mu}{\eta}bB^*P - \frac{r+\mu}{\eta\chi}mP - \frac{r+\mu}{\eta}bBP^* + \frac{r+\mu}{\eta\chi}mP^*
\end{aligned}$$

$$
\begin{aligned}
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(2 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{f(B)SI^*}{f(B^*)S^*I}\big) + \frac{r+\mu}{\eta}(\nu-\delta)B \\
&\quad - \frac{r+\mu}{\eta}(\nu-\delta)B^* - (r+\mu)I\frac{B^*}{B} + \frac{r+\mu}{\eta\chi}\chi bB^*P - \frac{r+\mu}{\eta\chi}mP - \frac{r+\mu}{\eta}bBP^* + \frac{r+\mu}{\eta\chi}mP^* \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(2 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{f(B)SI^*}{f(B^*)S^*I}\big) + \frac{r+\mu}{\eta}(\nu-\delta)B \\
&\quad - \frac{r+\mu}{\eta}(\nu-\delta)B^* - (r+\mu)I\frac{B^*}{B} - \frac{r+\mu}{\eta}bBP^* + \frac{r+\mu}{\eta}bB^*P^* \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(2 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{f(B)SI^*}{f(B^*)S^*I}\big) - \frac{B}{B^*}\alpha f(B^*)S^* \\
&\quad + \alpha f(B^*)S^* - (r+\mu)I\frac{B^*}{B} \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(3 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{B}{B^*} - \frac{f(B)SI^*}{f(B^*)S^*I}\big) - (r+\mu)I\frac{B^*I^*}{BI^*} \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(3 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{B}{B^*} - \frac{f(B)SI^*}{f(B^*)S^*I}\big) - \alpha f(B^*)S^*\frac{B^*I}{BI^*} \\
&= \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(3 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{B}{B^*} - \frac{f(B)SI^*}{f(B^*)S^*I} - \frac{B^*I}{BI^*}\big).
\end{aligned}
$$

So, we must show

$$
\dot{L} = \mu S^*\big(2 - \frac{S^*}{S} - \frac{S}{S^*}\big) + \alpha f(B^*)S^*\big(3 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{B}{B^*} - \frac{f(B)SI^*}{f(B^*)S^*I} - \frac{B^*I}{BI^*}\big) \leq 0.
$$

Similar calculations to those in Theorem 8, show $2 - \frac{S^*}{S} - \frac{S}{S^*} \leq 0$ and $3 - \frac{S^*}{S} + \frac{f(B)}{f(B^*)} - \frac{B}{B^*} - \frac{f(B)SI^*}{f(B^*)S^*I} - \frac{B^*I}{BI^*} \leq 0$ and so $\dot{L} \leq 0$. That is L is a Lyapunov function.

Now, $\dot{L} = 0$ implies $S = S^*$, $I = I^*$, and $B = B^*$. Equation (3.14) then implies $R = R^*$ while (3.15) implies $P = P^*$. So $\{Q_{PPEE}\}$ is the largest invariant subset where $\dot{L} = 0$. Therefore, by LaSalle's invariance principle [7], Q_{PPEE} is globally asymptotically stable in Γ^0.

□

CHAPTER 4: CHOLERA CONTROL STRATEGIES

We consider different strategies for controlling cholera. The strategies are broke into two categories; conventional control strategies and unconventional control strategies. The conventional strategies include practices that are currently being implemented while unconventional strategies consider controlling cholera by means of vibrio-phage interactions. Conventional strategies include decreasing intake of *V. cholerae* contaminated water as well as decreasing bacterial shedding into the environment. We see that all conventional control strategies aim to reduce $\mathcal{R}_0$ below 1. While this theoretically would eradicate the disease, unconventional strategies may reduce the disease to tolerable levels without the need to have $\mathcal{R}_0 < 1$. That is, the unconventional strategies allow for disease control despite $\mathcal{R}_0 > 1$.

4.1 Disease Impact of Vibrio Control

The basic reproduction number $\mathcal{R}_0$ gives a threshold value that determines if the disease persists or dies out. The basic reproduction number $\mathcal{R}_0$ is also a measure of control needed to prevent a disease outbreak where all infectious types are targeted equally. The target reproduction number is a threshold value used to measure effort needed to prevent a disease outbreak when targeting only certain infectious types. We follow the notation and methods used in [11]. The target reproduction number $\mathcal{T}_{i,j}$ targets the (i, j) entry of the next generation matrix K. This is interpreted as the effect on the infections that type j causes on type i. If we wish to target multiple entries of K, then we consider a target set S which consists of entries in K. Then the infectious effect on this set is $\mathcal{T}_S$. The target reproduction number $\mathcal{T}_S$ on a target set S is given by $\mathcal{T}_S = \rho(K_S(I - K + K_S)^{-1})$ where $[K_S]_{i,j} = [K]_{i,j}$ if $(i, j) \in S$ and 0 otherwise.

Now, recall the next generation matrix

$$K = \begin{bmatrix} \frac{\nu}{\delta} & \frac{\eta}{r+\mu} \\ \frac{\alpha\Lambda}{\mu\delta H} & 0 \end{bmatrix}.$$

We consider the target sets $S = \{(2,1)\}$, $S = \{(1,2)\}$, and $S = \{(2,1),(1,2)\}$. That is we target the $(2,1)$ entry, $(1,2)$ entry, and $(2,1),(1,2)$ entries together. We do not consider the strategies that target the $(1,1)$ entry or the $(2,2)$ entry as these are not considered feasible strategies. That is because the targeting the $(1,1)$ entry considers the impact bacteria have on themselves (bacterial growth) and the $(2,2)$ entry considers the impact infectious humans have on themselves (transmission from human-to-human contacts) which this model does not consider.

Targeting the (2,1) entry of K considers the consumption of bacteria by humans. An example of a control strategy considering this entry would be the implementation of water purification or drinking bottled water. The target reproduction number $\mathcal{T}_{2,1}$ is given by $\mathcal{T}_{2,1} = \frac{\Lambda\alpha\eta}{H\mu(r+\mu)(\delta-\nu)}$.

Targeting the (1,2) entry of K considers the shedding of bacteria into the environment by humans. An example of a control strategy considering this entry would be the implementation of sanitary waste disposal methods such as the use of latrines that do not contaminate water sources. The target reproduction number is given by $\mathcal{T}_{1,2} = \mathcal{T}_{2,1}$.

Targeting the set $S = \{(2,1),(1,2)\}$ considers all feasible strategies for the given model. We have $\mathcal{T}_S = \rho(K_S(I-K+K_S)^{-1}) = \rho\Big(\begin{bmatrix} 0 & \frac{\eta}{r+\mu} \\ \frac{\alpha\Lambda}{\mu H(\delta-\nu)} & 0 \end{bmatrix}\Big) = \sqrt{\frac{\Lambda\alpha\eta}{\mu H(r+\mu)(\delta-\nu)}} = \sqrt{\mathcal{T}_{1,2}}$. It is clear that $\mathcal{R}_S < 1$ if and only if $\mathcal{T}_{1,2} = \mathcal{T}_{2,1} < 1$.

So, all three strategies give the same threshold. Furthermore, we see

$$\begin{aligned} & \mathcal{T}_{2,1} = \frac{\Lambda\alpha\eta}{H\mu(r+\mu)(\delta-\nu)} < 1 \\ \iff & \frac{\Lambda\alpha\eta}{H\mu(r+\mu)} < \delta - \nu \\ \iff & \mathcal{R}_B = \frac{\Lambda\alpha\eta}{H\mu(r+\mu)\delta} + \frac{\nu}{\delta} < 1. \end{aligned}$$

This combined with Lemma 3, shows that the threshold values $\mathcal{R}_B$, $\mathcal{R}_0$, $\mathcal{T}_S$, and $\mathcal{T}_{1,2} = \mathcal{T}_{2,1}$ are all equivalent.

4.2 Disease Impact of Phage Control

We now turn to discuss unconventional control strategies. We discuss the impact the presence of phage have on an infected population and how the disease may be managed by environmental factors. To do this, we examine the bacterial and infectious components of the PPEE. That is, recall

$$B^* = \frac{m}{b\chi}$$

and

$$I^* = \frac{\Lambda\alpha m(\gamma+\mu)}{r\mu\alpha m + \mu(\gamma+\mu)\alpha m + \mu(r+\mu)(\gamma+\mu)\chi bH + m\mu(r+\mu)(\gamma+\mu)}.$$

We now consider B^* and I^* as functions of m. That is $B^*(m)$ and $I^*(m)$ are functions of the phage death rate m. It is clear that $B^*(m)$ is an increasing function. Now, computing the derivative of $I^*(m)$ yields

$$\frac{dI^*}{dm} = \frac{\Lambda\alpha(\gamma+\mu)\mu(r+\mu)(\gamma+\mu)\chi bH}{\left(r\mu\alpha m + \mu(\gamma+\mu)\alpha m + \mu(r+\mu)(\gamma+\mu)\chi bH + m\mu(r+\mu)(\gamma+\mu)\right)^2} > 0$$

and so $I^*(m)$ is also an increasing function. Since $B^*(m)$ and $I^*(m)$ are increasing functions; as $m \to 0^+$, $B^* \to 0$ and $I^* \to 0$. That is, bacteria and infection may be made arbitrarily small given a sufficiently small m. Moreover, $\mathcal{R}_P \to \frac{\Lambda\alpha\eta}{\mu\delta(r+\mu)H} + \frac{\nu}{\delta} = \mathcal{R}_B$ as $m \to 0^+$. With this in mind, we present the following lemma.

Lemma 13. *Suppose $\mathcal{R}_B > 1$ and $\delta > \nu$. Then, there exists $m_0 > 0$ such that $\mathcal{R}_P = 1$ and $I^*(m_0)$, I_* coincide.*

Proof. Suppose $\mathcal{R}_B > 1$ and $\delta > \nu$. This implies that Q_{PFEE} exists. So

$$I_* = \frac{(\gamma+\mu)\big[\Lambda\alpha\eta - (\delta-\nu)\mu(r+\mu)H\big]}{\eta(r+\mu\alpha+\mu(\mu+\gamma)\alpha+\mu(r+\mu)(\gamma+\mu))} > 0$$

So, $\Lambda\alpha\eta - (\delta-\nu)\mu(r+\mu)H > 0$. This along with the condition $\delta > \nu$ guarantee

$$m_0 = \frac{\chi b(\gamma+\mu)\big[\Lambda\alpha\eta - (\delta-\nu)\mu(r+\mu)H\big]}{(\delta-\nu)\big[r+\mu\alpha+\mu(\mu+\gamma)\alpha+\mu(r+\mu)(\gamma+\mu)\big]} > 0.$$

We have $\mathcal{R}_P(m_0) = 1$ and $I^*(m_0) = I_*$. □

Theorem 14. *Suppose $\mathcal{R}_B > 1$ and $\delta > \nu$. Then $I^*(m) < I_*$ whenever $0 < m < m_0$.*

Proof. Assume $\mathcal{R}_B > 1$ and $\delta > \nu$. Since $\mathcal{R}_P$ is a monotone decreasing function in m, for $0 < m < m_0$ we have $\mathcal{R}_P(m) > \mathcal{R}_P(m_0) = 1$. This guarantees existence of $I^*(m)$. Now, since I^* is monotone increasing in m, $I^*(m) < I^*(m_0) = I_*$ whenever $0 < m < m_0$. □

This theorem leads to an important corollary.

Corollary 15. *Suppose $\mathcal{R}_B > 1$ and $\delta > \nu$. Then for any $\epsilon > 0$, there exists $0 < m_\epsilon < m_0$ such that $I^*(m^*) < \epsilon$ whenever $0 < m < m_\epsilon$.*

A natural question to ask then, is how might the phage "death" rate be effected in reality? The addition of phage would effectively modify the "death" rate of the phage. Indeed, consider an addition of phage to P compartment that is proportional to the current phage population. That is, the new equation for $\dot{P}$ would become $\dot{P} = \chi bBP - mP + kP = \chi bBP - (m-k)P$. Now clearly $m - k < m$ effectively reducing the phage death rate.

Biologically, this corollary states that the disease may be brought down to an acceptable level provided the phage population is large enough. A small phage death rate obviously favors the phage population in the environment. In fact, looking at the equation $\dot{P} = \chi bBP - mP$, we see that if $m = 0$, then the phage population has a positive growth rate for all time.

CHAPTER 5: BIOLOGICAL IMPLICATIONS AND MODEL LIMITATIONS

5.1 Biological Implications

We now turn the discussion to the biological meaning of the previously described mathematical results. Understanding how cholera is contracted and how the bacteria behave in the environment may aid in determining strategies to get the disease under control. The mathematical model discussed previously sheds light on how phage and vibrios interact and how this affects the disease dynamics.

We have seen that if the critical number $\mathcal{R}_B$ is less than 1, then the disease free equilibrium is globally asymptotically stable. That is, if $\mathcal{R}_B < 1$, then the disease will die out over time. This is the ideal case as it ensure the disease does not persist in the given population.

Under the condition $\mathcal{R}_B > 1$, the disease free equilibrium is unstable. That is, the disease persists in the population. If this is the case, we saw that there are two possibilities. These possibilities are the scenario where $\mathcal{R}_P < 1$ and $\mathcal{R}_P > 1$.

In the scenario $\mathcal{R}_P < 1 < \mathcal{R}_B$, we saw that an endemic equilibrium exists and is stable. This equilibrium was absent of phage. For $\mathcal{R}_P < 1$, it is necessary the have the bacterial death rate to exceed the bacterial "birth" rate ($\delta > \nu$). That is the natural death rate of the bacteria exceeds the natural birth rate of the bacteria. This explains how the bacteria do not grow without bound. Biologically, the death rate of the bacteria is large enough to prevent the bacterial population from getting too out of control. In this case, the endemic equilibrium Q_{PFEE} is locally stable and so solutions starting near Q_{PFEE} tend to Q_{PFEE}.

In the scenario $1 < \mathcal{R}_P < \mathcal{R}_B$, we saw that a second endemic equilibrium exists. In this equilibrium, Q_{PPEE}, the phage population is nonzero. If $\delta > \nu$, then Q_{PFEE} exists along with Q_{PPEE} whereas if $\delta < \nu$, Q_{PPEE} is the only endemic equilibrium that exists. In this scenario, it was shown that Q_{PPEE} is globally asymptotically stable under the restriction $\gamma = 0$. Biologically speaking, $\gamma = 0$ means that once a human has recovered from an infection, they will never become susceptible to infection again.

We have discussed control strategies that are implemented in areas of endemic cholera and how they impact the disease. More than this, we have seen that the presence of phage plays a large role in controlling the bacteria population in the environment. We have seen that infectious human populations may be made arbitrarily small for sufficiently small values of m. The phage death rate may be effectively reduced by adding phage into the environment in an amount that is proportional to the phage population. That is, an environment that is favorable to the persistence of phage is also favorable to an infectious population.

5.2 Model Limitations

While this model may give a mathematical backing to previously known biology, it is not perfect and makes many simplifications. Realistically, humans lose immunity after a period of time and so the case $\gamma = 0$ is not the most biologically reasonable scenario. Moreover, humans will shed new phage into the environment by means of defecation/vomiting which this model does not consider. This model also does not consider the ability for bacteria to enter the state of dormancy, VBNC state, discussed in the introduction. While these simplifications were necessary for an effective model analysis they are important factors to consider when considering the accuracy of biological implications.

To reconcile these simplifications among others, we propose a new more accurate (read mathematically cumbersome) model in the next section as well as some conjectures about the model discussed in previous sections.

CHAPTER 6: OPEN PROBLEMS AND FUTURE WORK

6.1 Open Problems

Some results presented have not been proven in the most general context. Here, we state the conjectures:

Conjecture 16. *All trajectories are bounded.*

We have shown in section 3.1 that all trajectories are bounded given the restricted case $\delta > \nu$. It remains to be shown for $\nu \geq \delta$.

Conjecture 17. *If $\mathcal{R}_P < 1 < \mathcal{R}_B$, then Q_{PFEE} is globally asymptotically stable in Γ^0.*

The global stability of Q_{PFEE} has not been shown under these conditions.

Conjecture 18. *If $\mathcal{R}_P > 1$, then Q_{PPEE} is locally stable.*

Conjecture 19. *If $\mathcal{R}_P > 1$, then Q_{PPEE} is globally asymptotically stable in Γ^0.*

The global stability of Q_{PPEE} and Q_{PFEE} was proven for the case $\gamma = 0$. It remains to show global stability for $\gamma \neq 0$. As discussed in the previous chapter, the case $\gamma = 0$ does not make the most biological sense as a cholera infection yields a temporary immunity to the individual. After the period of temporary immunity, they return to the susceptible compartment. The local stability of Q_{PPEE} has yet to be shown due to the complexity of determining the sign of the eigenvalues of a rank 5 matrix.

6.2 Future Work

As discussed in the previous chapter, the model presented is a substantial simplification of an incredibly complex interaction of humans, bacteria, phage and environmental factors. The assumption that bacteria grow exponentially in absence of phage and human shedding may not be the most accurate as well as the lack of a human shedding term into the phage compartment. More over the process of bacteria entering a viable but not culturable state (VBNC) as discussed in the introduction was ignored and all bacteria were treated the same. To remedy these simplifications a more realistic (read more complicated) model is proposed.

In this model, bacteria are "born" into the culturable bacteria compartment where they grow logistically in absence of shedding and in absence of transition between bacteria compartments. Bacteria move to a non-culturable state at a rate τ and non-culturable bacteria move back to a culturable state at rate σ. Phage "attack" culturable bacteria at a rate of b and non-culturable bacteria at a rate d. The phage have a gain of χ from the culturable bacteria and a gain of ω from non-culturable bacteria. Humans shed phage into the environment at a rate of ζ. Moreover, bacteria only experience natural death from the non-culturable compartment at a rate of δ.

With these additional assumptions in mind the proposed model is given by

$$
\begin{cases}
\dot{S} & = \Lambda + \gamma R - \alpha f(B_C + B_{NC})S - \mu S \\
\dot{I} & = \alpha f(B_C + B_{NC})S - (r + \mu)I \\
\dot{R} & = rI - \gamma R - \mu R \\
\dot{B}_C & = \nu B_C(1 - \frac{B_C}{K}) + \eta I + \sigma B_{NC} - \tau B_C - bB_C P \\
\dot{B}_{NC} & = \tau B_C - \sigma B_{NC} - \delta B_{NC} - dB_{NC} P \\
\dot{P} & = \chi bB_C P + \zeta I + \omega dB_{NC} P - mP.
\end{cases}
$$

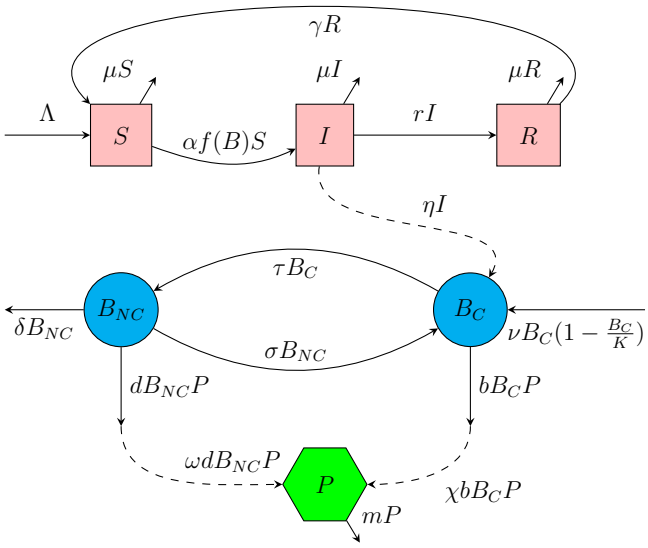

Figure 6.1: Flow diagram for proposed future model

A rigorous mathematical analysis on the proposed future model would provide further insight into the dynamics of cholera as influenced by the interaction between vibrios and phage.

APPENDIX

A 1. CALCULATION OF $\det(\bar{C} - tI)$ IN PROOF OF THEOREM 6

$$
\begin{aligned}
\det(\bar{C} - tI) &= \det\left(\begin{bmatrix} -\alpha f(B_*) - \mu - t & 0 & \gamma & -\frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} \\ \alpha f(B_*) & -(r+\mu) - t & 0\frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} & \\ 0 & r & -(\gamma+\mu) - t & 0 \\ 0 & \eta & 0 & \nu - \delta - t \end{bmatrix} \right) \\
&= \det\left(\begin{bmatrix} -\mu - t & -(r+\mu) - t & \gamma & 0 \\ \alpha f(B_*) & -(r+\mu) - t & 0 & \frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} \\ 0 & r & -(\gamma+\mu) - t & 0 \\ 0 & \eta & 0 & \nu - \delta - t \end{bmatrix} \right) \\
&= (-\mu - t)\det\left(\begin{bmatrix} -(r+\mu) - t & 0 & \frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} \\ r & -(\gamma+\mu) - t & 0 \\ \eta & 0 & \nu - \delta - t \end{bmatrix} \right) \\
&\quad - \alpha f(B_*)\det\left(\begin{bmatrix} -(r+\mu) - t & \gamma & 0 \\ r & -(\gamma+\mu) - t & 0 \\ \eta & 0 & \nu - \delta - t \end{bmatrix} \right) \\
&= (-\mu - t)(-(\gamma+\mu) - t)\det\left(\begin{bmatrix} -(r+\mu) - t & \frac{H(r+\mu)(\delta-\nu)}{\eta(H+B_*)} \\ \eta & \nu - \delta - t \end{bmatrix} \right) \\
&\quad - \alpha f(B_*)(\nu - \delta - t)\det\left(\begin{bmatrix} -(r+\mu) - t & \gamma \\ r & -(\gamma+\mu) - t \end{bmatrix} \right)
\end{aligned}
$$

$$
\begin{aligned}
&= (\mu+\mu)(\gamma+\mu+t)\big[(r+\mu+t)(t+\delta-\nu) - \frac{H(r+\mu)(\delta-\nu)}{H+B_*}\big] \\
&\quad + \alpha f(B_*)(t+\delta-\nu)\big[(r+\mu+t)(\gamma+\mu+t) - \gamma r\big] \\
&= (\mu+t)\big[\big((\gamma+\mu)(r+\mu) + (\gamma+\mu)t + (r+\mu)t + t^2\big)(t+\delta-\nu) \\
&\quad - \frac{H(r+\mu)(\delta-\nu)(\gamma+\mu)}{H+B_*} - \frac{H(r+\mu)(\delta-\nu)}{h+B_*}t\big] \\
&\quad + \alpha f(B_*)(t+\delta-\nu)\big((\mu+t)\gamma + (\mu+t)^2 + r(\mu+t)\big) \\
&= (\mu+t)\big[t^3 + \big(r+2\mu+\gamma+\delta-\nu+\alpha f(B_*)\big)t^2 \\
&\quad + \big(\alpha f(B_*)(\gamma+r+\mu+\delta-\nu) + (\gamma+\mu)(r+\mu) \\
&\quad + (r+2\mu+\gamma)(\delta-\nu) - \frac{H(r+\mu)(\delta-\nu)}{H+B_*}\big)t \\
&\quad + (\gamma+\mu)(r+\mu)(\delta-\nu) + \alpha f(B_*)(\gamma+r+\mu)(\delta-\nu) \\
&\quad - \frac{H(r+\mu)(\delta-\nu)(\gamma+\mu)}{h+B_*}\big]
\end{aligned}
$$

A 2. EIGENVALUES OF BLOCK UPPER-TRIANGULAR MATRICES

Consider an $n \times n$ square matrix of the form

$$M = \begin{bmatrix} A & * \\ 0 & B \end{bmatrix}$$

where A is an $m \times m$ square matrix and B is an $(n-m) \times (n-m)$ square matrix. Suppose ϕ is an eigenvalue of A with corresponding eigenvector v, and θ is an eigenvalue of B with corresponding eigenvector u. Now,

$$\begin{bmatrix} A & * \\ 0 & B \end{bmatrix} \begin{bmatrix} v \\ 0 \end{bmatrix} = \begin{bmatrix} Av \\ 0 \end{bmatrix} = \begin{bmatrix} \phi v \\ 0 \end{bmatrix} = \phi \begin{bmatrix} v \\ 0 \end{bmatrix}$$

So, ϕ is an eigenvalue of M. Recalling that M^T and M have the same eigenvalues, we have

$$\begin{bmatrix} A & 0 \\ * & B \end{bmatrix} \begin{bmatrix} 0 \\ u \end{bmatrix} = \begin{bmatrix} 0 \\ Bu \end{bmatrix} = \begin{bmatrix} 0 \\ \theta u \end{bmatrix} = \theta \begin{bmatrix} 0 \\ u \end{bmatrix}$$

and so θ is an eigenvalue of M^T. Since M^T and M have the same eigenvalues, θ is an eigenvalue of M. Now noting that $|\lambda(M)| = n = m + n - m = |\lambda(A)| + |\lambda(B)|$, we deduce that $\lambda(M) = \lambda(A) \cup \lambda(B)$.

REFERENCES

[1] P.A. Blake. Historical perspectives on pandemic cholera, p. 293-296. In I. K. Wachsmuth, P. A. Blake, and Ø. Olsvik (Eds.), *Vibrio cholerae* and cholera. Molecular to global perspectives. American Society for Microbiology, Washington, DC, 1994.

[2] C.T. Codeço. Endemic and epidemic dynamics of cholera: The role of the aquatic reservoir. BMC Infectious Diseases 1 (2001) 1.

[3] O. Diekmann, J.A. Heesterbeek, M.G. Roberts. The construction of next-generation matrices for compartmental epidemic models. Journal of the Royal Society Interface 7 (2010) 873–85.

[4] R.M. Donlan. Biofilms: Microbial Life on Surfaces. Emerging Infectious Diseases 8 (2002) 881–890.

[5] R.A. Finkelstein. Cholera,*Vibrio cholerae* O1 and O139 and other pathogenic vibrios. In: S. Baron (Ed.), Medical Microbiology, 4th edition, University of Texas, Galveston, TX, 1996, Ch. 24.

[6] K. Kierek, P.I. Watnick. Environmental determinants of *Vibrio cholerae* biofilm development. Applied and Environmental Microbiology 69 (2003) 5079–5088.

[7] J. P. LaSalle, The Stability of Dynamical Systems, Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, PA, 1976.

[8] L. Li, N. Mendis, H. Trigui, J.D. Oliver, S.P. Faucher. The importance of the viable but non-culturable state in human bacterial pathogens. Frontiers in Microbiology 5 (2014) 258.

[9] J.D. Murray. Mathematical Biology I: An Introduction, vol 17. Interdisciplinary applied mathematics, 3rd edition. Springer, NY, 2002.

[10] T. Ramamurthy, A. Ghosh, G.P. Pazhani, S. Shinoda. Current perspectives on viable but non-culturable (VBNC) pathogenic bacteria. Frontiers in Public Health 2 (2014) 103.

[11] Z. Shuai, J.A.P. Heesterbeek, P. van den Driessche. Extending the type reproduction number to infectious disease control targeting contacts between types. Journal of Mathematical Biology 67 (2013) 1067-1082.

[12] A.J. Silva, J.A. Benitez. *Vibrio cholerae* biofilms and cholera pathogenesis. PLoS Neglected Tropical Diseases 10 (2016) e0004330.

[13] A. Solís-Sánchez, U. Hernndez-Chias, A. Navarro-Ocaa, L.M. De, J. Xicohtencatl-Cortes, C. Eslava-Campos. Genetic characterization of ØVC8 lytic phage for *Vibrio cholerae* O1. Virology Journal 13 (2016) 47.

[14] J.K. Teschler, D. Zamorano-Sánchez, A.S. Utada , C.J. Warner , G.C. Wong, R.G. Linington, F.H. Yildiz. Living in the matrix: assembly and control of *Vibrio cholerae* biofilms. Nature Reviews Microbiology 13 (2015) 255–268.

[15] P. van den Driessche, J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical Biosciences 180 (2002) 29–48.

[16] WHO. Weekly epidemiological record. Number 38 (2016) 433–440.

[17] WHO (2019). Cholera, fact sheet. https://www.who.int/en/news-room/fact-sheets/detail/cholera retrieved on July 12, 2019.