A CHOLERA MODEL LINKING BETWEEN-HOST, WITHIN-HOST, AND ENVIRONMENTAL DISEASE DYNAMICS

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ABSTRACT

Cholera is an acute intestinal illness caused by infection with the *Vibrio cholerae* bacteria. The dynamics of the disease transmission are governed by human-human, environment-human, and within-human sub-dynamics. A model is presented to incorporate all three of these dynamical components. The model is divided into three subgroups where the dynamics are analyzed according to their respective time scales. Specifically, the within host system incorporates the interaction of virus and immune cell interaction with the vibrios. For each subgroup, the existence and uniqueness of a DFE (Disease Free Equilibrium) is discussed in light of the number R_0, when applicable, as well as the existence and uniqueness of a positive EE (Endemic Equilibrium). The conditions needed to achieve local and global stability in each system are reviewed. Finally, the three smaller models are combined to discuss the existence and uniqueness of a DFE and EE for the full system.

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LIST OF ABBREVIATIONS

DFE, Disease Free Equilibrium

EE, Endemic Equilibrium

LIST OF SYMBOLS

B, concentration of bacteria in contaminated water

β_H, human to human disease transmission rate

β_L, envirionment to human disease transmission rate

c_1, generation rate of human vibrios

c_2, generation rate of human viruses

d_1, killing rate of human vibrios

d_2, killing rate of human viruses

δ, natural death rate of bacteria

e_1, immune stimulation rate from human vibrios

e_2, immune stimulation rate from human viruses

γ, rate of recovery from disease

I, average number of infected individuals

M, concentration of host immune cells

μ, rate of death from disease

p, host immune cell removal rate

R, average number of recovered individuals

S, average number of susceptible individuals

τ, removal rate of human viruses

V, concentration of human viruses

$\xi(Z)$, removal rate of human vibrios

Z, concentration of human vibrios

CHAPTER 1

INTRODUCTION

The mathematical modeling of the disease cholera is significant both for its biological relevance and its unique behavior. The symptoms of cholera can be mild to severe, and it can often result in death if left untreated. This is why it is imperative to understand the behavior of the disease and its behavior. Cholera is an intestinal illness that causes severe acute diarrhea, and is caused by infection with the *Vibrio cholerae* bacteria. This bacteria is most often found in water or food sources that have been contaminated by shedding of the bacteria by infected persons. Infection with the disease results from the ingestion of the bacteria from these sources [1]. Because the bacteria exists both in the environment and within infected hosts, there are multiple pathways to consider when developing a mathematical model.

A recent model by Xueying Wang and Jin Wang [2] takes both within-host and between-host interactions into account. They employ a fast-slow analysis to account for the different time scales of the respective interactions. This paper furthers ideas presented in [2] by expanding the within-host dynamical system from one to three compartments in order to gain some new insight into the disease. In addition, we analyze the system first in three separate smaller systems, each of which acts on a very different time scale. We then couple the three smaller systems together into one final system. The first system we analyze represents the evolution of the vibrios within the environment. This is a one dimensional system provinding a link between the between-host and within-host dynamics, and happens at a very slow time scale. The second system, which happens at a medium time scale, consists of three equations and is a standard SIR model depicting the between-host dynamics of the disease. The third and final system happens at a very fast time scale, and represents the within-host dynamics of the vibrios. This fast-scale system consists of three equations. Thus, the final system is a seven-dimensional system. The remainder of the paper is organized as follows. In Chapter 2, we discuss the model and its

various components. In Chapter 3, we analyze the slow-scale system. In Chapter 4, we analyze the intermediate-scale system. In Chapter 5, we analyze the fast-scale system. In Chapter 6, we analyze the combined slow and intermediate-scale system. In Chapter 7, we analyze the full system. Each chapter follows the same general framework of verifying the existence and possibly uniqueness of a disease free equilibrium (DFE) solution, verifying the existence of a positive Endemic Equilibrium (EE) solution, and analyzing the stability of each. We also derive the basic reproduction number of the system using the next-generation technique where applicable.

CHAPTER 2

MODEL DESCRIPTION

As described in the introduction, our system is naturally subdivided into three smaller systems by the very different time scales at which they occur. The basic framework of the system, however, is a basic SIR model:

$$\begin{aligned}\frac{dS}{dt} &= \mu N - \beta_H SI - \beta_L SB - \mu S \\ \frac{dI}{dt} &= \beta_H SI + \beta_L SB - (\gamma + \mu)I \\ \frac{dR}{dt} &= \gamma I - \mu R.\end{aligned} \tag{2.1}$$

where S, I, and R represent the number of susceptible, infected, and recovered individuals, respectively. B represents the concentration of the bacteria *Vibrio cholerae* in the contaminated water supply. The system governing the within-host dynamics happens on a much faster time scale, while the system governing the environmental evolution of the vibrios happens on a much slower time scale.

The within-host dynamics for an average infected individual are described by

$$\begin{aligned}\frac{dZ}{dt} &= c_1 BV - d_1 MZ - \zeta Z, \\ \frac{dV}{dt} &= c_2 BV - d_2 MV - \tau V, \\ \frac{dM}{dt} &= e_1 MZ + e_2 MV - pM.\end{aligned} \tag{2.2}$$

where Z, V, and M represent the concentrations of human vibrios, viruses, and host immune cells, respectively. System 2.2 will be referred to as the fast-scale system.

The dynamics of the environmental evolution of the vibrios is goverened by the equation

$$\frac{dB}{dt} = \xi(Z)I - \delta B. \tag{2.3}$$

where $\xi(Z)$ is the host shedding rate that depends on the human vibrios. Equation 2.3 will be referred to as the slow-scale system. Due to the three different time scales in our model, the variable B will be treated as constant in the intermediate-scale and fast-scale system. Similarly, the variables Z and I will be considered at their steady states in the slow-scale system. For a full list of all parameter definitions, see the list of symbols on (p.vii).

CHAPTER 3

SLOW-SCALE SYSTEM DYNAMICS

The environmental evolution of the vibrios is governed by the equation

$$\frac{dB}{dt} = \xi(Z)I - \delta B. \tag{3.1}$$

Due to the slow time scale, we consider Z and I at their steady-states, or effectively as constant. By solving $(dB)/(dt) = 0$ for B, it is clear that the unique equilibrium solution is given by $B = \frac{\xi(Z)I}{\delta}$. We can also easily check the stability of this solution by solving for $B(t)$. By direct calculation, we can see that

$$B(t) = \frac{\xi(Z)I - \xi(Z)Ie^{-\delta t}}{\delta} + B(0)e^{-\delta t}. \tag{3.2}$$

Clearly, $B(t) \to \frac{\xi(Z)I}{\delta}$ as $t \to \infty$ regardless of the value of $B(0)$. This implies that the solution is globally asymptotically stable. It is worth noting that the ultimate value of the equilibrium of 2.3 is dependent on the value of Z. This should not come as a surprise, as B is the concentration of vibrios in the environment, and $\xi(Z)$ is the host shedding rate into the environment.

CHAPTER 4

INTERMEDIATE-SCALE SYSTEM DYNAMICS

The between-host dynamics are governed by the equations

$$\begin{aligned}\frac{dS}{dt} &= \mu N - \beta_H SI - \beta_L SB - \mu S \\ \frac{dI}{dt} &= \beta_H SI + \beta_L SB - (\gamma + \mu)I \\ \frac{dR}{dt} &= \gamma I - \mu R.\end{aligned} \tag{4.1}$$

We consider B as a constant throughout this analysis due to the difference in time scale.

4.1 Disease Free Equilibrium

First, we need to determine the existence and uniquenes of the DFE. Note that in order to achieve an equilibrium solution where $I = 0$, we must also assume that $B = 0$. This will reduce the system to a simplified SIR system. With this assumption, we can easily see that the DFE exists at $(S, I, R) = (N, 0, 0) = \mathbf{X}_0$. Furthermore, this solution is uniquely determined. Our next step is to utilize the next-generation matrix technique developed by van den Driessche and Watmough [3] to compute the basic reproduction number R_0. To do this, we focus specifically on the infection compartment, separating it as follows

$$\frac{dI}{dt} = [S(\beta_H I + \beta_L B)] - [I(\gamma + \mu)] = \mathscr{F} - \mathscr{V}$$

where $\mathscr{F}$ has elements that introduce new infections to the system, while $\mathscr{V}$ has elements that represent transitions from other population sets. The next generation matrix itself is given by FV^{-1} where

$$\begin{aligned}F &= \mathscr{D}\mathscr{F}(\mathbf{X}_0) = \quad [\beta_H N] \\ V &= \mathscr{D}\mathscr{V}(\mathbf{X}_0) = \quad [\gamma + \mu].\end{aligned}$$

From here, it is easy to see that $FV^{-1} = \frac{\beta_H N}{\gamma+\mu}$. Normally, the basic reproduction number is given by the spectral radius of the next-generation matrix. Since our next-generation matrix is only one element, we immediately get

$$R_0 = \frac{\beta_H N}{\gamma+\mu}. \tag{4.2}$$

It has also been shown by van den Driessche and Watmough [3] that the DFE of such a system is locally asymptotically stable when $R_0 < 1$, and is unstable when $R_0 > 1$. It remains to show that the DFE is globally asymptotically stable. To do so, we will follow this result proven by Castillo-Chavez *et al* [4].

Lemma 4.1.1. *Consider a system of the form*

$$\begin{aligned} \tfrac{dX_1}{dt} &= F(X_1, X_2), \\ \tfrac{dX_2}{dt} &= G(X_1, X_2), \quad G(X_1, 0) = 0 \end{aligned}$$

where $X_1 \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $X_2 \in \mathbb{R}^n$ denotes (its components) the number of infected individuals including latent, infectious, etc; $X_0 = (X_1^*, 0)$ denotes the DFE of the system. Also assume the conditions (H1) *and* (H2) *below:*

(H1) *For $dX_1/dt = F(X_1, 0)$, X^* is globally asymptotically stable;*

(H2) *$G(X_1, X_2) = AX_2 - \hat{G}(X_1, X_2), \hat{G}(X_1, X_2) \geq 0$ for $(X_1, X_2) \in \Omega$,*

where the Jacobian $A = (\frac{\partial G}{\partial X_2})(X_1^*, 0)$ is an M-matrix (off-diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense. Then the DFE $X_0 = (X_1^*, 0)$ is globally asymptotically stable when $R_0 < 1$.

With this lemma, we may proceed to the following result.

Theorem 4.1.2. *When $B = 0$, the DFE $X_0 = (N, 0, 0)$ is globally asymptotically stable if $R_0 < 1$.*

Proof. Let $X_1 = (S, R)^T$, $X_2 = I$ and $X_1^* = (N, 0)^T$, and let $B = 0$. Then the uninfected subsystem is given by

$$\frac{d}{dt}\begin{bmatrix} S \\ R \end{bmatrix} = F = \begin{bmatrix} \mu N - \beta_H SI - \mu S \\ \gamma I - \mu R \end{bmatrix}$$

and the infected subsystem by

$$\frac{dI}{dt} = G = \beta_H SI - (\gamma + \mu)I.$$

Note that when $I = 0$, the uninfected subsystem reduces to

$$\frac{d}{dt}\begin{bmatrix} S \\ R \end{bmatrix} = \begin{bmatrix} \mu(N-S) \\ -\mu R \end{bmatrix} \tag{4.3}$$

and the solution is given by

$$\begin{aligned} R(t) =& R(0)e^{-\mu t} \\ S(t) =& N - (N - S(0))e^{-bt}. \end{aligned}$$

We can see that as $t \to \infty$, $R(t) \to 0$ and $S(t) \to N$ independently of $R(0)$ and $S(0)$. Hence, X_1^* is globally asymptotically stable for

$$\frac{dX_1}{dt} = F(X_1, 0).$$

This satisfies condition (H1) in the above lemma. Next, we have

$$\begin{aligned} G =& \frac{\partial G}{\partial X_2}(N,0,0) - \hat{G} \\ =& [\beta_H N - (\gamma + \mu)]I - [\beta_H NI - \beta_H SI]. \end{aligned}$$

As the matrix $A = \frac{\partial G}{\partial X_2}(N,0,0)$ is a single element, it is an M-matrix. Furthermore, since $S \leq N$, we know that $\hat{G} \geq 0$. Thus, condition (H2) of the lemma is satisfied, and therefore the DFE $X_0 = (N,0,0)$ is globally asymptotically stable when $R_0 < 1$. ■

4.2 Endemic Equilibrium

In order to discuss the dynamics of the full intermediate system, we will first remove the assumption that $B = 0$. Recall that, in this case, a DFE cannot exist. Hence, there is no basic reproduction number to consider. With this in mind, we will proceed to determine the

existence and uniqueness of an endemic equilibrium (EE) solution to the system. That is, an equilibrium solution in which the infected compartment I is nonzero.

Theorem 4.2.1. *A unique positive EE solutions exists of the form*

$$X^* = (S^*, I^*, R^*)$$

where

$$\begin{aligned} S^* &= \frac{\mu N}{\beta_H I^* + \beta_L B + \mu} \\ I^* &= \frac{\mu\beta_H N - (\gamma+\mu)(\beta_L B+\mu) + \sqrt{[(\gamma+\mu)(\beta_L B+\mu) - \mu\beta_H N]^2 + 4(\gamma+\mu)\beta_H \mu \beta_L BN}}{2(\gamma+\mu)\beta_H} \\ R^* &= \frac{\gamma}{\mu} I^*. \end{aligned}$$

Proof. Due to the linear relationship between R and I, it is only necessary to consider the two dimensional system with $\frac{dS}{dt}$ and $\frac{dI}{dt}$. Setting both equal to zero and combining the two equations yields the quadratic equation for I

$$(\gamma+\mu)\beta_H I^2 + [(\gamma+\mu)(\beta_L B+\mu) - \mu\beta_H N]I - \mu\beta_L BN = 0$$

or

$$aI^2 + bI + c = 0$$

where

$$\begin{aligned} a &= (\gamma+\mu)\beta_H \\ b &= (\gamma+\mu)(\beta_L B+\mu) - \mu\beta_H N \\ c &= -\mu\beta_L BN. \end{aligned}$$

The two roots of the polynomial are given by the quadratic formula to be

$$\begin{aligned} I_1 &= \frac{-b + \sqrt{b^2 - 4ac}}{2a} \\ I_2 &= \frac{-b - \sqrt{b^2 - 4ac}}{2a}. \end{aligned}$$

Note that I_1 is guaranteed to be positive and real since the term $-4ac > 0$ and $2a > 0$. I_2 is real and negative for the same reason. Thus, I_1 represents the value of I at the endemic equilibrium solution. We can easily substitute this value into the first equation of (2.1) where $\frac{dS}{dt} = 0$ to obtain the value of S at the EE. The resulting solution is given by $(S,I) = (S^*, I^*)$ where

$$\begin{aligned} S^* =& \frac{\mu N}{\beta_H I^* + \beta_L B + \mu} \\ I^* =& \frac{\mu\beta_H N - (\gamma+\mu)(\beta_L B + \mu) + \sqrt{[(\gamma+\mu)(\beta_L B+\mu) - \mu\beta_H N]^2 + 4(\gamma+\mu)\beta_H \mu \beta_L B N}}{2(\gamma+\mu)\beta_H} \end{aligned} \tag{4.4}$$

Furthermore, this solution is uniquely determined, as it is the only solution where $I^* > 0$. ■

4.3 Local and Global Stability of EE

Consider the system

$$\begin{aligned} \frac{dS}{dt} =& \mu N - \beta_H SI - \beta_L SB - \mu S \\ \frac{dI}{dt} =& \beta_H SI + \beta_L SB - (\gamma+\mu)I. \end{aligned} \tag{4.5}$$

In order to achieve local asymptotic stability, it is necessary and sufficient that all eigenvalues of the Jacobian matrix have negative real parts when evaluated at the EE. The Jacobian matrix

$$\begin{bmatrix} -\beta_H I - \beta_L B - \mu & -\beta_H S \\ \beta_H I + \beta_L B & \beta_H S - (\gamma+\mu) \end{bmatrix}$$

when evaluated at $(S,I) = (S^*, I^*)$ leads to the characteristic polynomial $a\lambda^2 + b\lambda + c$ where

$$\begin{aligned} a =& 1 \\ b =& \beta_H I^* + \beta_L B + 2\mu + \gamma - \beta_H S^* \\ c =& (\gamma+\mu)(\beta_H I^* + \beta_L B + \mu) - \beta_H S^* \mu \end{aligned}$$

The Routh-Hurwitz stability criterion [5] guarantees that all roots of the above polynomial have negative real part provided that $a > 0$, $b > 0$, and $c > 0$. Clearly, we have that $a > 0$. Also,

consider (4.5) at the EE:

$$\frac{dI}{dt} = \beta_H S^* I^* + \beta_L S^* B - (\gamma + \mu) I^* = 0$$

Note that $\gamma + \mu > \beta_H S^*$, which immediately gives $b > 0$ and $c > 0$. Therefore, $Re(\lambda_1, \lambda_2) < 0$, and thus the EE is locally asymptotically stable.

Consider again the system described in (4.5) along with the function $g(S,I) = \frac{1}{I}$. We can now observe the modified system

$$\begin{aligned} P_1 g = \frac{dS}{dt} g = &\quad \frac{\mu N}{I} - \beta_H S - \beta_L \frac{SB}{I} - \frac{\mu S}{I} \\ P_2 g = \frac{dI}{dt} g = &\quad \beta_H S + \beta_L \frac{SB}{I} - (\gamma + \mu) \end{aligned} \tag{4.6}$$

Then $\frac{\partial}{\partial S} P_1 g + \frac{\partial}{\partial I} P_2 g < 0$. We have now satisfied Dulac's Criterion for the system, which guarantees global stability given the existence of a locally stable solution. [6]

CHAPTER 5

FAST-SCALE SYSTEM DYNAMICS

The within-host dynamics for an average infected individual are described by

$$\begin{aligned}\frac{dZ}{dt} &= c_1BV - d_1MZ - \zeta Z \\ \frac{dV}{dt} &= c_2BV - d_2MV - \tau V \\ \frac{dM}{dt} &= e_1MZ + e_2MV - pM.\end{aligned} \tag{5.1}$$

5.1 Trivial Equilibrium

The obvious trivial equilibrium solution to this system is given by (Z,V,M) = (0,0,0). To analyze the local stability of this system, we will once again consider the Jacobian matrix

$$J(Z,V,M) = \begin{bmatrix} -d_1M - \zeta & c_1B & -d_1Z \\ 0 & c_2B - d_2M - \tau & -d_2V \\ e_1M & e_2M & e_1Z + e_2V - p \end{bmatrix}$$

which, when evaluated at (Z,V,M) = (0,0,0) becomes

$$J(0,0,0) = J_0 = \begin{bmatrix} -\zeta & c_1B & 0 \\ 0 & c_2B - \tau & 0 \\ 0 & 0 & -p \end{bmatrix}.$$

To find the eigenvalues, note that

$$|J_0 - \lambda I| = \begin{vmatrix} -\zeta - \lambda & c_1B & 0 \\ 0 & c_2B - \tau - \lambda & 0 \\ 0 & 0 & -p - \lambda \end{vmatrix}.$$

The condition needed for local stability is that all eigenvalues have negative real parts. As this is an upper triangular matrix, the eigenvalues are the diagonal entries. Thus, all eigenvalues will have negative real parts if

$$c_2B - \tau < 0. \tag{5.2}$$

5.2 Trivial Equilibrium Boundary Case

We have now determined the behavior of the trivial equilibrium when $c_2B - \tau < 0$. To complete our analysis, we will now consider this solution specifically when $c_2B - \tau = 0$. Setting $B = \frac{\tau}{c_2}$, the original system reduces to the following system:

$$\begin{aligned} \frac{dZ}{dt} &= \frac{c_1\tau}{c_2}V - d_1MZ - \zeta Z \\ \frac{dV}{dt} &= -d_2MV \\ \frac{dM}{dt} &= e_1MZ + e_2MV - pM. \end{aligned} \tag{5.3}$$

To analyze the local stability of this edge case, we first need to decouple the variables. Evaluating the Jacobian matrix at the equilibrium yields the upper triangular matrix

$$J(0,0,0) = \begin{bmatrix} -\zeta & \frac{c_1\tau}{c_2} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -p \end{bmatrix}$$

from which we can see that the eigenvalues are $\lambda_1 = -\zeta, \lambda_2 = 0, \lambda_3 = -p$. The corresponding eigenvector matrix is given by

$$P^{-1} = \begin{bmatrix} 1 & \frac{c_1\tau}{c_2\zeta} & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

the inverse of which, the decoupling matrix, is given by

$$P = \begin{bmatrix} 1 & -\frac{c_1\tau}{c_2\zeta} & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

Our original system 5.3 can be decomposed into it's linear and nonlinear components in the following way:

$$\begin{bmatrix} \frac{dZ}{dt} \\ \frac{dV}{dt} \\ \frac{dM}{dt} \end{bmatrix} = A \begin{bmatrix} Z \\ V \\ M \end{bmatrix} + F$$

where

$$A = \begin{bmatrix} -\zeta & \frac{c_1\tau}{c_2} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -p \end{bmatrix}. \qquad F = \begin{bmatrix} -d_1MZ \\ -d_2MV \\ e_1MZ + e_2MV \end{bmatrix}$$

The decoupled matrix Y is given by $P(Z,V,M)^T$, so that

$$Y = \begin{bmatrix} Z - \frac{c_1\tau}{c_2\zeta}V \\ V \\ M \end{bmatrix} = \begin{bmatrix} y_1 \\ x \\ y_2 \end{bmatrix}.$$

The new system with the decoupled change of variables is given by $\frac{dY}{dt} = JY + PF$. Then

$$\frac{dY}{dt} = \begin{bmatrix} -\zeta y_1 \\ 0 \\ -py_2 \end{bmatrix} + \begin{bmatrix} -d_1y_1y_2 \\ -d_2y_2x \\ y_2(e_1y_1 + [\frac{c_1e_1\tau}{c_2\zeta} + e_2]x) \end{bmatrix}.$$

Simplifying the above expression gives

$$\frac{dY}{dt} = \begin{bmatrix} -y_1(\zeta + d_1 y_2) \\ -d_2 y_2 x \\ y_2(e_1 y_1 + [\frac{c_1 e_1 \tau}{c_2 \zeta} + e_2]x - p) \end{bmatrix}.$$

We can separate the above system into two parts

$$\frac{dx}{dt} = Cx + F(x,y) \qquad \frac{dy}{dt} = Py + G(x,y)$$

where

$$C = 0 \qquad F(x,y) = -d_2 y_2 x$$
$$P = \begin{bmatrix} -\zeta & 0 \\ 0 & -p \end{bmatrix}, \quad G(x,y) = \begin{bmatrix} -d_1 y_1 y_2 \\ y_2(e_1 y_1 + [\frac{c_1 e_1 \tau}{c_2 \zeta} + e_2]x) \end{bmatrix}.$$

We now use a series expansion to redefine y:

$$y = h(x) = \begin{bmatrix} h_1(x) \\ h_2(x) \end{bmatrix} = \begin{bmatrix} a_1 x^2 + ... \\ a_2 x^2 + ... \end{bmatrix}. \tag{5.4}$$

Then $y = h(x)$ defines a local center manifold for the system [7]. By differentiation with the chain rule we know that $Dh(x)[Cx + F(x,h(x))] = Ph(x) + G(x,h(x))$, where

$$\begin{aligned} Dh(x)[Cx + F(x,h(x))] &= \begin{bmatrix} 2a_1 x + ... \\ 2a_2 x + ... \end{bmatrix} [-d_2 x(a_2 x^2 + ...)] \\ Ph(x) + G(x,h(x)) &= \begin{bmatrix} -(a_1 x^2 + ...)(\zeta + d_1(a_2 x^2 + ...)) \\ (a_2 x^2 + ...)[e_1(a_1 x^2 + ...) + [\frac{c_1 e_1 \tau}{c_2 \zeta} + e_2]x - p] \end{bmatrix}. \end{aligned} \tag{5.5}$$

When equating the second rows of the two equations, we get

$$-d_2 x(2a_2 x + ...)(a_2 x^2 + ...) = (a_2 x^2 + ...)[e_1(a_1 x^2 + ...) + \left[\frac{c_1 e_1 \tau}{c_2 \zeta} + e_2\right] x - p].$$

The above equation is only satisfied when $h_2(x) = 0$. This can be seen by noting the constant $-p$ on the right, as there is no possibility of a constant term on the left. If $h_2(x) = 0$, we must also have $h_1(x) = 0$ by (5.5). Thus, we have $h(x) = 0$, and

$$\frac{dx}{dt} = F(x, (h(x)) = 0. \tag{5.6}$$

According to the local center manifold theorem [7], the flow on the center manifold is given by 5.6. Thus, the equilibrium solution is stable in the sense of Lyapunov, but not asymptotically stable.

5.3 Nontrivial Equilibrium (NTE)

Next, we seek the existence of a nontrivial positive equilibrium solution. Note that

$$\begin{aligned} M = \frac{c_2 B - \tau}{d_2} &\implies \frac{dV}{dt} = 0 \\ Z = \frac{c_1 BV}{d_1 M + \zeta} &\implies \frac{dZ}{dt} = 0 \\ p = e_1 Z + e_2 V &\implies \frac{dM}{dt} = 0. \end{aligned} \tag{5.7}$$

Combining these three equations yields the following values for the nontrivial equilibrium:

$$\begin{aligned} Z^* &= \frac{c_1 Bp}{c_1 e_1 B + e_2 (d_1 \frac{c_2 B - \tau}{d_2} + \zeta)} \\ V^* &= \frac{p(d_1 \frac{c_2 B - \tau}{d_2} + \zeta)}{c_1 e_1 B + e_2 (d_1 \frac{c_2 B - \tau}{d_2} + \zeta)} \\ M^* &= \frac{c_2 B - \tau}{d_2}. \end{aligned} \tag{5.8}$$

Letting $\frac{c_2 B - \tau}{d_2} = \alpha$ yields the simplified equations

$$\begin{aligned} Z^* &= \frac{c_1 Bp}{c_1 e_1 B + e_2 (d_1 \alpha + \zeta)} \\ V^* &= \frac{p(d_1 \alpha + \zeta)}{c_1 e_1 B + e_2 (d_1 \alpha + \zeta)} \\ M^* &= \alpha. \end{aligned} \tag{5.9}$$

Note that this equilibrium is positive and unique when $c_2B-\tau>0$, which is true iff $\alpha>0$. We will once again evaluate the jacobian matrix at the NTE in order to analyze its local stability.

Theorem 5.3.1. *The nontrivial equilibrium solution 5.9 of the system 2.2 is locally asymptotically stable iff $d_1>d_2$.*

Proof.

$$|J^*-\lambda I|=\begin{vmatrix} -d_1\alpha-\zeta-\lambda & c_1B & \frac{-d_1c_1Bp}{c_1e_1B+e_2(d_1\alpha+\zeta)} \\ 0 & -\lambda & \frac{-d_2p(d_1\alpha+\zeta)}{c_1e_1B+e_2(d_1\alpha+\zeta)} \\ e_1\alpha & e_2\alpha & -\lambda \end{vmatrix}$$

Evaluating this determinant yields the characteristic polynomial $a\lambda^3+b\lambda^2+c\lambda+d$ where

$$\begin{aligned} a&=-1 \\ b&=-(d_1\alpha+\zeta) \\ c&=-\frac{p\alpha[c_1d_1e_1B+d_2e_2(d_1\alpha+\zeta)]}{c_1e_1B+e_2(d_1\alpha+\zeta)} \\ d&=-d_2p\alpha(d_1\alpha+\zeta) \end{aligned} \tag{5.10}$$

Clearly, we have that $\alpha>0 \implies a,b,c,d<0$. The Routh-Hurwitz stability criterion [5] guarantees local stability when $bc>ad$ in (5.9). This condition is met as long as $d_1>d_2$. To see this, assume $d_1>d_2$. Then

$$\begin{aligned} bc=&p\alpha(d_1\alpha+\zeta)\frac{[c_1d_1e_1B+d_2e_2(d_1\alpha+\zeta)]}{c_1e_1B+e_2(d_1\alpha+\zeta)} \\ >&p\alpha(d_1\alpha+\zeta)\frac{[c_1d_2e_1B+d_2e_2(d_1\alpha+\zeta)]}{c_1e_1B+e_2(d_1\alpha+\zeta)} \\ =&d_2p\alpha(d_1\alpha+\zeta)\frac{[c_1e_1B+e_2(d_1\alpha+\zeta)]}{c_1e_1B+e_2(d_1\alpha+\zeta)} \\ =&d_2p\alpha(d_1\alpha+\zeta) \\ =&ad. \end{aligned}$$

Thus, the NTE is unique iff $c_2B-\tau>0$, and locally asymptotically stable iff $d_1>d_2$. ■

5.4 Nontrivial Equilibrium Boundary Case

The behavior of the system is unclear when $B = \frac{\tau}{c_2}$. Setting $B = \frac{\tau}{c_2}$ yields the following family of nontrivial equilibrium solutions to (5.1):

$$(Z^*, V^*, M^*) = (Z_0, \frac{c_2\zeta}{c_1\tau}Z_0, 0) \tag{5.11}$$

for some initial Z_0. We may shift our solution to the origin with the following change of variables

$$\begin{aligned} \tilde{Z} =& Z_0 - Z \\ \tilde{V} =& \frac{c_2\zeta}{c_1\tau}Z_0 - V \\ \tilde{M} =& M. \end{aligned} \tag{5.12}$$

This gives the equivalent equilibrium solution $(\tilde{Z}, \tilde{V}, \tilde{M}) = (0,0,0)$. We now have an analogous system with an equilibrium solution at the origin and can attempt to utilize the local center manifold theorem [7] once again to determine the stability of the solution. Evaluating the Jacobian matrix of the translated system at the origin yields

$$J(0,0,0) = \begin{bmatrix} -\zeta & a & -d_1Z_0 \\ 0 & 0 & bZ_0 \\ 0 & 0 & cZ_0 - p \end{bmatrix}$$

where $a = \frac{c_1\tau}{c_2}, b = \frac{-d_2c_2\zeta}{c_1\tau}, c = e_1 + \frac{c_2e_2\zeta}{c_1\tau}$, from which we can see that the eigenvalues are $\lambda_1 = -\zeta, \lambda_2 = 0, \lambda_3 = cZ_0 - p$. We can decouple the system with the further change of variables

$$Y = \begin{bmatrix} y_1 \\ y_2 \\ x \end{bmatrix} = \begin{bmatrix} \tilde{Z} - \frac{a}{\zeta}\tilde{V} + \alpha_2\tilde{M} \\ \tilde{M} \\ \tilde{V} + \alpha_1 M \end{bmatrix} \tag{5.13}$$

where $\alpha_1 = \frac{bZ_0}{p-cZ_0}$, and $\alpha_2 = \frac{Z_0(ab-d_1\zeta)}{\zeta(\zeta-p+cZ_0)}$. This change of variables gives rise to the decoupled system

$$\frac{dY}{dt} = \begin{bmatrix} \frac{dy_1}{dt} \\ \frac{dx}{dt} \\ \frac{dy_2}{dt} \end{bmatrix} = \begin{bmatrix} y_2[(e_1-d_1)y_1+\beta_1 y_2+\beta_2 x]-\zeta y_1 \\ y_2[\alpha_1 e_2 y_1+\beta_3 y_2+\beta_4 x] \\ y_2[e_1 y_1+\beta_5 y_2+\beta_6 x+cZ_0-p] \end{bmatrix} \tag{5.14}$$

where

$$\begin{aligned} \beta_1 =& (\alpha_2 - \frac{\alpha_1 a}{\zeta})(e_1-d_1) - \alpha_1(\alpha_2 e_2 - \frac{ad_2}{\zeta}) & \beta_2 =& \frac{a}{\tau}(d_1+d_2+e_1)+\alpha_2 e_2 \\ \beta_3 =& \alpha_1 e_2[\alpha_2 - \frac{\alpha_1 a}{\zeta} - \alpha_1(\alpha_1 e_1 + d_2)] & \beta_4 =& \alpha_1 e_1 + \frac{\alpha_1 e_2 a}{\tau} - d_2 \\ \beta_5 =& e_1\alpha_2 - e_2\alpha_1 - \frac{e_1\alpha_1 a}{\tau}, & \beta_6 =& e_2 + \frac{e_1 a}{\tau}. \end{aligned}$$

Let

$$\begin{aligned} y_1 =& h_1(x) = \quad a_1x^2 + b_1x^3 + ... \\ y_2 =& h_2(x) = \quad a_2x^2 + b_2x^3 + ... \end{aligned}$$

and consider the equation

$$Dh(x)[Cx+F(x,h(x))] = Ph(x)+G(x,h(x)).$$

Then we have

$$\begin{bmatrix} Dh_1(x) \\ Dh_2(x) \end{bmatrix} [h_2(x)(\alpha_1 e_2 h_1(x)+\beta_3 h_2(x)+\beta_4 x)] = \begin{bmatrix} h_2(x)[(e_1-d_1)h_1(x)+\beta_1 h_2(x)+\beta_2 x]-\zeta h_1(x) \\ h_2(x)[e_1 h_1(x)+\beta_5 h_2(x)+\beta_6 x+cZ_0-p] \end{bmatrix} \tag{5.15}$$

where $h_1(x)$ and $h_2(x)$ are of the form $(a_1x^2+b_1x^3+...)$ and $(a_2x^2+b_2x^3+...)$, respectively. By simply comparing the second row of each side of the equation, it can be seen that the smallest degree of x on the left is 4, while the smallest degree of x on the right is 2. This implies that $h_2(x)$ must be zero. Then the first row of each side of the equations implies $h_1(x) = 0$. By the local center manifold theorem [7], the flow of the center manifold defined by $[h_1(x), h_2(x)]^T$ is given by

$$\frac{dx}{dt} = F(x,h(x)) = 0. \tag{5.16}$$

Thus, all NTEs of the form (5.12) are stable in the sense of Lyapunov when $B = \frac{\tau}{c_2}$, but not asymptotically stable.

5.5 Global Stability of Nontrivial Equilibrium Using the Geometric Approach

In order to analyze the global stability of the unique NTE, we will follow the approach of Li and Muldowney outlined in [8]. The following result is the main result of [8]

Theorem 5.5.1. *Let the map $x \mapsto D$ from an open subset $D \subset \mathbb{R}^n$ to $\mathbb{R}^n$ be such that each solution $x(t)$ to the differential equation*

$$x' = f(x) \tag{5.17}$$

is uniquely determined by its initial value $x(0) = x_0$, and denote this solution by $x(t, x_0)$. Assume that

(D1) *D is simply connected;*

(D2) *there is a compact absorbing set $K \subset D$;*

(D3) *$\bar{x}$ is the only equilibrium of 5.17.*

Define

$$\bar{q_2} = \limsup_{t\to\infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t \mu(B(x(s, x_0)))ds,$$

where

$$B = A_f A^{-1} + A \frac{\partial f^{[2]}}{\partial x} A^{-1}$$

and $x \mapsto A$ is a $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function. Then the unique equilibrium $\bar{x}$ is globally stable in D if $\bar{q_2} < 0$.

Utilizing Theorem 5.5.1, we will now follow the approach outlined in [8] to show the conditions under which global stability of the system may be achieved.

Theorem 5.5.2. *Define*

$$k_1 = \frac{c_1 BV}{Z} + d_1 M + \tau - c_2 B - V max\left\{\frac{d_2 V}{Z}, d_1\right\}$$
$$k_2 = p - [e_1 Z + e_2 V + c_1 B + \frac{MZ}{V}(e_1 + e_2)].$$

If $k = min\{k_1, k_2\} > 0$, then the NTE (5.8) is globally stable.

Proof. Consider the Jacobian matrix of the system evaluated at the nontrivial equilibrium

$$J = \begin{bmatrix} -d_1 M - \zeta & c_1 B & -d_1 Z \\ 0 & c_2 B - d_2 M - \tau & -d_2 V \\ e_1 M & e_2 M & e_1 Z + e_2 V - p \end{bmatrix}.$$

The second additive compound matrix of J is given by

$$J^{[2]} = \begin{bmatrix} c_2 B - M(d_1 + d_2) - \zeta - \tau & -d_2 V & d_1 Z \\ e_2 M & -d_1 M + e_1 Z + e_2 V - \zeta - p & c_1 B \\ -e_1 M & 0 & -d_2 M + e_1 Z + e_2 V + c_2 B - \tau - p \end{bmatrix}.$$

Define $P = diag[1, \frac{Z}{V}, \frac{Z}{V}]$. Then

$$\begin{aligned} P_F P^{-1} =& diag\left[0, \quad \frac{Z'}{Z} - \frac{V'}{V}, \quad \frac{Z'}{Z} - \frac{V'}{V}\right] \\ PJ^{[2]}P^{-1} =& \begin{bmatrix} J_{11}^{[2]} & \frac{-d_2 V^2}{Z} & d_1 V \\ \frac{e_2 MZ}{V} & J_{22}^{[2]} & J_{23}^{[2]} \\ -\frac{e_1 MZ}{V} & J_{32}^{[2]} & J_{33}^{[2]} \end{bmatrix} \end{aligned} \tag{5.18}$$

The matrix $Q = P_F P^- 1 + PJ^{[2]}P^{-1}$ can be written in block form in the following way:

$$Q = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix}$$

where

$$
\begin{aligned}
Q_{11} =& c_2B - M(d_1+d_2) - \zeta - \tau \\
Q_{12} =& \begin{bmatrix} \frac{-d_2V^2}{Z} & d_1V \end{bmatrix} \\
Q_{21} =& \begin{bmatrix} \frac{e_2MZ}{V} \\ -\frac{e_1MZ}{V} \end{bmatrix} \\
Q_{22} =& \begin{bmatrix} -d_1M + e_1Z + e_2V - \zeta - p + \frac{Z'}{Z} - \frac{V'}{V} & c_1B \\ 0 & -d_2M + e_1Z + e_2V + c_2B - \tau - p + \frac{Z'}{Z} - \frac{V'}{V} \end{bmatrix}
\end{aligned}
$$

Let m denote the Lozinskii measure with respect to the norm $|(x_1,x_2,x_3)| = max\{|x_1|,|x_2|,|x_3|\}$. Then $m(Q) = sup\{g_1,g_2\}$ with

$$
\begin{aligned}
g_1 =& m_1(Q_{11}) + |Q_{12}| \\
g_2 =& |Q_{21}| + m_1(Q_{22})
\end{aligned}
$$

where $|Q_{12}|$ and $|Q_{21}|$ are the matrix norms induced by the L_1 norm and m_1 denotes the Lozinskii measure with respect to the L_1 norm. We have

$$
\begin{aligned}
m_1(Q_{11}) =& c_2B - M(d_1+d_2) - \zeta - \tau \\
|Q_{12}| =& V max\left\{\frac{d_2V}{Z}, d_1\right\} \\
|Q_{21}| =& \frac{MZ}{V}(e_1+e_2)
\end{aligned}
$$

Also,

$$
\begin{aligned}
m_1(Q_{22}) =& max(a_{11} + |a_{21}|, |a_{12}| + a_{22}) \\
=& e_1Z + e_2V - p + \frac{Z'}{Z} + max\{-d_1M - \zeta - \frac{V'}{V}, c_1B + c_2B - d_2M - \tau - \frac{V'}{V}\} \\
=& e_1Z + e_2V - p + \frac{Z'}{Z} + max\{-d_1M - \zeta - \frac{V'}{V}, c_1B\} \\
=& e_1Z + e_2V - p + \frac{Z'}{Z} + c_1B
\end{aligned}
$$

Combining the above expressions yields

$$g_1 = c_2 B + V max\left\{\frac{d_2 V}{Z}, d_1\right\} - M(d_1 + d_2) - \zeta - \tau$$
$$g_2 = \frac{Z'}{Z} + e_1 Z + e_2 V + c_1 B + \frac{MZ}{V}(e_1 + e_2) - p.$$

Let $k = min\{k_1, k_2\}$ where

$$k_1 = \frac{c_1 BV}{Z} + d_1 M + \tau - c_2 B - V max\left\{\frac{d_2 V}{Z}, d_1\right\}$$
$$k_2 = p - [e_1 Z + e_2 V + c_1 B + \frac{MZ}{V}(e_1 + e_2)].$$

Then we have $m(t) = sup\{g_1, g_2\} \leq \frac{Z'}{Z} - k$. For sufficiently large t, since $Z(t)$ is bounded, we have

$$\frac{ln(Z(t)) - ln(Z(0))}{t} \leq \frac{k}{2}$$

Therefore,

$$\frac{1}{t}\int_0^t m(s)ds \leq \frac{1}{t}\int_0^t \left(\frac{Z'(s)}{Z(s)} - k\right) ds = \frac{ln(Z(t)) - ln(Z(0))}{t} - k \leq -\frac{k}{2}$$

for sufficiently large t. This now implies $\bar{q}_2 \leq -\frac{k}{2} < 0$. According to theorem 5.5.1, it must be that the EE (5.8) is globally stable. ■

CHAPTER 6

SLOW AND INTERMEDIATE COUPLED SYSTEM

We now consider the system consisting of (1.1) and (2.1) together:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta_H SI - \beta_L SB - \mu S \\
\frac{dI}{dt} &= \beta_H SI + \beta_L SB - (\gamma + \mu) I \\
\frac{dR}{dt} &= \gamma I - \mu R. \\
\frac{dB}{dt} &= \xi(Z) I - \delta B.
\end{aligned} \tag{6.1}$$

6.1 Disease Free Equilibrium Analysis

It can be observed that the DFE of this system exists at $(S, I, R, B) = (N, 0, 0, 0)$ We will now proceed with the next generation matrix analysis to compute the basic reproduction number R_0. Consider the components of the system that are directly related to the infection

$$\begin{bmatrix} \frac{dI}{dT} \\ \frac{dB}{dT} \end{bmatrix} = \begin{bmatrix} S(\beta_H I + \beta_L B) \\ 0 \end{bmatrix} - \begin{bmatrix} (\gamma + \mu) I \\ \delta B - \xi(Z) I \end{bmatrix} = \mathscr{F} - \mathscr{V}, \tag{6.2}$$

where compartment $\mathscr{F}$ represents new infections and $\mathscr{V}$ represents transitions from other population sets. The next generation matrix is FV^{-1} where

$$F = \mathscr{D}\mathscr{F}(X_0) = \begin{bmatrix} \beta_H N & \beta_L N \\ 0 & 0 \end{bmatrix}, \qquad V = \mathscr{D}\mathscr{V}(X_0) = \begin{bmatrix} \gamma + \mu & 0 \\ -\xi(Z) & \delta \end{bmatrix} \tag{6.3}$$

where X_0 is the DFE of the system. We have

$$V^{-1} = \frac{-1}{\gamma+\mu}\begin{bmatrix} -1 & 0 \\ \frac{-\xi(Z)}{\delta} & -\frac{\gamma+\mu}{\delta} \end{bmatrix}.$$

Hence, the next generation matrix is given by

$$FV^{-1} = \frac{1}{\gamma+\mu}\begin{bmatrix} N(\frac{\beta_L\xi(Z)}{\delta}+\beta_H) & N\frac{(\gamma+\mu)\beta_L}{\delta} \\ 0 & 0 \end{bmatrix}.$$

The spectral radius $\rho(FV^{-1}) = max_{1\leq i\leq 2}|\lambda_i|$, where λ_i is the ith eigenvalue, can be found to be

$$R_0 = \frac{N}{\gamma+\mu}\left[\beta_H + \frac{\beta_L\xi(Z)}{\delta}\right]. \tag{6.4}$$

Once again, by van den Driessche and Watmough [3], we obtain local asymptotic stability of the DFE when $R_0 < 1$ and instability when $R_0 > 1$.

We now move on to determining the global stability of the DFE. We will follow the same approach used in the analysis of the intermediate-scale system. Using Lemma 4.1, we may establish the following theorem.

Theorem 6.1.1. *When* $R_0 = \frac{N}{\gamma+\mu}\left[\beta_H + \frac{\beta_L\xi(Z)}{\delta}\right] < 1$, *the DFE* $X_0 = (N,0,0,0)$ *is globally asymptotically stable.*

Proof. Assume $R_0 < 1$ Let $X_1 = (S,R)^T$, $X_2 = (I,B)^T$, and $X_1^* = (N,0)^T$. Then the uninfected subsystem is given by

$$\frac{d}{dt}\begin{bmatrix} S \\ R \end{bmatrix} = F = \begin{bmatrix} \mu(N-S) - S(\beta_H I + \beta_L B) \\ \gamma I - \mu R \end{bmatrix} \tag{6.5}$$

and the infected subsystem by

$$\frac{d}{dt}\begin{bmatrix} I \\ B \end{bmatrix} = G = \begin{bmatrix} S(\beta_H I + \beta_L B) - I(\gamma+\mu) \\ \xi(Z)I - \delta B \end{bmatrix}. \tag{6.6}$$

Note that when $X_2 = 0$, the uninfected subsystem reduces to

$$\frac{d}{dt}\begin{bmatrix} S \\ R \end{bmatrix} = \begin{bmatrix} \mu(N-S) \\ -\mu R \end{bmatrix} \tag{6.7}$$

and the solution is given by

$$R(t) = R(0)e^{-\mu t}, \quad S(t) = N - (N - S(0))e^{-bt}.$$

We can see that as $t \to \infty$, $R(t) \to 0$ and $S(t) \to N$ independently of $R(0)$ and $S(0)$. Thus, X_1^* is globally asymptotically stable for

$$\frac{dX_1}{dt} = F(X_1, 0)$$

This satisfies condition (H1) of Lemma 4.1. Next, we have

$$\begin{aligned} G &= \frac{\partial G}{\partial X_2}(N,0,0,0) - \hat{G} \\ &= \begin{bmatrix} \beta_H N - (\gamma+\mu) & \beta_L N \\ \xi(Z) & -\delta \end{bmatrix} \begin{bmatrix} I \\ B \end{bmatrix} - \begin{bmatrix} (N-S)(\beta_H I + \beta_L B) \\ 0 \end{bmatrix} \end{aligned} \tag{6.8}$$

Note that the matrix $A = \frac{\partial G}{\partial X_2}(N,0,0,0)$ has non-negative off-diagonal entries. Also, $\hat{G} \geq 0$ since $N \geq S$. This satisfies condition (H2) of Lemma 4.1. Thus, by Lemma 4.1, the DFE is globally asymptotically stable when $R_0 < 1$. ■

6.2 Endemic Equilibrium Analysis

By setting each of the four equations in (4.1) to zero, we are able to explicitly solve for the unique endemic equilibrium solution:

$$
\begin{aligned}
S^* =& (\gamma+\mu)\left(\beta_H + \frac{\beta_L \xi(Z)}{\delta}\right)^{-1} \\
I^* =& \frac{\mu(N-S^*)}{\gamma+\mu} \\
R^* =& \frac{\gamma(N-S^*)}{\gamma+\mu} \\
B^* =& \frac{\mu\xi(Z)(N-S^*)}{\delta(\gamma+\mu)}
\end{aligned}
\tag{6.9}
$$

Note that we need $R_0 > 1$ in order for $I^* > 0$.

First, we will analyze the local stability of the system. The jacobian matrix evaluated at the EE is given by

$$
\begin{bmatrix}
-\beta_H I^* - \beta_L B^* - \mu & -S*\beta_H & 0 & -S^*\beta_L \\
\beta_H I^* & \beta_H S - \gamma - \mu & 0 & \beta_L S^* \\
0 & \gamma & -\mu & 0 \\
0 & \xi(Z) & 0 & -\delta
\end{bmatrix}
$$

Then the characteristic polynomial is given by

$$
\begin{aligned}
Det(\lambda I - J^*) \quad = \quad & (\lambda+\mu)\big[(\lambda+\mu)(\lambda - S^*\beta_H + \gamma + \mu)(\lambda+\delta) + (\beta_H I^* + \beta_L B^*)(\lambda+\gamma+\mu)(\lambda+\delta) \\
& -(\lambda+\mu)S^*\beta_L\xi(Z)\big]
\end{aligned}
\tag{6.10}
$$

The EE is locally asymptotically stable iff all roots have a negative real part. This is clear for $\lambda = -\mu$. As for the remaining three roots, we can observe the expression in brackets above to be $a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, where

$$
\begin{aligned}
a_0 =& 1 \\
a_1 =& \beta_H I^* + \beta_L B^* + \delta + 2\mu + \gamma - \beta S^* \\
a_2 =& \mu^2 + (\beta_H I^* + \beta_L B^*)\delta + (\beta_H I^* + \beta_L B^*)(\mu+\gamma) + 2\delta\mu + \delta\gamma + \mu\gamma - \delta\beta_H S^* - \beta_L S^*\xi(Z) - \beta_H S^*\mu \\
a_3 =& \delta\mu^2 + \delta\mu(\beta_H I^* + \beta_L B^*) + \delta\gamma((\beta_H I^* + \beta_L B^*) + \delta\gamma\mu - \delta\beta_H S^*\mu - \beta_L S^*\xi(Z)\mu
\end{aligned}
\tag{6.11}
$$

In order for the roots of the above polynomial to have negative real parts, the Routh-Hurwitz stability criterion [5] requires that $a_0 > 0$, $a_1 > 0$, $a_2 > 0$, $a_3 > 0$, and $a_1 a_2 > a_0 a_3$. We will need to make use of the following lemma.

Lemma 6.2.1. *When $R_0 > 1$, S^* satisfies the following:*

$$\mu + \gamma - S^* \beta_H > 0 \quad \text{and} \quad \delta(\gamma + \mu) = \beta_L \xi(Z) S^* + \delta \beta_H S^*.$$

Proof. Let $R_0 > 0$. Then

$$\begin{aligned} \frac{\beta_H}{\beta_H + \frac{\beta_L \xi(Z)}{\delta}} < 1 \quad &\Longrightarrow \quad (\mu + \gamma) \frac{\beta_H}{\beta_H + \frac{\beta_L \xi(Z)}{\delta}} < \mu + \gamma \\ &\Longrightarrow \quad S^* \beta_H < \mu + \gamma \\ &\Longrightarrow \quad \mu + \gamma - S^* \beta_H > 0 \end{aligned}$$

Next, we note that

$$\begin{aligned} \frac{S^*}{\gamma + \mu} \left(\frac{\beta_L \xi(Z)}{\delta} + \beta_H \right) = 1 \quad &\Longrightarrow \quad S^* (\beta_L \xi(Z) + \beta_H \delta) = \delta(\gamma + \mu) \\ &\Longrightarrow \quad \delta(\gamma + \mu) = \beta_L \xi(Z) S^* + \delta \beta_H S^* \end{aligned}$$

■

Theorem 6.2.2. *The polynomial $a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, with a_0, a_1, a_2, and a_3 as defined in (4.10), satisfies the inequalities $a_0 > 0$, $a_1 > 0$, $a_2 > 0$, $a_3 > 0$, and $a_1a_2 > a_0a_3$.*

Proof. Using Lemma 4.1, we can easily show the following inequalities:

$$\begin{aligned} a_1 &= \beta_H I^* + \beta_L B^* + \delta + 2\mu + \gamma - \beta_H S* \\ &= \beta_H I^* + \beta_L B^* + \delta + \mu + (\mu + \gamma - \beta_H S^*) \\ &> 0. \end{aligned}$$

$$\begin{aligned} a_2 &= \mu^2 + (\beta_H I^* + \beta_L B^*)\delta + (\beta_H I^* + \beta_L B^*)(\mu + \gamma) + 2\delta\mu + \delta\gamma + \mu\gamma \\ & ds - \delta\beta_H S^* - \beta_L S^* \xi(Z) - \beta_H S^* \mu \\ &= (\beta_H I^* + \beta_L B^*)(\mu + \gamma + \delta) + \delta\mu + \mu(\mu + \gamma - \beta_H S^*) + \delta(\gamma + \mu) - \beta_L S^* \xi(Z) - \delta\beta_H S^* \\ &> 0. \end{aligned}$$

$$\begin{aligned} a_3 &= \delta\mu^2 + \delta\mu(\beta_H I^* + \beta_L B^*) + \delta\gamma((\beta_H I^* + \beta_L B^*) + \delta\gamma\mu - \delta\beta_H S^*\mu - \beta_L S^* \xi(Z)\mu \\ &= \mu[\delta(\gamma + \mu) - \beta_L S^* \xi(Z) - \delta\beta_H S^*] + \delta(\gamma + \mu)(\beta_H I^* + \beta_L B^*) \\ &= \delta(\gamma + \mu)(\beta_H I^* + \beta_L B^*) \\ &> 0. \end{aligned}$$

$$\begin{aligned} a_1a_1 - a_0a_3 &> \delta a_2 - a_0a_3 \\ &= \delta\mu^2 + \delta(\beta_H I^* + \beta_L B^*)(\mu + \gamma + \delta) + \mu\gamma\delta + \delta\mu(\mu + \gamma - \beta_H S^* + \delta^2\mu \\ &- \delta(\gamma + \mu)(\beta_H I^* + \beta_L B^*) \\ &> \delta(\mu + \gamma + \delta)(\beta_H I^* + \beta_L B^*) - \delta(\gamma + \mu)(\beta_H I^* + \beta_L B^*) \\ &> 0 \end{aligned}$$

■

We now move on to determine the criteria for global stability of the EE. In order to do this, we will employ the geometric approach as before [8].

Theorem 6.2.3. *If $2\beta_H S^* - \gamma \leq 0$, then the unique EE (6.9) is globally stable.*

Proof. First, we let $P = diag[1, \frac{I}{B}, \frac{I}{B}]$. Then

$$\begin{aligned} P^{-1} &= diag\left[1, \frac{B}{I}, \frac{B}{I}\right] \\ P_F &= diag\left[0, \left(\frac{I}{B}\right)', \left(\frac{I}{B}\right)'\right] \\ P_F P^{-1} &= diag\left[0, \frac{I'}{I} - \frac{B'}{B}, \frac{I'}{I} - \frac{B'}{B}\right] \end{aligned} \tag{6.12}$$

The Jacobian matrix of the system is given by

$$J = \begin{bmatrix} -\beta_H I - \beta_L B - \mu & -\beta_H S & \beta_L S \\ \beta_H I + \beta_L B & \beta_H S - \gamma - \mu & \beta_L S \\ 0 & \xi(Z) & -\delta \end{bmatrix}.$$

The second additive compound matrix is then given by

$$J^{[2]} = \begin{bmatrix} \beta_H(S-I) - \beta_L B - (\gamma + 2\mu) & \beta_L S & \beta_L S \\ \xi(Z) & -(\beta_H I + \beta_L B + \mu + \delta) & -\beta_H S \\ 0 & \beta_H I + \beta_L B & \beta_H S - (\gamma + \mu + \delta) \end{bmatrix}$$

and then

$$PJ^{[2]}P^{-1} = \begin{bmatrix} \beta_H(S-I) - \beta_L B - (\gamma + 2\mu) & \beta_L \frac{SB}{I} & \beta_L \frac{SB}{I} \\ \xi(Z)\frac{I}{B} & -(\beta_H I + \beta_L B + \mu + \delta) & -\beta_H S \\ 0 & \beta_H I + \beta_L B & \beta_H S - (\gamma + \mu + \delta) \end{bmatrix}.$$

Thus, we can find the matrix $Q = P_F P^{-1} + PJ^{[2]}P^{-1}$. We can write Q in block form as follows:

$$Q = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix}$$

where

$$Q_{11} = \beta_H(S-I) - \beta_L B - (\gamma+2\mu)$$
$$Q_{12} = \begin{bmatrix} \beta_L \frac{SB}{I} & \beta_L \frac{SB}{I} \end{bmatrix}$$
$$Q_{21} = \begin{bmatrix} \xi(Z)\frac{I}{B} \\ 0 \end{bmatrix}$$
$$Q_{22} = \begin{bmatrix} -(\beta_H I + \beta_L B + \mu + \delta) & -\beta_H S \\ \beta_H I + \beta_L B & \beta_H S - (\gamma+\mu+\delta) \end{bmatrix}$$

We define m as in (3.5). Then $m(Q) = sup\{g_1, g_2\}$ with

$$g_1 = m_1(Q_{11}) + |Q_{12}|$$
$$g_2 = |Q_{21}| + m_1(Q_{22})$$

By direct calculation, we see that

$$\begin{aligned} g_1 &= \beta_H(S-I) - (\beta_L B + \gamma + 2\mu) + \frac{\beta_L SB}{I} \\ g_2 &= \frac{\xi(Z)I}{B} - (\mu+\delta) + \frac{I'}{I} - \frac{B'}{B} + sup\{0, 2\beta_H S - \gamma\} \end{aligned} \tag{6.13}$$

Equivalently,

$$\begin{aligned} g_1 &= \frac{I'}{I} - \beta_H I - \beta_L B - \mu \\ g_2 &= \frac{I'}{I} + sup\{0, 2\beta_H S - \gamma\} - \mu \end{aligned} \tag{6.14}$$

From this, we wee that if $2\beta_H S - \gamma \leq 0$, then $m(t) = sup\{g_1, g_2\} \leq \frac{I'}{I} - \mu$. Now, for sufficiently large t, since $0 \leq I(t) \leq N$, we have

$$\frac{ln(I(t)) - ln(I(0))}{t} \leq \frac{\mu}{2}$$

Therefore,

$$\frac{1}{t}\int_0^t m(s)ds \leq \frac{1}{t}\int_0^t \left(\frac{I'(s)}{I(s)} - \mu\right) ds = \frac{ln(I(t)) - ln(I(0))}{t} - \mu \leq -\frac{\mu}{2}.$$

for sufficiently large t. This now implies $\bar{q}_2 \leq -\frac{\mu}{2} < 0$. According to theorem 5.5.1, it must be that the EE (6.9) is globally stable. ■

CHAPTER 7

FULL SYSTEM ANALYSIS

Now that we have analyzed each of the three separate components of the full system, we will move on to the full system, with all three subsystems coupled together.

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta_H SI - \beta_L SB - \mu S \\
\frac{dI}{dt} &= \beta_H SI + \beta_L SB - (\gamma + \mu) I \\
\frac{dR}{dt} &= \gamma I - \mu R. \\
\frac{dB}{dt} &= \xi(Z) I - \delta B \\
\frac{dZ}{dt} &= c_1 BV - d_1 MZ - \zeta Z, \\
\frac{dV}{dt} &= c_2 BV - d_2 MV - \tau V, \\
\frac{dM}{dt} &= e_1 MZ + e_2 MV - pM.
\end{aligned} \tag{7.1}$$

Note that in this system, some terms that were previously considered as constant are no longer considered constant.

7.1 DFE and Basic Reproduction Number

As in the intermediate scale system, we will first calculate the DFE and basic reproduction number of the system. Before we begin, we assume $\xi(0) > 0$ and $\xi'(Z) \geq 0$. It is clear to see that one possible DFE exists at $(S, I, R, B, Z, V, M)^T = (N, 0, 0, 0, 0, 0, 0)^T = X_0$. With the additional condition that each of the seven variables must be nonnegative, it follows that this DFE is unique. The basic reproduction number of the system can be calculated using the next-generation matrix technique as before. We consider the infection related components of

the system only, separating them into matrices $\mathscr{F}$ and $\mathscr{V}$.

$$\begin{bmatrix} \frac{dI}{dt} \\ \frac{dB}{dt} \\ \frac{dZ}{dt} \\ \frac{dV}{dt} \end{bmatrix} = \begin{bmatrix} S(\beta_H I + \beta_L B) \\ 0 \\ 0 \\ 0 \end{bmatrix} - \begin{bmatrix} (\gamma+\mu)I \\ \delta B - \xi(Z)I \\ (d_1 M + \zeta)Z - c_1 BV \\ (d_2 M + \tau)V - c_2 BV \end{bmatrix} = \mathscr{F} - \mathscr{V}. \tag{7.2}$$

The next generation matrix is given by FV^{-1} where

$$\begin{aligned} F =& \mathscr{D}\mathscr{F}(X_0) = \begin{bmatrix} \beta_H N & \beta_L N & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \\ V =& \mathscr{D}\mathscr{V}(X_0) = \begin{bmatrix} \gamma+\mu & 0 & 0 & 0 \\ -\xi(0) & \delta & 0 & 0 \\ 0 & 0 & \zeta & 0 \\ 0 & 0 & 0 & \tau \end{bmatrix} \end{aligned} \tag{7.3}$$

Then

$$FV^{-1} = \begin{bmatrix} \frac{\beta_H N}{\gamma+\mu} + \frac{\beta_L N \xi(0)}{\delta(\gamma+\mu)} & \frac{\beta_L N}{\delta} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

The basic reproduction number R_0 is the spectral radius of the next generation matrix. Thus, we have $R_0 = \frac{\beta_H N}{\gamma+\mu} + \frac{\beta_L N \xi(0)}{\delta(\gamma+\mu)}$. We know by van den Driessche and Watmough [3] that the DFE is stable whenever $R_0 < 1$, and unstable when $R_0 > 1$.

7.2 Endemic Equilibria

We now seek all possible equilibrium solutions $(S^*, I^*, R^*, B^*, Z^*, V^*, M^*)$ in which the infected population persists. As such, we assume $I^* \neq 0$. It follows immediately that $R^* \neq 0$ and $S^* \neq 0$. We now have multiple cases to consider.

Case 1: Suppose $R_0 > 1$, $\frac{dX}{dt} = 0$, $B^* \neq 0$ and $V^* = 0$. Then $\frac{dZ}{dt} = 0$ implies $Z^* = 0$ and $\frac{dM}{dt} = 0$ implies $M^* = 0$. The remaining four variables are uniquely determined by the remaining equations. Therefore, Case 1 yields the solution

$$\begin{aligned} S^* &= \frac{\delta N}{\delta(R_0 - 1) + 1} \\ I^* &= \frac{\delta\mu(R_0 - 1)}{\delta\beta_H + \beta_L\xi(0)} \\ R^* &= \frac{\delta\gamma(R_0 - 1)}{\delta\beta_H + \beta_L\xi(0)} \\ B^* &= \frac{\mu\xi(0)(R_0 - 1)}{\delta\beta_H + \beta_L\xi(0)} \\ Z^* &= 0 \\ V^* &= 0 \\ M^* &= 0 \end{aligned} \tag{7.4}$$

Note that S^*, I^*, R^*, and B^* are all positive since $R_0 > 1$. This solution can also be reached by changing the initial assumption $V^* = 0$ to $Z^* = 0$. This first case reduces to a system that reflects inactivity within the hosts, while environmental bacteria and the infected population persist.

Case 2: Suppose $R_0 > 1$, $\frac{dX}{dt} = 0$, $B^* \neq 0$, $Z \neq 0$ and $M^* = 0$. It follows that each remaining variable must be nonzero. $\frac{dV}{dt} = 0$ tells us that $B^* = \frac{\tau}{c_2}$. Knowing this value for B^*, we may use the first two equations to solve for S^* and I^*. In doing so, the solution for I^* presents itself in the form of a quadratic equation:

$$I_0^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

where

$$\begin{aligned} a =& c_2\beta_h(\gamma+\mu) \\ b =& (\gamma+\mu)(\beta_L\tau+c_2\mu)-c_2\mu\beta_H N \\ c =& -\mu\tau\beta_L N. \end{aligned}$$

Note that the solution with the positive root is guaranteed to be positive, since $a > 0$ and $c < 0$. Now that we have obtained this value for I^*, the rest of the solution variables may be determined to be as follows:

$$\begin{aligned} S^* =& \frac{c_2\mu N}{c_2(\beta_H I_0^*+\mu)+\beta_L\tau} \\ I^* =& I_0^* \\ R^* =& \frac{\gamma}{\mu} I_0^* \\ B^* =& \frac{\tau}{c_2} \\ Z^* =& \xi^{-1}\left(\frac{\delta\tau}{I_0^* c_2}\right) \\ V^* =& \frac{c_2\zeta}{c_1\tau}\xi^{-1}\left(\frac{\delta\tau}{I_0^* c_2}\right) \\ M^* =& 0 \end{aligned} \tag{7.5}$$

This equilibrium represents a state in which the host immune cells are depleted, but the virus and vibrios persist within the human body.

Finally, we will establish the existence of an entirely positive EE solution. If we assume that each variable must be nonzero, we may solve the system 7.1 to obtain the system

$$
\begin{aligned}
S^* =& \frac{\delta(\gamma+\mu)}{\delta\beta_H+\beta_L\xi(Z^*)} \\
I^* =& \frac{\mu N}{\gamma+\mu} - \frac{\mu\delta}{\delta\beta_H+\beta_L\xi(Z^*)} \\
R^* =& \frac{\gamma N}{\gamma+\mu} - \frac{\gamma\delta}{\delta\beta_H+\beta_L\xi(Z^*)} \\
B^* =& \frac{\mu N\xi(Z^*)}{\delta(\gamma+\mu)} - \frac{\mu\xi(Z^*)}{\delta\beta_H+\beta_L\xi(Z^*)} \\
Z^* =& \frac{c_1pB^*}{c_1e_1B^*+c_1e_2M^*+e_2\zeta} \\
V^* =& \frac{p-e_1Z^*}{e_1} \\
M^* =& \frac{c_2B^*-\tau}{d_2}.
\end{aligned} \tag{7.6}
$$

Note that the existence of a solution depends on Z^*. In particular, we may expand Z^* in the following way:

$$
\begin{aligned}
Z^* =& \frac{c_1pB^*}{c_1e_1B^*+c_1e_2\left[\frac{c_2B^*-\tau}{d_2}\right]+e_2\zeta} \\
=& \frac{c_1pB^*}{B^*\left[c_1e_1+\frac{c_1c_2e_2}{d_2}\right]-\frac{c_1e_2\tau}{d_2}+e_2\zeta} \\
\implies & c_1B^*\left[e_1+\frac{c_2e_2}{d_2}\right]Z^* = c_1pB^*+e_2\left[\frac{c_1\tau}{d_2}-\zeta\right]Z^* \\
\implies & \left[\frac{N}{\delta(\gamma+\mu)}-\frac{1}{\delta\beta_H+\beta_L\xi(Z^*)}\right][(d_2e_1+c_2e_2)Z^*-pd_2] = \frac{e_2d_2}{\mu}\left[\frac{\tau}{d_2}-\frac{\zeta}{c_1}\right]\frac{Z^*}{\xi(Z^*)}.
\end{aligned}
$$

Let

$$
\begin{aligned}
f_1(Z^*) =& \left[\frac{N}{\delta(\gamma+\mu)}-\frac{1}{\delta\beta_H+\beta_L\xi(Z^*)}\right][(d_2e_1+c_2e_2)Z^*-pd_2] \\
f_2(Z^*) =& \frac{e_2d_2}{\mu}\left[\frac{\tau}{d_2}-\frac{\zeta}{c_1}\right]\frac{Z^*}{\xi(Z^*)}.
\end{aligned}
$$

If the two above equations have exactly one intersection point Z_0^*, then this point will determine a unique solution for the system.

Theorem 7.2.1. *Suppose $c_1\tau < d_2\zeta$, $\xi''(Z^*) < 0$ and $R_0 > 1$. Then there exists a unique point $Z_0^* \in \left(0, \frac{pd_2}{d_2e_1+c_2e_2}\right)$ such that $f_1(Z_0^*) = f_2(Z_0^*)$. Furthermore, if*

$$
Z_0^* > \xi^{-1}\left(\frac{-b+\sqrt{b^2-4ac}}{2a}\right).
$$

where

$$a = \frac{c_2\mu\beta_L N}{\delta(\gamma+\mu)}$$
$$b = \frac{c_2\mu\beta_H N}{\gamma+\mu} - \tau\beta_L - c_2\mu$$
$$c = -\tau\delta\beta_H,$$

then Z_0^* generates a unique positive EE solution to 7.1.

Proof. First, note that $R_0 > 1$ implies

$$\left[\frac{N}{\delta(\gamma+\mu)} - \frac{1}{\delta\beta_H + \beta_L\xi(Z^*)}\right] > 0.$$

Then we have $f_1(0) < 0$ and $f_2(0) = 0$. If we let

$$\alpha = \frac{e_2 d_2}{\mu}\left[\frac{\tau}{d_2} - \frac{\zeta}{c_1}\right]$$

the assumption $c_1\tau < d_2\zeta$ gives $\alpha < 0$. Then

$$f_2'(Z^*) = \alpha\frac{\xi(Z^*) - Z^*\xi'(Z^*)}{[\xi(Z^*)]^2} < 0.$$

Since $f_1(Z^*)$ is continuous on the interval $\left(0, \frac{pd_2}{d_2e_1+c_2e_2}\right)$ with a negative left endpoint and a right endpoint equal to zero, the two functions $f_1(Z^*)$ and $f_2(Z^*)$ are guaranteed to have at least one intersection point Z_0^* on the interval. We now proceed to show the uniqueness of this intersection. To do this, we will demonstrate that $f_1(Z^*)$ is concave up for all points on the interval $\left(0, \frac{pd_2}{d_2e_1+c_2e_2}\right)$. The first and second derivative of $f_1(Z^*)$ are given by

$$f_1'(Z^*) = h_2(Z^*)[(d_2e_1 + c_2e_2)Z^* - pd_2] + \left[\frac{N}{\delta(\gamma+\mu)} - \frac{1}{\delta\beta_H + \beta_L\xi(Z^*)}\right](d_2e_1 + c_2e_2)$$
$$f_1''(Z^*) = h_1(Z^*)[(d_2e_1 + c_2e_2)Z^* - pd_2] + 2h_2(Z^*)(d_2e_1 + c_2e_2).$$

where

$$h_1(Z^*) = \frac{\beta_L\xi''(Z^*)(\delta\beta_h + \beta_L\xi(Z^*)) - 2(\beta_L\xi'(Z^*))^2}{(\delta\beta_H + \beta_L\xi(Z^*))^3}$$
$$h_2(Z^*) = \frac{\beta_L\xi'(Z^*)}{(\delta\beta_H + \beta_L\xi(Z^*))^2}$$

With our assumption $\xi''(Z^*) < 0$, it is clear that $h_1(Z^*) < 0$. Thus, since $h_2(Z^*) > 0$, we have $f_1''(Z^*) > 0$ for all $Z^* \in \left(0, \frac{pd_2}{d_2e_1+c_2e_2}\right)$. Since $f_2(Z^*)$ is a linear decreasing function passing through the origin, and $f_1(Z^*)$ is negative and concave up for all $Z^* \in \left(0, \frac{pd_2}{d_2e_1+c_2e_2}\right)$, there exists a unique point $Z_0^* \in \left(0, \frac{pd_2}{d_2e_1+c_2e_2}\right)$ such that $f_1(Z_0^*) = f_2(Z_0^*)$.

Given the existence of such a point Z_0^*, we must also consider how to achieve $X^* > 0$. It is clear that $S^* > 0$ from 7.6 since $\xi(Z^*) \geq 0$. From 7.6, it is clear that $B^* > 0$ if and only if

$$N - \frac{\delta(\gamma+\mu)}{\delta\beta_H + \beta_L\xi(Z^*)} > 0.$$

Since $R_0 = \frac{N(\delta\beta_H+\beta_L\xi(0))}{\delta(\gamma+\mu)} > 1$, we have

$$\begin{aligned} N - \frac{\delta(\gamma+\mu)}{\delta\beta_H+\beta_L\xi(Z^*)} &> N - \frac{N(\delta\beta_H+\beta_L\xi(0))}{\delta(\gamma+\mu)}\frac{\delta(\gamma+\mu)}{\delta\beta_H+\beta_L\xi(Z^*)} \\ &> N - \frac{N(\delta\beta_H+\beta_L\xi(Z^*))}{\delta(\gamma+\mu)}\frac{\delta(\gamma+\mu)}{\delta\beta_H+\beta_L\xi(Z^*)} \\ &= N - N \\ &= 0. \end{aligned} \tag{7.7}$$

Thus, $B^* > 0$. By the same argument, we have that $I^* > 0$ and $R^* > 0$. Moving on, we want to determine if it is possible for $M^* > 0$. First, it will be helpful to solve $M^* = 0$ for $\xi(Z^*)$ where M^* is defined in 7.6. After substituting for B^* from 7.6, we get a quadratic equation in $\xi(Z^*)$ of the form

$$M^* = a\xi^2(Z^*) + b\xi(Z^*) + c \tag{7.8}$$

where

$$\begin{aligned} a &= \frac{c_2\mu\beta_L N}{\delta(\gamma+\mu)} \\ b &= \frac{c_2\mu\beta_H N}{\gamma+\mu} - \tau\beta_L - c_2\mu \\ c &= -\tau\delta\beta_H. \end{aligned} \tag{7.9}$$

So, in order for $M^* > 0$, we need the equation 7.8 to be greater than zero. First, we will attempt to find a positive zero for the equation, as $\xi(Z^*)$ must be positive. The possible zeros are given by

$$\frac{-b \pm \sqrt{b^2 - 4ac}}{2a}.$$

A positive zero of 7.8 is given by

$$\frac{-b+\sqrt{b^2-4ac}}{2a} \tag{7.10}$$

since $a>0$ and $c<0$. Now that we have found a value of $\xi(Z^*)$ that gives $M^*=0$, we can determine the values of $\xi(Z^*)$ that M^* positive. Specifically, note that M^* as a function of $\xi(Z^*)$ is concave up. So M^* is increasing at the zero 7.10, and hence $M^*>0$ whenever

$$\xi(Z^*) > \frac{-b+\sqrt{b^2-4ac}}{2a}$$

or

$$Z^* > \xi^{-1}\left(\frac{-b+\sqrt{b^2-4ac}}{2a}\right).$$

We must also look to 7.6 to see that $V^*>0$ requires $Z^*<\frac{p}{e_1}$. Hence, M^* cannot be positive unless

$$\xi^{-1}\left(\frac{-b+\sqrt{b^2-4ac}}{2a}\right) < \frac{p}{e_1}$$

holds. Since $\frac{pd_2}{d_2e_1+c_2e_2} < \frac{p}{e_1}$ our solution point Z_0^* determines a unique positive EE solution to the system 7.1 only if

$$Z_0^* > \xi^{-1}\left(\frac{-b+\sqrt{b^2-4ac}}{2a}\right).$$

■

7.3 Local Bifurcation Analysis

A first step towards understanding the stability of the EE of the full system is to analyze its behavior near the bifurcation point $R_0=1$. The following result was established in [9].

Lemma 7.3.1. *Consider a general system of ODEs with a real parameter β:*

$$\frac{dx}{dt} = f(x,\beta); \quad f:\mathbb{R}^n\times\mathbb{R}\to\mathbb{R}^n, \quad \textit{and} \quad f\in C^2(\mathbb{R}^n\times\mathbb{R}). \tag{7.11}$$

Assume $x=X_0$ is an equilibrium of system 7.11 for all β. Also assume

(A1) *$A=D_xf(X_0,\beta^*)=\left(\frac{\partial f_i}{\partial x_j}(X_0,\beta^*)\right)$ is the linearization matrix of system 7.11 at the equilibrium $x=X_0$ with β evaluated at β^*. Zero is a simple eigenvalue of A and all*

other eigenvalues of A have negative real parts.

(A2) *Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the kth component of f and,

$$a = \sum_{k,i,j=1}^{4} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(X_0, \beta^*).$$
$$b = \sum_{k,i=1}^{3} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(X_0, \beta^*).$$

The local dynamics of the system 7.11 around $x = X_0$ are totally determined by a and b.

(i) $a > 0,\ b > 0$. *When $\beta - \beta^* < 0$ with $|\beta - \beta^*| \ll 1$, $x = X_0$ is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \beta - \beta^* \ll 1$, $x = X_0$ is unstable and there exists a negative and locally asymptotically stable equilibrium;*

(ii) $a < 0,\ b < 0$. *When $\beta - \beta^* < 0$ with $|\beta - \beta^*| \ll 1$, $x = X_0$ is unstable; when $0 < \beta - \beta^* \ll 1$, $x = X_0$ is locally asymptotically stable, and there exists a positive unstable equilibrium;*

(iii) $a > 0,\ b < 0$. *When $\beta - \beta^* < 0$ with $|\beta - \beta^*| \ll 1$, $x = X_0$ is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \beta - \beta^* \ll 1$, $x = X_0$ is stable, and a positive unstable equilibrium appears;*

(iv) $a < 0,\ b > 0$. *When $\beta - \beta^*$ changes from negative to positive, $x = X_0$ changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

With the use of this result, we will demonstrate that a local forward bifurcation occurs at this point.

Theorem 7.3.2. *When $R_0 - 1$ changes from negative to positive, the DFE X_0 changes its stability from stable to unstable. Furthermore, the EE becomes locally asymptotically stable.*

Proof. First, we will verify condition (A1) of 7.3.1. Setting $R_0 = 1$ and solving for the parameter β_H gives

$$\beta_H^* = \frac{\gamma+\mu}{N} - \frac{\beta_L \xi(0)}{\delta}.$$

The jacobian matrix $A = J(X_0, \beta_H^*)$ is given by

$$A = \begin{bmatrix} -\mu & -\beta_H^* N & 0 & -\beta_L N & 0 & 0 & 0 \\ 0 & \beta_H^* N - \gamma - \mu & 0 & \beta_L N & 0 & 0 & 0 \\ 0 & \gamma & -\mu & 0 & 0 & 0 & 0 \\ 0 & \xi(0) & 0 & -\delta & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\zeta & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\tau & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -p \end{bmatrix}.$$

From columns 1, 5, 6 and 7 it can be seen that four eigenvalues of A are $-\mu$, $-\zeta$, $-\tau$ and $-p$. The remaining three eigenvalues can be determined from the smaller matrix

$$B = \begin{bmatrix} \beta_H^* N - \gamma - \mu & 0 & \beta_L N \\ \gamma & -\mu & 0 \\ \xi(0) & 0 & -\delta \end{bmatrix}.$$

After some simplification, we have

$$det(B - \lambda I) = \lambda(-\mu - \lambda)(\delta + \frac{\beta_L \xi(0)}{\delta} + \lambda).$$

Thus, the remaining three eigenvalues are given by $-\mu$, $-(\delta + \frac{\beta_L \xi(0)}{\delta})$, and 0. The conditions of (A1) are then satisfied.

Consider again the Jacobian matrix A. Denote $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)^T$, a right eigenvector such that

$$\begin{bmatrix} -\mu w_1 - \beta_H^* N w_2 - \beta_L N w_4 \\ (\beta_H^* N - \gamma - \mu) w_2 + \beta_L N w_4 \\ \gamma w_2 - \mu w_3 \\ \xi(0) w_2 - \delta w_4 \\ -\zeta w_5 \\ -\tau w_6 \\ -p w_7 \end{bmatrix} = 0.$$

Setting $w_4 = 1$ and solving the system gives

$$w = \left(\frac{-\delta(\gamma+\mu)}{\mu\xi(0)}, \frac{\delta}{\xi(0)}, \frac{\gamma\delta}{\mu\xi(0)}, 1, 0, 0, 0 \right)^T.$$

Similarly, denote $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)$, a left eigenvector such that

$$\begin{bmatrix} -\mu v_1 \\ -\beta_H^* N v_1 + (\beta_H^* - \gamma - \mu) v_2 + \gamma v_3 + \xi(0) v_4 \\ -\mu v_3 \\ -\beta_L N v_1 + \beta_L N v_2 - \delta v_4 \\ -\zeta v_5 \\ -\tau v_6 \\ -p v_7 \end{bmatrix} = 0.$$

Solving the system along with the addtional condition

$$v_4 \left(\frac{\delta^2 + \beta_L N \xi(0)}{\beta_L N \xi(0)} \right) = 1$$

gives

$$v = \left(0, \frac{\delta\xi(0)}{\delta^2 + \beta_L N \xi(0)}, 0, \frac{\beta_L N \xi(0)}{\delta^2 + \beta_L N \xi(0)}, 0, 0, 0 \right).$$

Now we have $v \cdot w = 1$, $A \cdot w = 0$ and $v \cdot A = 0$. From (A2) in 7.3.1, it follows that

$$a = \frac{-2\delta^3(\gamma+\mu)^2}{\mu N\xi(0)[\delta^2+\beta_L N\xi(0)]} < 0$$
$$b = \frac{\delta^2 N}{\delta^2+\beta_L N\xi(0)} > 0.$$

Thus, based on 7.3.1, we have verified the conditions under which the result of the theorem holds. ■

CHAPTER 8

CONCLUSION

In this paper, a simple SIR model framework is extended to include both environmental and within-host dynamics. Specifically, the within-host dynamical system proposed in [2] is expanded to include the influence of human virus and immune cell interaction with the infectious vibrios. When analyzed in isolation, the slow-scale and intermediate scale systems act predictably. The one-dimensional slow-scale system has a single globally stable equilibrium solution. The three dimensional intermediate-scale system has a unique, globally stable DFE when $R_0 < 1$ and $B = 0$. When $B \neq 0$, however, there is a unique globally stable positive EE solution. It is then determined that the dynamics of the fast-scale system are dependent on the value of $c_2B - \tau$. The dynamics of the smaller of the two combined systems depends mostly on R_0, as expected. We are able to provide sufficient conditions for the existence of a unique positive EE for the fully combined system. Then using a result from [9] we are able to conduct a localized bifurcation analysis of the full system.

Moving forward, there are several unanswered questions that are available for future research. A more complete stability analysis of the equilibrium of the full system is of particular interest. Additionally, numerical simulation using real world data could shed more light onto the likelihood of various assumptions. Overall, this research provided a groundwork for the development of a cholera model that has great potential to shed new light onto the behavior of the disease.

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