A Chemostat Model of Bacteriophage-Bacteria Interaction

with Infinite Distributed Delays

by

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ABSTRACT

Bacteriophage (phage) are viruses that infect bacteria. Typical laboratory experiments show that in a chemostat containing phage and susceptible bacteria species, a mutant bacteria species will evolve. This mutant species is usually resistant to the phage infection and less competitive compared to the susceptible bacteria species. In some experiments, both susceptible and resistant bacteria species, as well as phage, can coexist at an equilibrium for hundreds of hours. The current research is inspired by these observations, and the goal is to establish a mathematical model and explore sufficient and necessary conditions for the coexistence.

In this dissertation a model with infinite distributed delay terms based on some existing work (e.g. [26] and [34]) is established. A rigorous analysis of the well-posedness of this model is provided, and it is proved that the susceptible bacteria persist. To study the persistence of phage species, a "Phage Reproduction Number" (PRN) is defined. The mathematical analysis shows phage persist if $PRN > 1$ and vanish if $PRN < 1$. A sufficient condition and a necessary condition for persistence of resistant bacteria are given. The persistence of the phage is essential for the persistence of resistant bacteria. Also, the resistant bacteria persist if its fitness is the same as the susceptible bacteria and if $PRN > 1$.

A special case of the general model leads to a system of ordinary differential equations, for which numerical simulation results are presented.

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CHAPTER 1

INTRODUCTION

The interaction between the virulent bacteriophages (phages) and bacteria has been an interesting topic in both biological and mathematical fields for decades. The quantitative study of this interaction dates back to 1930's (e.g., see Ellis and Delbrück [13]). Recent work appears in ecology includes [25, 40, 31, 9]. As far as we know, the first two mathematical models were proposed in 1960's (see Campbell [11]) and 1970's (see Levin, Stewart and Chao [26]). Both are in the form of systems consisting of differential equations. Since then, numerous mathematicians and biologists have devoted considerable attention and effort to related studies. Based on different assumptions and methodologies, researchers from various field have developed a series of theories.

In this dissertation we will study a chemostat model of phage-bacteria interaction and mainly focus on the persistence of species. This model is formulated by a system of ordinary differential equations (ODEs) and delay differential equations (DDEs). To make this model more realistic, we introduced terms with infinite distributed delays. As a serious study in the mathematical sense, we analyzed some fundamental properties of this system, and studied the persistence and extinction of bacteria and phages. To better illustrate these results, we also performed numerical simulations on a special case of this model.

1.1 Pioneering Works

Ellis and Delbrück [13] is one of the earliest papers on the interaction between phages and bacteria. Their work answered a number of fundamental questions and led to various succeeding studies. Ellis and Delbrück confirmed that the infection of phages can be divided into 3 stages: adsorption, latent period and ly-

sis. First, a free phage particle attaches itself to a susceptible bacterium and it is called "adsorption". The adsorption is followed by a significant latent period, after which the infected bacterium will lyse and release a number of new phage particles. The total number of new phage particles released per bacterium is called the "burst size". Besides the division of infection stages, Ellis and Delbrück [13] also accomplished:

1. An anti-*E. Coli* phages species is isolated and its behavior was studied.

2. The adsorption rate is proportional to the concentration of phages and to the concentration of (susceptible) bacteria. The rate was measured.

3. Showed the average latent period varies with the temperature while the burst size does not. Neither latent period nor burst size is affected by concentrations of micro-organisms. Both latent period and burst size were measured.

These observations are widely accepted by researchers in succeeding works nowadays. In particular, we would like to emphasize two pioneering mathematical models proposed by Campbell [11] and Levin, Stewart and Chao [26].

The first mathematical model was established by Campbell in 1961, he considered an ODE system consists of one bacteria species and one phage species:

$$
\begin{aligned}
\frac{dB_1}{dt} &= B_1 \left[k_{B_1} \left(1 - \frac{B_1}{L} \right) - \alpha - k_A P \right], \\
\frac{dP}{dt} &= k_A N \left[B_1(t - l) P_1(t - l) \right] - k_A P B_1 - k_I P - \alpha P.
\end{aligned}
\tag{1.1}
$$

He also extended it into a model with one susceptible bacteria species and one resistant bacteria species:

$$\frac{dB_1}{dt} = B_1 \left[k_{B_1} \left(1 - \frac{B_1 + B_2}{L} \right) - \alpha - k_A P \right],$$

$$\frac{dB_2}{dt} = B_2 \left[k_{B_2} \left(1 - \frac{B_1 + B_2}{L} \right) - \alpha \right], \tag{1.2}$$

$$\frac{dP}{dt} = k_A N \left[B_1(t-l) P_1(t-l) \right] - k_A P B_1 - k_I P - \alpha P.$$

In (1.1) and (1.2), B_1 and B_2 are concentrations of susceptible and resistant bacteria species, respectively. P represents the concentration of phages. Parameter α is the flow rate, k_A is the adsorption rate, k_I is the spontaneous inactivation rate of phages. The normal growth of bacteria is logistic with the growth rate k_{B_i} for $i = 1, 2$, and carrying capability L. And the average burst size is N.

Note by assuming bacteria growth is logistic, the nutrient concentration is not explicitly involved in Campbell's model (1.1) and (1.2). The author did not provide any mathematical analysis except for solving steady states. However, (1.1) is adapted and studied extensively by mathematicians and biologists in the following decades. For reference, please see [3, 4, 2, 15, 16, 28].

By solving equilibria for (1.1) and (1.2), Campbell commented in [11, Page 158–159] that

> Now, in the absence of phages, the faster-growing bacterial species will always displace the slower. The only case in which the net effect of the presence of phages is to create a selective disadvantage for its host is when t he two growth rates are exactly equal. When the host for the phages has a selective advantage, even a very slight one, the competitor has no effect on the final density of the host bacterium or on the stability of the steady state. It merely fills up the space which the susceptible species leaves vacant, and, indirectly, reduces the level of phages.

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This comment was concluded only by comparing values of equilibria of (1.1) and (1.2). But it addresses an important question: what role do phages play in the presence of resistant bacteria? As pointed out by Campbell, at a steady state, the faster-growing species always drives the other one to extinction. However, if phages are introduced into the system and its host is the superior bacteria species, the coexistence of both bacteria species may be feasible as an equilibrium.

Another pioneering work on modeling this machinery was accomplished in Levin, Stewart and Chao [26]. In this paper, the authors not only formulated mathematical models, but also performed a series of experiments. The basic device used by the authors is called a "chemostat", it is a laboratory device and is assumed to be an idealization of some nature environments. According to Smith and Waltman [35], an abstract chemostat should have three components: the feed bottle, the culture vessel, and the collection bottle. Some limiting nutrient is pumped from the feed bottle into the culture vessel. All interactions between micro-organisms take place in this vessel. Products of culture vessel are pumped out and collected by the third bottle. In laboratory, the device is generally much more complicated, for more details, please see Section 2.1 and [35].

In [26], Levin, Stewart and Chao proposed a general model that consists of multiple nutrients, susceptible bacteria species and phage species. This model is written as

$$
\begin{aligned}
\dot{r}_j &= \rho(C_j - r_j) - \sum_{i=i}^{I} \phi_{ij}\left(n_i + \sum_{k=1}^{K} m_{ik}\right), \\
\dot{n}_i &= n_i \sum_{j=1}^{J} \frac{\phi_{ij}}{e_{ij}} - \rho n_i - \sum_{k=1}^{K} \gamma_{ik} n_i p_k, \\
\dot{m}_{ik} &= \gamma_{ik} n_i p_k - \rho m_{ik} - e^{-\rho l_{ik}} \gamma_{ik} n_i(t - l_{ik}) p_k(t - l_{ik}), \\
\dot{p}_k &= \sum_{i=1}^{I} b_{ik} e^{-\rho l_{ik}} \gamma ik n_i(t - l_{ik}) p_k(t - l_{ik}) - \rho p_k - \sum_{i=1}^{I} \gamma_{ik} n_i p_k.
\end{aligned}
\tag{1.3}
$$

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In (1.3), r_j's for $1 \leq j \leq J$ are j types of different nutrients, n_i's for $1 \leq i \leq I$ are susceptible bacteria species, each m_{ik} for $1 \leq i \leq I$ and $1 \leq k \leq K$ is the i-th bacteria species infected by the k-th phage species, and p_k's for $1 \leq k \leq K$ are phage species. Constant ρ is the flow rate, each C_j is the concentration of j-th nutrient. The i-th bacteria takes up the j-th resource at a rate ϕ_{ij}. Moreover, e_{ij}'s are yield constants, γ_{ik}'s are adsorption rates, and l_{ik}'s are corresponding latent periods.

By assuming the adsorption rate γ_{ik} is 0, it is easy to see the i-th bacteria species can be considered as "resistant" to the k-th phage species. The main differences between Campbell's model (1.1) – (1.2) and (1.3) is that the limiting nutrient was taken into account in (1.3).

Levin, Stewart and Chao also considered two special cases of (1.3). The first simplification consists of one susceptible bacteria and one phage species:

$$
\begin{aligned}
\dot{r} &= \rho(C - r) - \phi(r)(n + m), \\
\dot{n} &= n\frac{\phi(r)}{e_n} - \rho n - \gamma n p, \\
\dot{m} &= \gamma n p - \rho m - e^{-\rho l}\gamma n(t - l)p(t - l), \\
\dot{p} &= be^{-\rho l}\gamma n(t - l)p(t - l) - \rho p - \gamma n p.
\end{aligned}
\tag{1.4}
$$

In the second case, besides susceptible bacteria and phage species, a resistant bacteria species was introduced into the system:

$$
\begin{aligned}
\dot{r} &= \rho(C - r) - \phi(r)(n_1 + n_2 + m), \\
\dot{n}_1 &= n_1\frac{\phi(r)}{e_1} - \rho n_1 - \gamma n_1 p, \\
\dot{n}_2 &= n_2\frac{\phi(r)}{e_2} - \rho n_1, \\
\dot{m} &= \gamma n_1 p - \rho m - e^{-\rho l}\gamma n_1(t - l)p(t - l), \\
\dot{p} &= be^{-\rho l}\gamma n_1(t - l)p(t - l) - \rho p - \gamma n_1 p.
\end{aligned}
\tag{1.5}
$$

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The authors also examined equilibria of (1.5) and stated the following paragraph in [26, Page 9]:

> Consider a habitat where a population of primary consumers is in equilibrium with a predator. Suppose that a second species of consumer is at a relative disadvantage with respect to resource utilization but is immune to predation. If the second species can survive on the resource level which obtains at the two-species equilibrium, then there is an equilibrium with the predator and both primary consumers present.

Stduies of models and experiments related to[26] include [25, 31, 8, 7, 6, 5, 29, 32, 34]. For more details about models related to [26], please see Section 1.3.

1.2 Motivation and Goal

Though mathematical models in [11] and [26] are different, all authors noticed that for a system consisting of one susceptible bacteria species, one resistant bacteria species and one phage species, the following facts are true at equilibria:

O1. Without the phage species, the bacteria species which is more successful in the competition of resource will survive and the other will go extinct.

O2. With the presence of phages, it is possible for the resistant bacteria to coexist with the phage-sensitive bacteria, even if the phage-sensitive bacteria is the superior competitor.

The first assertion (**O1**) is often referred as "Competitive Exclusion Principle" (CEP). It has been studied extensively in both ecological and mathematical senses. For example, in a chemostat containing more than one micro-organism competing for the same nutrient, the one which consumes the nutrient most efficiently will be the solo survivor and all other species will be eventually washed

out. There are numerous experimental results on CEP under different assumptions and circumstances, e.g., see Hansen and Hubbell [20]. Mathematical results are available in different references too, the following is an incomplete list of literature:

1. If the removal rate of all species are identical and response functions are of the Michaelis-Menten type, see Hsu, Hubbell and Waltman [23];

2. If the removal rate of all species are identical but response functions are general monotone functions, see Armstrong and McGehee [1];

3. If removal rates are different but response functions are of the Michaelis-Menten type, see Hsu [22];

4. If removal rates are different and response functions are of certain types (including monotone and non-monotone types), see Wolkowicz and Lu [41];

5. If removal rates are different and response functions are non-monotone functions, see Li [27].

However, (**O2**) states that (**O1**) may fail if a phage species is introduced into the chemostat and prey on the superior competitor. All authors of [11] and [26] noticed (**O2**) is true at equilibria, even if the susceptible bacteria species fits better. Observation (**O2**) is confirmed by other laboratory experiments too. For instance, Chao, Levin and Stewart [12] performed a series of experiments in a continuous culture (i.e., chemostat) by using *E. Coli* bacteria and phage T7. The authors observed two scenarios. In the first one, a mutant strain of *E. Coli* was discovered, it is resistant to the phage infection and it evolved within a few hundred hours. And after that, a mutant phage species evolved and it preys both the original and mutant *E. Coli* bacteria. In another replicate of the experiment,

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the author noticed the same mutant strain of *E. Coli* evolved and was resistant to both original and mutant phage species. Chao, Levin and Stewart also did a pairwise competition experiment in a phage-free chemostat to compare the fitness of phage-sensitive bacterial strain and phage-resistant (mutant) strains, it turned out that the resistant mutants were inferior competitors relative to the susceptible bacteria. Bohannan and Lenski [9] argued that the resistance is closely related to the fitness of mutant bacteria. They claimed, in general, a bacterium gains the resistance by losing of modifying the receptor molecule, so that a phage particle will not be able to bind itself to the bacterium. However, this receptor is often involved in the bacterial metabolism, thus it can be considered as a trade-off between the resistance and competitive fitness.

Campbell [11] and Levin, Stewart and Chao [26] only studied the dynamics at equilibria, hence it is still not known if (O1)–(O2) is generally true. Bohannan and Lenski [9] stress that the presence of resistant bacteria will not drive susceptible bacteria or phage species to extinction provided the following conditions hold:

L1. The resistant mutant suffers some cost of resistance. To be more precise, the competitive ability for limiting resource is reduced and inferior compared to the sensitive strain.

L2. The mutant's resistance to phages is absolute.

The main purpose of the current research is to study a mathematical model of the phage-bacteria interaction involving a phage-sensitive bacteria species, a virulent phage species, and an absolutely phage-resistant bacteria species which is an inferior competitor for nutrient relative to the phage-sensitive bacteria. We aim to confirm whether the phage-sensitive bacteria and phages are able to persist pro-

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vided (**L1**)–(**L2**) hold. Moreover, we would like to examine whether (**L1**)–(**L2**) are sufficient for the persistence of the resistant bacteria species (For the mathematical definition of persistence, please see Appendix A.3). Therefore, the goal of this research can be summarized as:

1. Establish a mathematical model based on the pioneering work [26] and the recent work [34].

2. Use proper frameworks to study the well-posedness of this model.

3. Investigate whether the criteria for persistence/extinction of the sensitive bacteria developed in [34] is affected by introducing the new resistant bacterial strain. Similarly, verify if the sharp criteria for persistence/extinction of phages in [34] still holds.

4. Explore sufficient or necessary conditions for the persistence of resistant bacteria.

5. Perform numerical simulations based on parameter values suggested by ecological literature.

Besides all goals above, we will also discuss how to apply this new model to more general cases, for details, please see Chapter 6.

1.3   Recent Works and Review

In this section we will briefly review mathematical models related to Levin, Stewart and Chao [26].

In 2008, an ODE analogue (1.4) was studied in Qiu [29]:

$$\frac{dC(t)}{dt} = D(C^0 - C(t)) - \frac{1}{\alpha}B(C(t))S(t),$$

$$\frac{dS(t)}{dt} = -DS(t) + B(C(t))S(t) - \delta S(t)P(t),$$

$$\frac{dL(t)}{dt} = -DL(t) + \delta S(t)P(t) - qL(t), \tag{1.6}$$

$$\frac{dP(t)}{dt} = -DP(t) + \beta qL(t) - \delta S(t)P(t),$$

where $C(t), S(t), L(t), P(t)$ stand for the nutrient, susceptible bacteria, infected bacteria, and phages, respectively. C^0 is the concentration of the nutrient in the input flow, $B(C)$ is the uptake function of susceptible bacteria, α is the yield constant, δ is the adsorption rate, β is average burst size of phages, and $\frac{1}{q}$ can be explained as the time delay between infection and lysis.

The author found there are three possible equilibria, $E^0 = (C^0, 0, 0, 0)$, $E^\partial = (C^\partial, S^\partial, 0, 0)$ and $E^* = (C^*, S^*, L^*, P^*)$. E^0 always exists, it is globally asymptotically stable if $B(C^0) < 0$ and unstable if $B(C^0) > D$. To determine the stability of E^∂, the author defined a "basic reproduction number" R_0, and claimed that E^∂ exists if $B(C^0) > D$, it is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Equilibrium E^* exists if $R_0 > 1$, and it may undergo a Hopf bifurcation. The author also proved the system persists uniformly when $B(C^0) > D$ and $R_0 > 1$.

For DDE model (1.4), partial results were presented in Beretta, Solimano and Tang [7] and Smith [32, Chapter 8]. In [7], the authors worked on the

following model:

$$\frac{dR(t)}{dt} = \mu(C - R(t)) - \alpha(R)rS(t),$$

$$\frac{dS(t)}{dt} = \alpha(R)S(t) - \mu S(t) - \delta S(t)P(t),$$

$$\frac{dI(t)}{dt} = \delta S(t)P(t) - \mu I(t) - e^{-\mu\tau}\delta S(t-\tau)P(t-\tau), \tag{1.7}$$

$$\frac{dP(t)}{dt} = \beta e^{-\mu\tau}\delta S(t-\tau)P(t-\tau) - \mu P(t) - \delta S(t)P(t),$$

where R, S, I, P are concentrations of nutrient, susceptible bacteria, infected bacteria, and phages, respectively. C is the nutrient concentration of the input flow, μ is the flow rate, $\alpha(R)$ is the uptake function of S, r is the yield constant, δ is the adsorption rate and τ is the latent period.

After rescaling (1.7), Beretta, Solimano and Tang showed there are three possible equilibria, $E_1 = (1, 0, 0, 0)$, $E_2 = \overline{R}, 1 - \overline{R}, 0, 0)$ and $E_* = (R_*, S_*, I_*, P_*)$. Existence conditions and local stability of all equilibria are stated in [7]. For the local stability of E_*, the authors claimed it is stable for small delay τ and may become unstable as τ increases, and if τ exceeds another critical value, E_* will become stable again. Beretta, Solimano and Tang [7] also gave a sufficient condition for the persistence of phages P. This sufficient condition was later improved in Smith [32]. And it was proved in [34] that this is also a necessary condition, if one treats (1.7) as a special case of models discussed in [34].

The recent work by Smith and Thieme [34] established two models related to (1.4). The authors gave a rigorous mathematical analysis on these models and obtained some interesting results.

The first model in [34] is a generalization of (1.4), the authors replaced the single discrete delay by an infinite distributed delay:

$$R'(t) = D(R^\diamond - R(t)) - f(R(t))[S(t) + \mu I(t)],$$

$$S'(t) = (f(R(t)) - D)S(t) - kS(t)P(t),$$

$$I'(t) = kS(t)P(t) - DI(t) - \int_0^\infty e^{-D\tau}kS(t-\tau)P(t-\tau)d\nu(\tau), \quad (1.8)$$

$$P'(t) = -DP(t) - k[S(t) + pI(t)]P(t)$$
$$+ \int_0^\infty b(\tau)e^{-D\tau}kS(t-\tau)P(t-\tau).$$

In (1.8), $R(t), S(t), I(t), P(t)$ stand for nutrient, susceptible bacteria, infected bacteria, and phages, respectively. The concentration of the nutrient in the input flow is $R^\diamond$, and $f(R)$ is the uptake function. Parameter k is the adsorption rate, D is the flow rate, and the infected bacteria may consume nutrient at a fraction $\mu \in [0,1]$ of the rate of healthy cells. Similarly, a phage particle may attempt to attach itself to an infected bacteria at the rate kp, where $p \in [0,1]$. Moreover, the authors assumed the fraction of infected bacteria which lyse at time $s \in [0,\tau]$ is given by a cumulative distribution function $\eta(\tau)$, and $\nu(\tau)$ is the probability measure associated to η. And $b(\tau)$ is the average burst size at latent period τ.

The authors introduced a "phage reproduction number", called $\overline{\mathscr{R}}$, and studied the existence of equilibria. It is shown that the (unique) positive coexistence equilibrium exists if and only if $\overline{\mathscr{R}} > 1$.

For (1.8), the authors emphasized that if $\eta(\tau) = H(\tau - \tilde{\tau})$ is the Heaviside function, $b(\tau) = b$ is a constant, and $p = 0$, then (1.8) is reduced to (1.4). Another special case mentioned in [34] is when $\eta(\tau)$ is a Gamma distribution, we will investigate this case in the current research as well, please see Chapter 4 for the details.

Another model studied in [34] is an infection-age model by substituting the followings for differential equations of I and P in (1.8):

$$I(t) = \int_0^\infty u(t,a)da,$$

$$P'(t) = -DP(t) - k[S(t) + pI(t)]P(t) + \int_0^\infty b(a)u(t,a)\frac{-\mathscr{F}'(a)}{\mathscr{F}(a)}da. \quad (1.9)$$

In (1.9), $\mathscr{F}(a)$ is the probability that an infected bacterium has not yet lysed a time units after infection.

$$u(t,a) = \begin{cases} kS(t-a)P(t-a)e^{-Da}\mathscr{F}(a), & t > a \geq 0, \\ u(0,a-t)e^{-Dt}\frac{\mathscr{F}(a)}{\mathscr{F}(a-t)}, & 0 \leq t < a. \end{cases}$$

The authors argued that the differential equations of P in (1.8) and (1.9) agree when

$$u(0,a) = kS(-a)P(-a)e^{-Da}\mathscr{F}(a), \qquad a \geq 0,$$

According to [34], model (1.9) is "more general, more flexible and also more natural from a biological point of view".

The main conclusion of [34] is that for (1.9), the followings hold:

1. Susceptible bacteria S always persists.

2. Phage species P persists if $\overline{\mathscr{R}} > 1$ and goes extinct if $\overline{\mathscr{R}} < 1$.

This seems to be the first known sharp criteria on the persistence and extinction of phages on DDEs derived from (1.4). The main model of the current research will be an elaboration on (1.8).

All models in [29, 7, 32, 34] are considering only one bacteria species in the chemostat. As we are interested in models containing resistant bacteria species, it would be convenient to review the study of Beretta, Sakakibara and Takeuchi on (1.5).

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This study was reported by Beretta, Sakakibara and Takeuchi in two papers [5] and [6], the authors explored the following model (the differential equation of infected bacteria species is omitted in [5]):

$$\dot{r}(t) = \rho(C - r(t)) - \phi_1(n_1(t) + m_1(t)) - \phi_2 n_2(t),$$

$$\dot{n}_1(t) = n_1(t)\frac{\phi_1}{e_1} - \rho n_1(t) - \gamma_1 n_1(t)p(t),$$

$$\dot{n}_2(t) = n_2(t)\frac{\phi_2}{e_2} - \rho n_2(t), \tag{1.10}$$

$$\dot{m}_1(t) = \gamma_1 n_1(t)p(t) - \rho m_1(t) - \gamma_1 e^{-\rho l_1} n_1(t - l_1)p(t - l_1),$$

$$\dot{p}(t) = b_1\gamma_1 e^{-\rho l_1} n_1(t - l_1)p(t - l_1) - \rho p(t) - \gamma_1 n_1 p(t).$$

Here again, r, n_1, n_2, m_1, p represent the nutrient, susceptible bacteria, resistant bacteria, infected bacteria, and phages, respectively. C is the nutrient concentration of the input flow, ϕ_1 and ϕ_2 are uptake functions, e_1 and e_2 are yield constants, ρ is the flow rate, γ_1 is the adsorption rate, b_1 is the average burst size, and l_1 is the latent period between infection and lysis.

The authors showed there are five possible equilibria: $E_0 = (C, 0, 0, 0, 0)$, $E_1 = (\overline{r}_1, \overline{n}_1, 0, 0, 0)$, $E_2(\overline{r}_2, 0, \overline{n}_2, 0, 0)$, $E_3 = (\hat{r}, \hat{n}_1, 0, \hat{m}_1, \hat{p})$, and the last one is $E_4 = (r^*, n_1^*, n_2^*, m_1^*, p^*)$. Existence conditions of equilibria are stated. Instead of introducing phage reproduction number, the authors gave a critical value of delay, called $l_1^*(\overline{r}_1)$ and proved the stability of E_2 is determined by the sign of $l_1 - l_1^*(\overline{r}_1)$. In [5, 6], sufficient conditions for global stability of boundary equilibria E_0 and E_1 are given. And more interestingly, the authors proved E_4 is globally asymptotically stable for $l_1 = 0$ provided E_4 exists. It is also mentioned that the global stability of E_4 may not hold for all $0 < l_1 < l_1^*(r^*)$. The authors performed a numerical simulation to support these arguments. However, no persistence results were discussed in these papers. It appears that [5, 6] are the only known papers analyzing (1.5) from the mathematical point of view.

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The current dissertation is organized as follows: Chapter 2 will focus on the formulation of the main model (2.7), some elementary but fundamental mathematical results are discussed in this chapter. Chapter 3 is the kernel of this research, we will present persistence and extinction results on bacteria and phage species. Chapter 4 and Chapter 5 study a special case of (2.7). All analytical results are represented in Chapter 4 and numerical simulations and comments are summarized in Chapter 5. Chapter 6 will discuss a few ways to generalize this model; some interesting analytical outcomes are stated in the first section of this chapter. And lastly, Chapter 7 summarizes all important conclusions of this research.

CHAPTER 2

THE MODEL WITH INFINITE DISTRIBUTED DELAYS

In this chapter we will model the phage-bacteria interaction by a DDE system involving infinite distributed delay terms.

The formulation of this model is straight-forward. The chemostat model of bacteria competition has been well studied in both mathematical and biological fields. Based on facts observed and confirmed as in [13, 25, 26] and many other papers, we adopt similar assumptions as in [35, 34]. With these assumptions, we can introduce the phage species into the classical phage-free chemostat model. And it leads to a differential equation system consisting of infinite delays.

We will have to justify the well-posedness of this model due to the following reasons:

Firstly, a DDE systems contains infinite distributed delay terms are generally difficult to analyze. In particular, some important mathematical properties such as the existence, uniqueness, and continuation of solutions are not obvious. A careful choice of the state space is crucial and necessary.

Secondly, it is well known that a mathematically valid model may not necessarily lead to a biologically reasonable solution. For example, all variables in our model represent concentration of differential strains, one should expect that a non-negative initial data will lead to a non-negative solution and this solution should be bounded for all future times.

2.1   Formulation of the Model

In a chemostat, the input flow containing nutrient for bacteria is pumped into the vessel continuously, and in the meantime, the output flow carrying utilized resources and micro-organisms (both bacteria and phages) are pumped out.

As mentioned in [26], there are three trophic levels in the chemostat: 1) primary resources, 2) first-order consumers or prey (bacteria), and 3) predators (phages).

Two species of bacteria compete with each other for nutrient. One of them is susceptible (sensitive) to the phages and the other is resistant.

Free phage particles attack susceptible bacteria by attaching themselves to the surface of bacteria, phage inject their genetic material (DNA or RNA) into the bacterial cell and turn it into an infected bacterium. The infection process can be considered as instantaneous.

In an infected bacterium, phage's nucleic acid is reproduced. For example, when virulent phage T4 infects *E. Coli*, the injected DNA transcribes itself into mRNA. After the enzyme synthesis phase, the DNA is replicated. Structural proteins used for the head and the tail are produced when the replication of DNA is done. As soon as all components are ready in the infected bacterium, they are assembled into complete phage. The new phage produces an enzyme to break down the bacteria cell wall and release themselves to the chemostat solution. The infected bacteria cell is destroyed and lyses.

The progress from the infection to the lysis is usually called the lytic cycle of virulent phage. For virulent phage T4, it takes about 30 minutes at 37°C [13].

All these biological facts are summarized as below:

H1. The chemostat consists of three tropic levels: the nutrient (resources R), the prey (susceptible bacteria S and resistant bacteria M) and the predator (phages P).

H2. The input flow containing water and nutrient is supplied continuously at a constant rate. The washout flow carrying nutrient and all microorganisms

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is pumped out at the same rate. The concentration of nutrient in the input flow is a constant.

H3. The input flow mixes with the culture instantaneously. Only susceptible and resistant bacteria consume the nutrient.

H4. The infected bacteria I will lyse and release new phage after a latent period (the length of the lytic cycle). The fraction of infected bacteria which lyse at time $s \in [0, \tau]$ after infection is given by a cumulative distribution function $\eta(\tau)$. And the new phage particles released from a single infected bacterium (average burst size) at an infection age τ is $b(\tau)$.

Now we proceed to the formulation of the model. First we adapt the classical chemostat model as studied in [35] by adding an adsorption term:

$$
R'(t) = \underbrace{-DR(t)}_{\text{dilution}} + \underbrace{DR_0}_{\text{input}} - \underbrace{\gamma_S f_S(R(t))S(t)}_{\text{consumption of } S} - \underbrace{\gamma_M f_M(R(t))M(t)}_{\text{consumption of } M},
$$

$$
S'(t) = \underbrace{-DS(t)}_{\text{dilution}} + \underbrace{f_S(R(t))S(t)}_{\text{growth}} - \underbrace{kS(t)P(t)}_{\text{adsorption}}, \tag{2.1}
$$

$$
M'(t) = \underbrace{-DM(t)}_{\text{dilution}} + \underbrace{f_M(R(t))M(t)}_{\text{growth}}.
$$

Here R is the incoming nutrient carried by the input flow, S represents the phage-sensitive bacteria and M is resistant to phage infection. Thus the only adsorption term appears in the differential equation of S.

In (2.1), γ_S and γ_M are yield constants, R_0 is the nutrient concentration of the input flow, D is the dilution rate, and k is the adsorption rate of phage. Functions f_S and f_M are nutrient uptake functions for microbes S and M, respectively. Both functions should be continuously differentiable, increasing functions vanishing at zero. This is a reasonable assumption, as according to [26, Page 7], "it

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is biologically plausible and experimentally verifiable" that the uptake function is an increasing function which equals 0 at 0 and has a finite limit as $R \to \infty$. The assumption on the continuity and differentiability is merely for the mathematical convenience. We also make the following hypotheses:

F1. $f_i(R_0) > D$, $i = S, M$.

F2. $f_S(R) > f_M(R)$, $0 < R \leq R_0$.

Hypothesis (**F1**) ensures that each bacterium can survive in the chemostat with nutrient concentration R_0 and dilution rate D in the absence of competition and phage. To be more precise, $f_S^{-1}(D)$ and $f_M^{-1}(D)$ are called break-even values of susceptible and resistant bacteria, respectively. This is the minimum nutrient concentration at which a bacteria species can survive in the chemostat with dilution rate D, if there is neither competition for resource nor phage infection. It can be shown that when the input nutrient level is less then the break-even value (or $f_i(R) < D$ for all $R \geq 0$, where $i \in \{S, M\}$), this particular bacteria species will be eventually washed out regardless of its phage-sensitivity. For more details, please see Lemma 6.1.1.

And more importantly, (**F2**) indicates that resistant bacteria is less competitive compared to susceptible bacteria S. In other words, to be resistant to phage infection, the resistant bacteria suffers a cost in the form of a reduced growth rate. This is observed and studied by Bohannan and Lenski in [9], as discussed in Section 1.2.

Besides representing the biological facts, (**F2**) also indicates that susceptible bacteria S are the superior competitor in the chemostat (i.e., the species with least break-even value). In classical chemostat models, such as those in [35, 27, 41], the "competitive exclusion principle" always holds, and thus the superior competitor

will be the solo survivor in the chemostat, all other species which are inferior to the superior competitor will be washed out. Suppose M is the superior competitor, S will be driven to extinction even without phage infection, and the coexistence of S and M is impossible if S is inferior to M. We also studied alternative set-ups on **(F2)** in Section 6.1.

A popular choice of f_S and f_M is Michaelis-Menten type functions given by $f_i(R) = \frac{v_i R}{u_i + R}$ where $u_i, v_i > 0$ for $i = S, M$. According to Bohannan and Lenski [9], it is plausible to assume $u_S < u_M$ or $v_M < v_S$ or both. However, it is not necessary to assume f_S and f_M are Michaelis-Menten type functions in this research except for the simulation part.

To formulate differential equations of infected bacteria I and phage P, we must take lysis into account. It is observed in the laboratory that this latent period varies from a few minutes to hours. Following [34], we describe variation in the latent period by a cumulative probability distribution $\eta(\tau)$. More precisely, for $\tau > 0$ fixed, the probability of an infected bacterium lyses during the time period $[0, \tau]$ following infection is $\eta(\tau)$. Mathematically, let $\eta(\tau) = \nu([0, \tau])$, where ν is a probability measure on $[0, \infty)$ and

$$\int_0^\infty d\nu(\tau) = 1.$$

and assume the probability measure associated to this distribution is ν, namely, $\eta(\tau) = \nu([0, \tau])$.

The adsorption term in (2.1) is $-kS(t)P(t)$, which is the infection at time t. Nevertheless, the new phage will only be released after certain latent period, by considering the dilution, we conclude that the lysis of infected bacteria I at time t is

$$k \int_0^\infty e^{-D\tau} S(t - \tau) P(t - \tau) d\nu(\tau),$$

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and for new born phage, the integrand is multiplied by burst size $b(\tau)$, the average burst size at latent period τ. As observed in [13], $b(\tau)$ is usually more than 50. However, for simplicity, here we assume $b(\tau) < b_0$ for some $b_0 > 1$. The average number of new phage eventually released by an infected bacterium is denoted by B, it is given by the Laplace transform of the measure $b\nu$ evaluated at D, that is,

$$B = \int_0^\infty e^{-D\tau} b(\tau) d\nu(\tau),$$

Consequently, the differential equations of I and P are

$$I'(t) = \underbrace{-DI(t)}_{\text{dilution}} + \underbrace{kS(t)P(t)}_{\text{infection}} - \underbrace{k \int_0^\infty e^{-D\tau} S(t-\tau)P(t-\tau) d\nu(\tau)}_{\text{lysis}},$$

$$P'(t) = \underbrace{-DP(t)}_{\text{dilution}} - \underbrace{kS(t)P(t)}_{\text{infection}} + \underbrace{k \int_0^\infty b(\tau) e^{-D\tau} S(t-\tau)P(t-\tau) d\nu(\tau)}_{\text{lysis}}.$$

(2.2)

We combine (2.1) and (2.2) to obtain the model with infinite distributed delays. Before stating the whole model, we can scale out yield constant γ_S and γ_M by using auxiliary variables and parameter

$$\widetilde{S} = \gamma_S S, \ \widetilde{M} = \gamma_M M, \ \widetilde{I} = \gamma_S I, \ \widetilde{P} = \gamma_S P, \ \widetilde{k} = \frac{k}{\gamma_S}.$$

Thus we may always assume yield constant are 1 and write the model as

$$R'(t) = D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t),$$

$$S'(t) = (f_S(R(t)) - D)S(t) - kS(t)P(t),$$

$$M'(t) = (f_M(R(t)) - D)M(t),$$

(2.3)

$$I'(t) = -DI(t) + kS(t)P(t) - k \int_0^\infty e^{-D\tau} S(t-\tau)P(t-\tau) d\nu(\tau),$$

$$P'(t) = -DP(t) - kS(t)P(t) + k \int_0^\infty b(\tau) e^{-D\tau} S(t-\tau)P(t-\tau) d\nu(\tau).$$

This is the main model of our study. Table 1 summarizes all parameters and variables used in (2.7).

Table 1.Variables and parameters of DDE model (2.7)

R	mg/ml	nutrient concentration in the chemostat
S	cells/ml	susceptible bacteria
M	cells/ml	resistant bacteria
I	cells/ml	infected bacteria
P	particles/ml	phage
R_0	mg/ml	Nutrient concentration of the input flow
D	h^{-1}	dilution rate
k	ml/h	adsorption rate
$b(\tau)$	particles	average burst size at latent period τ

In the special case that the latent period distribution function is Heaviside function $H(\tau - \bar{\tau})$ where $\bar{\tau} > 0$ is a fixed number, (2.3) is reduced to a DDE model with one single discrete delay.

Generally speaking, since (2.3) contains infinite distributed delay terms, its phase space and initial data must be chosen very carefully. The discussion is deferred to the following section.

2.2 Well-posedness and Phase Space of DDE Model

As pointed out by Busenberg and Cooke [10], a mathematical valid initial value may not guarantee a biological reasonable solution. A simple counterexample can be constructed by the following way: let $P(t), S(t) > 0$ for $t < 0$, $I(0) = S(0) = P(0) = 0$, and $\eta(\tau)$ be normal distribution, then

$$I'(0) = -k \int_0^\infty e^{-D\tau} S(-\tau) P(-\tau) d\nu(\tau) < 0,$$

and consequently $I(t) < 0$ for $t > 0$ but small. Since I represents the population of infected bacteria, clearly it should remain non-negative at all the time.

Here we follow the idea in [34] and many other papers, calculate the formal solution of $I(t)$ and obtain

$$I(t) = k \int_0^\infty \left(\int_{t-\tau}^t e^{-D(t-r)} S(r) P(r) dr \right) d\nu(\tau). \tag{2.4}$$

Let $s = t - r$ and interchange the order of integration,

$$I(t) = k \int_0^\infty \mathscr{F}(s) e^{-Ds} S(t-s) P(t-s) ds, \tag{2.5}$$

where

$$\mathscr{F}(s) = \int_s^\infty d\nu(\tau) = 1 - \eta(s).$$

is the sojourn function (see [37]), i.e., the probability that an infected bacterium survives from lysis s time units after infection. In (2.5), $kS(t-s)P(t-s)$ is the infection at time $t-s$, and $\mathscr{F}(s)e^{-Ds}$ is the probability that infected bacteria have not yet lysed or been washed out.

To make sure (2.5) is indeed a solution of (2.3), it must extend to $t = 0$ and consequently

$$I(0) = k \int_0^\infty e^{-Ds} \mathscr{F}(s) S(-s) P(-s) ds. \tag{2.6}$$

Note $I(t)$ is not involved in any differential equation other than itself, and it can be explicitly solved by (2.5) provided the history of S and P are known, thus we can consider a subsystem of (2.3) without I:

$$
\begin{aligned}
R'(t) &= D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t), \\
S'(t) &= (f_S(R(t)) - D)S(t) - kS(t)P(t), \\
M'(t) &= (f_M(R(t)) - D)M(t), \\
P'(t) &= -DP(t) - kS(t)P(t) + k \int_0^\infty b(\tau)e^{-D\tau}S(t-\tau)P(t-\tau)d\nu(\tau).
\end{aligned}
\tag{2.7}
$$

Though sometimes it is convenient to include I in the argument (for example, in the proof Lemma 2.3.4), we will use model (2.7) as the main model of this research hereafter.

Now we turn to phase space and initial data of (2.7). We follow the framework stated in Appendix A.1, first define two subspaces of $C((-\infty, 0], \mathbb{R})$: C^0 and C_γ.

Function space C^0 is the collection of all constant functions on $(-\infty, 0]$. For every function $\varphi \in C^0$, the norm of φ is simply $|\varphi(0)|$. To simplify the notation, we may omit the difference between C^0 and $\mathbb{R}$.

The second subspace C_γ is defined as

$$C_\gamma = \{\varphi \in C((-\infty, 0], \mathbb{R})) : |\lim_{s \to -\infty} e^{\gamma s} \varphi(s)| \text{ exists and is finite}\},$$

where $\gamma > 0$ is a fixed number. Define a norm on C_γ as

$$\|\varphi\|_\gamma = \sup_{-\infty < s \leq 0} e^{\gamma s} |\varphi(s)|$$

for all $\varphi \in C_\gamma$.

Now define $\mathscr{B}_D = C^0 \times C_\gamma \times C^0 \times C_\gamma$, let it be equipped with the maximum norm $\|\cdot\|_D$. Then it is easy to check $\mathscr{B}_D$ satisfies axiom (**B1**) – (**B2**) if $H = 1, K = 1$, $N(s) = e^{-\gamma s}$ and $\mathbb{R}^4$ takes the maximum norm.

Since we are mostly interested in non-negative initial data and solutions, we define the positive cone of $\mathscr{B}_D$ as $\mathscr{B}_D^+$. Each component of an element of $\mathscr{B}_D^+$ is a function in $C((-\infty, 0], \mathbb{R}_+)$, where $\mathbb{R}_+ = [0, \infty)$.

As we will show in Lemma 2.3.3, $\mathscr{B}_D^+$ is forward invariant, thus we take $\mathscr{B}_D^+$ as the phase space hereafter. And the initial data of (2.7) is given by $x = (R(0), S(\cdot), M(0), P(\cdot)) \in \mathscr{B}_D^+$. By omitting the difference between C^0 and $\mathbb{R}$, we can write

$$R(0) \geq 0, \ M(0) \geq 0, \ S \in C_\gamma^+, \ P \in C_\gamma^+,$$

where C_γ^+ is the positive cone of C_γ.

Also, though theoretically $\gamma > 0$ can be arbitrary, to ensure two integrals in (2.7) are convergent, we assume that

$$\gamma < \frac{D}{2}.$$

2.3 Fundamental Properties of Solutions

Since (2.7) involves some infinite delay terms, fundamental properties of its solutions, such as existence, uniqueness, continuation, and continuous dependence on parameters and initial values are not trivial. Here we apply the theory developed by Hale and Kato as stated in Appendix A.1 to (2.7) and obtain these properties.

Since the existence and uniqueness theorem apply to abstract FDE A.1 with admissible phase space $\mathscr{B}$. they apply to (2.7) with $\mathscr{B}_D$ as well. Thus the following theorem is a direct corollary of Theorem A.1.1.

Theorem 2.3.1. *For any $(\sigma, \varphi) \in \mathbb{R} \times \mathscr{B}_D$, there exists a solution of (2.7) through (σ, φ).*

To apply the uniqueness result Theorem A.1.2, we have to verify the vector field of (2.7) is locally Lipschitz. It suffices to verify the integral term in differential equation of P is locally Lipschitz. Suppose $\varphi = (R^\varphi, S^\varphi(\cdot), M^\varphi, P^\varphi(\cdot)) \in \mathscr{B}_D$, and for any $\phi = (R^\phi, S^\phi(\cdot), M^\phi, P^\phi(\cdot)) \in \mathscr{B}_D$ in the δ-neighborhood of φ, we have

$$\left| k \int_0^\infty e^{-D\tau} b(\tau) \left(S^\varphi(t-\tau) P^\varphi(t-\tau) - S^\phi(t-\tau) P^\phi(t-\tau) \right) d\mu(\tau) \right|$$

$$\leq k b_0 \int_0^\infty e^{-D\tau} |S^\varphi(t-\tau)||P^\varphi(t-\tau) - P^\phi(t-\tau)| d\nu(\tau)$$

$$\quad + k b_0 \int_0^\infty e^{-D\tau} |P^\phi(t-\tau)||S^\varphi(t-\tau) - S^\phi(t-\tau)| d\nu(\tau)$$

$$\leq k b_0 \left(\|S^\varphi\|_\gamma \|P^\varphi - P^\phi\|_\gamma + \|P^\phi\|_\gamma \|S^\varphi - S^\phi\|_\gamma \right) \int_0^\infty e^{-(D-2\gamma)\tau} d\mu(\tau)$$

$$\leq \left((2\|\varphi\|_D + \delta) k b_0 \int_0^\infty e^{-(D-2\gamma)\tau} d\mu(\tau) \right) \|\varphi - \phi\|_D.$$

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Note the term in the parentheses is a finite number (because $D > 2\gamma$ as assumed), this integral term is locally Lipschitz and so is the vector field. Thus we can apply Theorem A.1.2 to (2.7).

Theorem 2.3.2. *For any $(\sigma, \varphi) \in \mathbb{R} \times \mathscr{B}_D$, there exists a unique solution of (A.1) through (σ, φ).*

Moreover, Theorem A.1.3 and Theorem A.1.4 apply to (2.7) too. So solutions of (2.7) depends on parameters and initial data continuously. For more details, please see Appendix A.1.

Now we would like to show non-negativity and boundedness of solutions of (2.7). Thereby, we can show the existence of a compact global attractor K_D, which is the maximal compact invariant set $K_D \subset \mathscr{B}_D$ such that k_D attracts all bounded sets in $\mathscr{B}$.

Lemma 2.3.3 (Positivity of solutions). *Suppose x is the locally unique solution of (2.7) with $x_0 = \phi \in \mathscr{B}_D^+$ on $[0, A]$, where A is a positive constant or infinity, then $x(t) \geq 0$ for all $t \in [0, A]$.*

Proof. We consider the R component first. If $R(0) = 0$, then $R'(0) = DR_0 > 0$ and $R(t) > 0$ for $t > 0$ small. If $R(0) > 0$, by the continuity of $R(t)$, $R(t) > 0$ for small t as well. Thus if $R(t) < 0$ for some $t > 0$, there exists a smallest $t_0 > 0$ such that $R(t_0) = 0$ and $R(t) > 0$ on $(0, t_0)$. However, since $R'(t_0) = DR_0 > 0$ and $R(t_0) = 0$, we can find an $\epsilon > 0$ such that $R(t) < 0$ on $(t_0 - \epsilon, t_0)$, which contradicts that fact that $R(t)$ is strictly positive on $(0, t_0)$. Therefore, $R(t) > 0$ for all $t > 0$.

Note $S(t)$ and $M(t)$ are always non-negative because for all $t \geq t_0$,

$$S(t) = S(t_0) \exp\left(\int_{t_0}^{t} f_1(R(s)) - D - kP(s)ds\right), \tag{2.8}$$

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and

$$M(t) = M(t_0) \exp\left(\int_{t_0}^{t} f_2(R(s)) - D \, ds\right). \tag{2.9}$$

In particular, (2.8) and (2.9) hold for $t_0 = 0$. And $\varphi(0) \geq 0$ implies that both $S(0), M(0) \geq 0$, thus $S(t), M(t) \geq 0$ for all $t \geq 0$.

For $P(t)$, consider an auxiliary system $\dot{x}(t) = F(x_t) + \mu e$, where F is the vector field of (2.7) and $e = (0, 0, 0, 0, 1)^T$ is a vector. Let $\widetilde{P}(t)$ be the corresponding component of the solution of this system, by the same argument as in the proof of positivity of $R(t)$, we can prove $\widehat{P}(t) > 0$ for all $t > 0$. Letting $\mu \to 0$ implies $P(t) \geq 0$ for all $t \geq 0$.

The positivity of $I(t)$ is guaranteed by its formal solution (2.4), $I(t) \geq 0$ provided both S and P are non-negative on $(-\infty, t]$. $\qquad\qquad\square$

It is also worth to mention that the formal solution of P can be written as

$$P(t) = \exp\left(-\int_{t_0}^{t} D + kS(s) ds\right)\left(\int_{t_0}^{t} J(s) e^{\int_{t_0}^{s} D + kS(r) dr} ds + P(t_0)\right), \tag{2.10}$$

where $J(s)$ is the integral term in the differential equation of P.

In Lemma 2.3.3, note $x(t) \geq 0$ for all $t \in [0, A]$ is equivalent to $x_t(s) \geq 0$ for any given $t \in [0, A]$ and all $s \in (-\infty, 0]$. Therefore, $\mathscr{B}_D^+$ is forward invariant and can be considered as the phase space.

Lemma 2.3.4 (Boundedness of solutions). *Under the same assumption as in the previous lemma, assume $\phi \geq 0$ on $(-\infty, 0]$, define*

$$L_0 = R(0) + S(0) + M(0) + \frac{P(0)}{b_0} + \frac{k}{D - 2\gamma}\|\phi\|_D^2.$$

Then for all $t \in [0, A]$,

$$\|x_t\|_D \leq L := b_0 \max\{L_0, R_0\} + \|\phi\|_D.$$

And this constant is independent from A.

Proof. The infected bacteria species is not included by $\mathscr{B}_D^+$ or ϕ, but $I(0)$ is given by (2.6), thus we have the following estimate on $I(0)$:

$$I(0) \leq \int_0^\infty e^{-Ds} kS(-s)P(-s)ds \leq k\int_0^\infty e^{-(D-2\gamma)s}\|S\|_\gamma\|P\|_\gamma ds \leq \frac{\alpha}{D-2\gamma}\|\phi\|_D^2,$$

because $\mathscr{B}_D^+$ takes the maximum norm and $D - 2\gamma > 0$.

Let $Y(t) = R(t) + S(t) + M(t) + I(t) + \frac{1}{b_0}P(t)$, then

$$Y'(t) \leq D(R_0 - Y(t)),$$

and $Y(0) \leq L_0$. Therefore, $Y(t) \leq \max\{L_0, R_0\}$.

By (c) in (**B1**),

$$\|x_t\|_D \leq \sup_{0 < s \leq t} |x(s)| + e^{-\gamma t}\|\phi\|_D \leq b_0 \max\{L_0, R_0\} + \|\phi\|_D,$$

and the proof is complete. $\square$

These positivity and boundedness results allow us to apply Theorem A.1.5 to (2.7), the following one is a direct application of this theorem.

Corollary 2.3.5. *Suppose $\varphi \in \mathscr{B}_D^+$ and $\varphi \geq 0$ on $(-\infty, 0]$, then the locally unique solution x of (2.7) extends to $\mathbb{R}_+ = [0, \infty)$ uniquely.*

Now we can introduce a semiflow associated with (2.7), let

$$\Phi : [0, \infty) \times \mathscr{B}_D^+ \to \mathscr{B}_D^+.$$

For each $\varphi \in \mathscr{B}_D^+$, let x be the solution of (2.7) through $(0, \varphi)$, define $\Phi(t, \varphi) = x_t$ for every $t \in [0, \infty)$. Then it satisfies the following properties:

1. $\Phi(0, x) = x$ for all $x \in \mathscr{B}_D^+$;

2. $\Phi(s, \Phi(t, x)) = \Phi(s + t, x)$ for all $x \in \mathscr{B}_D^+$ and $t, s \geq 0$.

Thus we can show the following existence theorem of the compact global attractor.

Theorem 2.3.6. *System (2.7) has a compact global attractor K_D. That is, there exists a maximal compact invariant set $K_D \subset \mathscr{B}_D^+$ such that K_D attracts all bounded sets in $\mathscr{B}_D^+$.*

Proof. In our context, phase space $\mathscr{B}_D^+$ satisfies all (**B1**) – (**B4**) and $K(t) = 1$, $N(t) = e^{-\gamma t}$.

By Lemma 2.3.4, positive orbits of bounded sets are bounded. And lastly, to show Φ is point dissipative, it suffices to show there exists a bounded set V in $\mathscr{B}_D^+$ such that for any $\phi \in \mathscr{B}_D$, $\Phi(t, \phi)$ is attracted by V.

For any $\phi \in \mathscr{B}_D$, let $Y(t)$ be defined as in the proof of Lemma 2.3.4, then $\limsup\limits_{t \to \infty} Y(t) \le R_0$. That is, there exists some $t_0 > 0$ such that $Y(t) \le R_0 + 1$ for all $t \ge t_0$.

Note if $t > t_0$, by (c) in (**B1**),

$$
\begin{aligned}
\|\Phi(t, \phi)\|_D &= \|\Phi(t - t_0, \Phi(t_0, \phi))\|_D \\
&\le \sup_{0 \le s \le t - t_0} |\Phi(t - t_0, \Phi(t_0, \phi))(s)| + e^{-\gamma(t - t_0)} \|\Phi(t_0, \phi)\|_D \\
&\le \sup_{0 \le s \le t - t_0} b_0 |Y(s)| + e^{-\gamma(t - t_0)} \|\Phi(t_0, \phi)\|_D \\
&\le b_0(R_0 + 1) + e^{-\gamma(t - t_0)} \|\Phi(t_0, \phi)\|_D.
\end{aligned}
$$

For t large enough, $e^{-\gamma(t - t_0)} \|\Phi(t_0, \phi)\|_D \le 1$.

Define $V = \{\varphi \in \mathscr{B}_D^+ : 0 \le \|\varphi\|_D \le b_0(R_0 + 1) + 1\}$, then $\Phi(t, \phi) \to V$ as $t \to \infty$. Since $\varphi \in \mathscr{B}_D^+$ is arbitrary, V attracts all points in $\mathscr{B}_D^+$ and Φ is point dissipative.

Therefore, by Theorem A.1.6, (2.7) has a compact global attractor K_D. $\square$

Since K_D attracts all bounded sets in $\mathscr{B}_D$, it contains the asymptotic behavior of every solution of (2.7). Now we show another boundedness result of trajectories in K_D:

Theorem 2.3.7. *For any $\phi \in K_D$, there exists a unique total trajectory x_t defined for all $t \in \mathbb{R}$ with $x_0 = \phi$. Moreover, $x(t) = x_t(0) : \mathbb{R} \to \mathbb{R}^4$ is bounded.*

Proof. By Proposition 3.23 in [33], K_D consits of points in $\mathscr{B}_D^+$ such that there exists a bounded total trajectory through this point.

Therefore, $\{\|x_t\|_D : t \in \mathbb{R}\}$ is bounded, in particular, $x_t(0) \leq \|x_t\|_D$ implies $x : \mathbb{R} \to \mathbb{R}^4$ is bounded. $\qquad\square$

In this chapter we formulated a DDE model with infinite distributed delay (2.3) and later reduced it into (2.7). For (2.7), we defined a phase space $\mathscr{B}_D^+$ and proved some fundamental properties of solutions. We also proved there exists a compact global attractor which attracts all bounded sets.

CHAPTER 3

PERSISTENCE ON DDE MODEL

Persistence is always an interesting question in mathematical models of biological processes, population sciences, and the epidemiology field. Roughly speaking, the persistence means for a given species, the population will remain a positive value after a long-term evolution. In other words, persistence measures if a species is capable to survive in the natural environment or a proper closed system.

And sometimes, if a species fails to persist, it may go extinct. There are a number of factors may lead to the extinction of a species, e.g., lack of necessary nutrient or resources, less competitive comparing to other species, an aggressive predator, and etc. However, showing the persistence is usually more complicated and difficult.

The persistence or extinction may be conditional, that is, different parameter values or different initial data may result in significantly different scenarios. Finding out the threshold value of parameters and initial states is also an interesting topic and sometimes requires advanced techniques and theories.

In this chapter, we will focus on (2.7), again, as assumed, we consider only the phase space $\mathscr{B}_D^+$, which does not contain the infected bacteria $I(t)$. The main result of this chapter, as well as this study, is the persistence of the susceptible bacteria S, the conditional persistence of phage P and the resistant bacteria M. To perform this analysis, we need a precise definition of persistence (uniformly weak persistence and uniform persistence in our context), as well as different theorems leading to the persistence results as studied in [33]. All notations, terminology, and key results regarding the general persistence theory are summarized in Appendix A.3.

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This chapter is organized in the following way. In the first section we will investigate equilibria and their local stability of (2.7). Due to the complicated nature of DDEs with infinite dealy terms, we will use theories developed in Ruess and Summers [30] to study the linearized stability of equilibria. We will introduce two important quantitative values called "Phage Reproduction Number" (PRN) and "Resistant Bacteria Reproduction Number" (MRN) and show that they are linked to the existence and local stability of corresponding equilibria.

The remaining part of this chapter is devoted to persistence results. We show the unconditional persistence of susceptible bacteria S and give an upper bound of total bacteria population in the chemostat. For the conditional persistence of phage P, we discover that the persistence or extinction of both P and I are associated with threshold value PRN. This result is similar to the conclusion of [34].

And by the end of this chapter, we will give a sufficient condition for the persistence of resistant bacteria M.

3.1   Equilibria and Local Stability

As the infected cell density is determined by the other densities via its formal solution (2.4), the phase space is taken as $\mathscr{B}_D^+$ and the state vector is $(R, S(\cdot), M, P(\cdot))$.

As a direct consequence of (**F1**) – (**F2**), there are three non-negative equilibria that always exist:

$$E_0 = (R_0, 0, 0, 0), \; E_S = (R_S, \overline{S}, 0, 0), \; E_M = (R_M, 0, \overline{M}, 0).$$

where $f_i(R_i) = D$, $i = S, M$, $\overline{S} = R_0 - R_S$, and $\overline{M} = R_0 - R_M$. Recall R_i for $i = S, M$ are break-even values for susceptible bacteria and resistant bacteria, respectively. Note that phage P is absent from all equilibria above.

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Moreover, E_0 and E_M are unstable. E_0 is unstable to colonization by either S or M. And E_M is unstable because by (**F2**), the break-even value of S is less than R_M.

As noted in [34], the local stability of E_S is determined by the "Phage Reproduction Number", or RRN for short. We define the "Phage Reproduction Number at bacteria density S" by:

$$PRN(S) = \frac{BkS}{D+kS}. \tag{3.1}$$

The "Phage Reproduction Number" is defined as $PRN = PRN(\overline{S})$, namely, the evaluation of $PRN(S)$ at $S = \overline{S}$.

We claim that E_S is locally asymptotically stable if $PRN < 1$ and unstable if $PRN > 1$. This is proved in Theorem 3.1.1, which is deferred to the end of this section.

The calculation shows that there are two more possible equilibria of (2.7) which include phage:

$$E_{SP} = (R^*, S^*, 0, P^*), \; E_{SMP} = (R_M, S^*, M^\#, P^\#).$$

Note E_{SP} and E_{SMP} share the same S component, which is solved by $PRN(S^*) = 1$ and $R^* \in (0, R_0)$ is the unique root of $DR^* + f_S(R^*)S^* = DR_0$ with in this interval. And $P^* = \frac{1}{k}(f_S(R^*) - D)$ and $P^\# = \frac{1}{k}(f_S(R_M) - D)$. And $M^\#$ satisfies $D(R_M + M^\#) + f_S(R_M)S^* = DR_0$.

We summarize necessary and sufficient conditions for existence and positivity of equilibria by Table 2.

The resistant bacteria M can survive only when phage P presents. Therefore, it is natural to consider if M can invade E_{SP}. And this is the case if and only if

$$MRN = \frac{f_M(R^*)}{D} > 1, \tag{3.2}$$

Table 2.Equilibria and local stability of DDE model (2.7)

Equilibrium	existence conditions	stability
$E_R = (R_0, 0, 0, 0)$	none	unstable by (F1)
$E_S = (R_S, \overline{S}, 0, 0)$	$\frac{f_S(R_0)}{D} > 1$	see Theorem 3.1.1
$E_M = (R_M, 0, \overline{M}, 0)$	$\frac{f_M(R_0)}{D} > 1$	unstable by (F2)
$E_{SP} = (R^*, S^*, 0, P^*)$	$PRN = Bk\overline{S}/(D + k\overline{S}) > 1$	see Theorem 3.1.2
$E_{SMP} = (R_M, S^*, \widehat{M}, \widehat{P})$	$MRN = f_M(R^*)/D > 1$	unknown

where the nutrient level R^* is determined by E_{SP}. Actually it can be easily proved that E_{SMP} exists and is a positive equilibrium if and only if $MRN > 1$. Similar to PRN, MRN is called the reproductive number of resistant bacteria in the E_{SP} environment.

The local stability of E_{SP} and E_{SMP} is very difficult to analyze. However, the stability of E_{SP} is linked to the existence of E_{SMP}. To be more precise, E_{SP} will be unstable if E_{SMP} is a positive equilibrium. It is very difficult to give criteria for stability and instability of E_{SP}, and even more difficult for E_{SMP}. However, if E_{SMP} does not exist, or equivalently $MRN < 1$, the local stability of E_{SP} is still not completely clear.

The following part of this section is devoted to the local stability of E_S and E_{SP}. Here we use framework developed in Ruess and Summers [30] to conduct this discussion. For more details, please see Appendix A.2

By using notations as in Appendix A.2, first we assume $\widehat{\mathcal{X}} = \mathbb{R}^4_+$, $\widehat{\mathcal{B}} = \mathcal{B}_D^+$, let $\varphi = (R, S(\cdot), M, P(\cdot))$ and rewrite the (2.7) as

$$\frac{d\varphi^T(t)}{dt} = -D\varphi + F(\varphi_t^T),$$

where $F : \mathcal{B}_D^+ \to \mathbb{R}_+^4$ is defined as

$$F\begin{pmatrix} R \\ S_t \\ M \\ P_t \end{pmatrix} = \begin{pmatrix} DR_0 - f_S(R(t))S(t) - f_M(R(t))M(t) \\ f_S(R(t))S(t) - kS(t)P(t) \\ f_M(R(t))M(t) \\ -kS(t)P(t) + k\int_0^\infty b(\tau)e^{-D\tau}S(t-\tau)P(t-\tau)d\nu(\tau) \end{pmatrix}.$$

Note now A is 0 operator hence it is clearly accretive. Then (a) – (d) in (**R1**) are automatically satisfied. Now we show (e) in (**R1**) is true, note the solution of (A.3) is

$$\varphi_x(s) = e^{\frac{s}{\lambda}}x + e^{\frac{s}{\lambda}}\int_s^0 \psi(r)e^{-\frac{r}{\lambda}}dr \geq 0$$

for all $s \in (-\infty, 0]$, thus

$$
\begin{aligned}
0 \leq e^{\gamma s}\varphi_x(s) &= e^{\left(\frac{1}{\lambda}+\gamma\right)s}\left[x + \int_s^0 \psi(r)e^{\gamma r}e^{-\left(\frac{1}{\lambda}+\gamma\right)rdr}\right] \\
&\leq e^{\left(\frac{1}{\lambda}+\gamma\right)s}\left[\psi(0) + \|\psi\|_\gamma \int_s^0 e^{-\left(\frac{1}{\lambda}+\gamma\right)rdr}\right] \\
&\leq \max\{x, \|\psi\|_\gamma\}e^{\left(\frac{1}{\lambda}+\gamma\right)s}\left[1 + \frac{1}{\frac{1}{\lambda}+\gamma}e^{-\left(\frac{1}{\lambda}+\gamma\right)s} - \frac{1}{\frac{1}{\lambda}+\gamma}\right] \\
&\leq \max\{x, \|\psi\|_\gamma\}\left[e^{\left(\frac{1}{\lambda}+\gamma\right)s} + \frac{1}{\frac{1}{\lambda}+\gamma}\right] \\
&\leq \max\{x, \|\psi\|_\gamma\}\left[1 + \frac{1}{\frac{1}{\lambda}+\gamma}\right] < \infty,
\end{aligned}
$$

because $s \in (-\infty, 0]$. Thus (**R2**) is satisfied. And since operator A in A.2 is 0, (**R3**) is trivial.

Therefore, we are able to use Theorem A.2.1 to analyze the local stability of E_S and E_{SP}.

Theorem 3.1.1. *The boundary equilibrium E_S is locally asymptotically stable if $PRN < 1$ and is unstable if $PRN > 1$.*

Proof. The linearization of (2.7) about E_S is given by

$$R'(t) = -(D + \overline{S}f_S'(R_S))R(t) - DS(t) - f_M(R_S)M(t)$$

$$S'(t) = f_S'(R_S)\overline{S}R(t) - k\overline{S}P(t)$$

$$M'(t) = (f_M(R_S) - D)M(t) \tag{3.3}$$

$$P'(t) = -DP(t) - k\overline{S}P(t) + k\overline{S}\int_0^\infty b(\tau)e^{-D\tau}P(t-\tau)d\nu(\tau).$$

Setting $(R, S, M, P) = xe^{\lambda t}$ we find that λ and x must satisfy $A(\lambda)x = 0$ where $A(\lambda)$ is given by

$$\begin{pmatrix} -D - f_S'(R_S)\overline{S} - \lambda & -D & -f_M(R_S) & 0 \\ \overline{S}f_S'(R_S) & -\lambda & 0 & -k\overline{S} \\ 0 & 0 & f_M(R_S) - D - \lambda & 0 \\ 0 & 0 & 0 & -D - k\overline{S} - \lambda + k\overline{S}\widetilde{B} \end{pmatrix}$$

and $\widetilde{B} = \widehat{b\nu}(\lambda + D)$ is the Laplace transform of $b\nu$.

Because $(R_S, \overline{S})$ is asymptotically stable in the linear approximation for the subsystem with $M, P = 0$ and because

$$f_M(R_S) - D < f_S(R_S) - D = 0,$$

it is easily seen that the stability analysis is reducible to the following scalar "phage invasion equation":

$$P'(t) = -(D + k\overline{S})P(t) + k\overline{S}\int_0^\infty b(\tau)e^{-D\tau}P(t-\tau)d\nu(\tau). \tag{3.4}$$

By inserting the ansatz $P = e^{\lambda t}$, we can obtain the characteristic equation associated with (3.4). The equation for λ is

$$\lambda + D + k\overline{S} = k\overline{S}\int_0^\infty b(\tau)e^{-(D+\lambda)\tau}d\nu(\tau). \tag{3.5}$$

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It has a positive real root if $PRN > 1$. To see this simply plot both sides of (3.5) and note that they intersect for positive λ precisely when $PRN > 1$ holds. On the other hand, if there is a root λ of (3.5) with $\Re\lambda \geq 0$ then it is easy to see that $PRN \geq 1$. Indeed, if $\Re\lambda \geq 0$ then

$$D + k\overline{S} \leq |\lambda + D + k\overline{S}| = |k\overline{S}\int_0^\infty b(\tau)e^{-D\tau}e^{-\lambda\tau}d\nu(\tau)| \leq Bk\overline{S}$$

Therefore, $\Re\lambda < 0$ for all roots of 3.5) if $PRN < 1$. And by Theorem A.2.1, E_S is linearly asymptotically stable for (2.7). $\qquad\square$

The stability of E_{SP} is complicated. We propose only a partial result here.

Theorem 3.1.2. *E_{SP} is linearly asymptotically stable for (2.7) if it is linearly asymptotically stable for the system without M and if $MRN < 1$. It is linearly unstable for (2.7) if it is linearly unstable for the system without M or if $MRN > 1$.*

Proof. We again calculate the linearization of (2.7) about E_{SP}.

Set $(R, S, M, P) = xe^{\lambda t}$, then λ and x satisfy $A(\lambda)x = 0$, where $A(\lambda)$ is

$$\begin{pmatrix} -D - f_S'(R^*)S^* - \lambda & -f_S(R^*) & -f_M(R^*) & 0 \\ S^*f_S'(R^*) & -\lambda & 0 & -kS^* \\ 0 & 0 & f_M(R^*) - D - \lambda & 0 \\ 0 & -kP^*(1-\widetilde{B}) & 0 & -D - kS^*(1-\widetilde{B}) - \lambda \end{pmatrix}$$

and $\widetilde{B} = \widehat{b\nu}(\lambda + D)$.

If E_{SP} is asymptotically stable for the system without M, then the linearized stability of E_{SP} with M is determined by the characteristic root $f_M(R^*) - D$. In this case, $MRN < 1$ is equivalent to $f_M(R^*) - D < 0$ and all roots have negative real parts.

If $MRN > 1$ or if E_{SP} is unstable for the system without M, then there must be at least one characteristic root λ such that $\Re \lambda > 0$ so E_{SP} is unstable for the system with M. $\qquad \square$

It is well-known that E_{SP} can lose stability through a supercritical Hopf bifurcation for the system without M (see [7, 32]) for the special case of fixed latent period duration. However, a rigorous analysis on the bifurcation scenario is still left open. Numerical results on local stability and bifurcation when η is a Gamma distribution is presented in Section 5.3.

3.2   Persistence of Susceptible Bacteria

As proved in [23, 1, 22, 41, 35, 42, 27], without the phage infection, the bacteria species with lowest break-even value will be the only survivor in the chemostat. In our model, by (**F2**), susceptible bacteria S will drive resistant bacteria M to extinction if $P \equiv 0$. However, by introducing phage P, the dynamics become more complicated. On one hand, S is still superior to M while on the other hand, phage infection may reduce the density of S significantly. A natural question arising here is, will S still be able to persist? The main result of this section gives a positive answer to this question.

One can also imagine that, since phage P consumes susceptible S, there may be spare nutrient available to M, hence the density of M may increase. Will the total concentration of all bacteria species ((including susceptible, resistant, and infected ones) exceed the maximal density of bacteria in the phage-free system? Since M consumes the nutrient less efficiently, it seems reasonable to expect that total bacteria density will be eventually bounded by $\overline{S}$. And the second result of this section is to confirm this conjecture.

In this section and following sections, we will use concepts such as uniform persistence, uniformly weak persistence along with a number of results in general persistence results. For details of terminology, notations and concepts, please see Appendix A.3 and A.4. To simplify the writing, we also induce the following projection map from $\mathscr{B}_D^+$ to its subspaces. By omitting the difference between C_0 and $\mathbb{R}$, we can write an arbitrary point $x \in \mathscr{B}_D^+$ as $x = (R, S(\cdot), M, P(\cdot))$. Projection maps $\pi_R(x) := R$ and $\pi_M(x) := M$. For the other two components, $\pi_S(x) := S(\cdot) \in C_\gamma$ and $\pi_P(x) := P(\cdot) \in C_\gamma$.

The first lemma states that if P vanishes, then E_S is globally asymptotically stable.

Lemma 3.2.1. *If $\pi_P(\Phi(t,x))(0) \to 0$ and $S(0) > 0$, then $\Phi(t,x) \to E_S$.*

Proof. By the definition of projection map π_P, it is easy to see $\pi_P(\Phi(t,x))(0) \to 0$ is equivalent to $P(t) \to 0$.

Consider the following 3-dimensional non-autonomous ODE system by taking $P(t)$ as a time-dependent function:

$$R'(t) = D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t),$$
$$S'(t) = (f_S(R(t)) - D)S(t) - kS(t)P(t), \qquad (3.6)$$
$$M'(t) = (f_M(R(t)) - D)M(t).$$

Since $P(t) \to 0$, (3.6) is an asymptotically autonomous system with a limit equation:

$$R'(t) = D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t),$$
$$S'(t) = (f_S(R(t)) - D)S(t), \qquad (3.7)$$
$$M'(t) = (f_M(R(t)) - D)M(t).$$

By Theorem 3.2 in [35], all trajectories of (3.7) are attracted by one of its equilibria: $E_0 = (R_0, 0, 0)$, $E_S = (R_S, \overline{S}, 0)$ or $E_M = (R_M, 0, \overline{M})$. Note the acyclicity

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and isolation property are satisfied. By Theorem A.4.2, every solution of (3.6) is attracted by an equilibrium of (3.7).

On the other hand, the formal solution of $S(t)$ is given by (2.8). Suppose $R(t) \to R_M > R_S = f_S^{-1}(D)$, i.e., the solution is attracted by E_M, then $S(t) \to 0$. Since $P(t) \to 0$, we can find a $\delta > 0$ and $T > 0$ such that $f_S(R(t)) - D - kP(t) > \delta$ when $t > T$. Also, $S(T) > 0$ because $S(0) > 0$, hence

$$S(t) > S(T)e^{\delta(t-T)} \to \infty$$

as $t \to \infty$, which contradicts that $S(t) \to 0$. Thus the solution cannot be attracted by E_M. Similarly, it cannot converge to E_0 either. Therefore, E_S attracts the solution. $\qquad\square$

The following theorem gives the uniformly weak persistence of S. A possible way of showing the weak persistence of S is to use "topological approach" and apply Theorem A.3.1. Nevertheless, similar to the argument in [33], we can show the uniformly weak persistence by a more direct way.

Lemma 3.2.2. *Susceptible bacteria S persists uniformly weakly. To be more precise,*

$$\limsup_{t \to \infty} S(t) \geq \min\{\overline{S}, \frac{D}{Bk}\}.$$

Proof. Suppose $S(0) > 0$ but $S^\infty < \frac{D}{Bk}$. Fix $\epsilon > 0$. By suitably translating the solution, we may assume that $S(t) < S^\infty + \epsilon$ and $P(t) < P^\infty + \epsilon$ for all $t \geq 0$.

By the fluctuation argument, we can choose $\{t_j\}_{j=1}^{\infty}$ in $\mathbb{R}_+$ such that $t_j \to \infty$, $P'(t_j) \to 0$, and $P(t_j) \to P^{\infty}$. Then

$$P'(t_j) \le -DP(t_j) + k \int_0^{\infty} e^{-D\tau} b(\tau) S(t_j - \tau) P(t_j - \tau) d\nu(\tau)$$

$$= -DP(t_j) + k \int_0^{t_j} e^{-D\tau} b(\tau) (S^{\infty} + \epsilon)(P^{\infty} + \epsilon) d\nu(\tau)$$

$$+ k \int_{t_j}^{\infty} e^{-D\tau} b(\tau) S(t_j - \tau) P(t_j - \tau) d\nu(\tau)$$

$$\le -DP(t_j) + k \int_0^{t_j} e^{-D\tau} b(\tau) (S^{\infty} + \epsilon)(P^{\infty} + \epsilon) d\nu(\tau) \qquad (3.8)$$

$$+ k \int_{t_j}^{\infty} e^{-(D-2\gamma)\tau} b_0 \|S_0\|_{\gamma} \|P_0\|_{\gamma} d\nu(\tau)$$

$$\le -DP(t_j) + k \int_0^{t_j} e^{-D\tau} b(\tau) (S^{\infty} + \epsilon)(P^{\infty} + \epsilon) d\nu(\tau)$$

$$+ e^{-(D-2\gamma)t_j} b_0 \|S_0\|_{\gamma} \|P_0\|_{\gamma},$$

where $S_0(s) = S(0+s)$ for all $s \in (-\infty, 0]$ is the initial data for S and P_0 is read in the same way.

Therefore, by taking $j \to \infty$,

$$0 \le -DP^{\infty} + Bk(S^{\infty} + \epsilon)(P^{\infty} + \epsilon).$$

Because $\epsilon > 0$ is arbitrary,

$$0 \le -DP^{\infty} + BkS^{\infty}P^{\infty}.$$

Since $S^{\infty} < \frac{D}{Bk}$ as assumed, we assert $P^{\infty} = 0$. By Lemma 3.2.1, $S(t) \to \overline{S}$.

Therefore, either $S^{\infty} \ge \frac{D}{Bk}$ or $S(t) \to \overline{S}$, and $S^{\infty} \ge \min\{\overline{S}, \frac{D}{Bk}\}$ follows. $\square$

As we have proved the uniformly weak persistence of S, it is only one step away from the uniform persistence of S. Note that attractor K_D will serve the role of U in Theorem A.3.2, and (2.8) implies that there exists no $x \in \mathcal{B}_D^+$ such that $\pi_S(x)(0) > 0$ and $\pi_S(\Phi(t, x))(0) = 0$ for some $t > 0$, therefore, the following theorem becomes a direct corollary of Theorem A.3.2.

Theorem 3.2.3. *Susceptible bacteria S persists. To be more precise, there exists an $\epsilon > 0$ such that*

$$\liminf_{t \to \infty} S(t) > \epsilon,$$

for all solutions with $S(0) > 0$.

And the second main result of this section is stated below.

Lemma 3.2.4. *The total density of all bacteria species in the chemostat satisfies*

$$(S + M + I)^\infty \le \overline{S}.$$

Proof. Define $Y = (S + M + I)$, note

$$Y'(t) = f_S(R(t))S(t) + f_M(R(t))M(t) - DY(t)$$

$$- k \int_0^\infty e^{-D\tau} b(\tau)S(t-\tau)P(t-\tau)d\nu(\tau)$$

$$\le f_S(R(t))(S(t) + M(t)) - DY(t) \le (f_S(R(t)) - D)Y(t).$$

By the same argument as in Lemma 2.3.4, if we let $Z = R + S + M + I + \frac{P}{b_0}$, then $Y(0) \le Z(0)$ and $Y'(t) \le Z'(t)$. Moreover,

$$Z'(t) \le D(R_0 - Z(t)),$$

thus $(Y + R)^\infty \le Z^\infty \le R_0$, hence by a fluctuation method applied to the Y equation,

$$0 \le (f_S((R + Y)^\infty - Y^\infty) - D)Y^\infty \le (f_S(R_0 - Y^\infty) - D)Y^\infty.$$

So either $Y^\infty = 0$ or $f_S(R_0 - Y^\infty) \ge D$; the latter case is equivalent to $Y^\infty \le R_0 - R_S = \overline{S}$. Therefore, in both cases we obtain $Y^\infty \le \overline{S}$. $\square$

So far we have proved susceptible bacteria S persists uniformly. That means, even though Phage P are attacking S, the density of S in the chemostat

cannot drop below some certain value. As we will see later in Section 5.3, the simulation suggests: when P persists, the concentration of S decreases dramatically compared to the phage-free case, however, susceptible bacteria S is always bounded away from 0, at least in the mathematical sense.

3.3   Persistence and Extinction of Phage

The persistence of phage P and infected bacteria I is conditional. In [34], the authors claim that the persistence of Phage and infected bacteria is determined by PRN. Here we apply a similar argument to (2.7) and proved that P and I persists uniformly when $PRN > 1$ and both go extinct if $PRN < 1$.

The essential tool we employ in this section is Laplace transform. It is well-known that Laplace transform can be used to solve some differential equations. And in the field of mathematical models of biology and population studies, Laplace transform can be applied to (partial and ordinary) differential equations to show the persistence or extinction of a species. For instance, Laplace transform was used in [37, Section 22.3] and [38, 34].

In this section, we will apply Laplace transform to the differential equation of P. Since this differential equation contains an integral term of infinite delay, we will have to justify the existence of the Laplace transform.

Before stating these results, we first recall the definition of Laplace transform. For a bounded and continuously differentiable function $f(t)$, its Laplace transform is defined as

$$\widehat{f}(\lambda) = \int_0^\infty e^{-\lambda t} f(t) dt,$$

for all $\lambda \geq 0$. And $\widehat{f'}(\lambda) = \lambda \widehat{f}(\lambda) - f(0)$. If $f(t)$ is a non-negative function, its Laplace transform $\widehat{f}(\lambda)$ is non-negative too.

In (2.7), we calculate the Laplace transform of $P'(t)$ and it gives

$$(\lambda + D)\widehat{P}(\lambda) = P(0) - k\widehat{SP}(\lambda)$$
$$+ k\int_0^\infty e^{-\lambda t}\int_0^\infty b(\tau)e^{-D\tau}S(t-\tau)P(t-\tau)d\nu(\tau)dt. \tag{3.9}$$

Since $\widehat{P}(\lambda)$ and $\widehat{SP}(\lambda)$ both exist, so does the integral term. And by the Fubini-Tonelli Theorem (Theorem 2.37 in [14]), we can interchange the order of the iterated integral. Thus

$$(\lambda + D)\widehat{P}(\lambda) = P(0) - k\widehat{SP}(\lambda)$$
$$+ k\int_0^\infty b(\tau)e^{-D\tau}\int_0^\infty e^{-\lambda t}S(t-\tau)P(t-\tau)dt\,d\nu(\tau)$$
$$= P(0) - k\widehat{SP}(\lambda)$$
$$+ k\int_0^\infty b(\tau)e^{-D\tau}\int_{-\tau}^\infty e^{-\lambda(r+\tau)}S(r)P(r)dr\,d\nu(\tau)$$
$$= P(0) - k\widehat{SP}(\lambda) + kC_0 + k\widehat{SP}(\lambda)\int_0^\infty b(\tau)e^{-(\lambda+D)\tau}d\nu(\tau), \tag{3.10}$$

where, as $2\gamma < D$,

$$C_0 = \int_0^\infty b(\tau)e^{-(\lambda+D)\tau}\left(\int_{-\tau}^0 e^{-\lambda r}S(r)P(r)dr\right)d\nu(\tau)$$
$$\leq \int_0^\infty b(\tau)e^{-(\lambda+D)\tau}\left(\tau e^{(\lambda+2\gamma)\tau}\|S_0\|_\gamma\|P_0\|_\gamma\right)d\nu(\tau)$$
$$\leq b_0\|S_0\|_\gamma\|P_0\|_\gamma\int_0^\infty \tau e^{-(D-2\gamma)\tau}d\nu(\tau) < \infty.$$

Again, $S_0(\cdot)$ and $P_0(\cdot)$ are initial values.

The following theorem shows that P persists uniformly when $PRN > 1$ and $S(0) > 0$. Note this is slightly different from the uniform persistence definition in Appendix A.3, besides the assumption that $P(0) > 0$, here we also need $S(0) > 0$ because otherwise $S(t) \equiv 0$ by (2.8) and P will go extinct due to the lack of prey.

This theorem is a direct application of Theorem A.3.1 and A.3.2.

Theorem 3.3.1. *The phage species P persists uniformly if $PRN > 1$. That is, there exists $\epsilon > 0$ such that*

$$\liminf_{t \to \infty} P(t) > \epsilon,$$

for all solutions with $P(0) > 0$ and $S(0) > 0$.

Proof. Define the state space as $X = \{x \in \mathscr{B}_D^+ : \pi_S(x)(0) > 0\}$. Note that X is positively invariant for Φ. Because S persists uniformly and semiflow Φ has a compact attractor of bounded sets in $\mathscr{B}_D^+$, the restriction of Φ to X has a compact attractor of points in X, hence assumption (**C**) is satisfied.

Let $\rho : X \to [0, \infty)$, defined as $\rho(x) = \pi_P(x)(0)$, be the persistence function. Notice that for a given solution $(R(t), S_t(\cdot), M(t), P_t(\cdot))$, $\pi_P(x)(0) = P_t(0) = P(t)$. Define $X_0 = \{x \in X : \rho(\Phi(t, x)) = 0, \ \forall t \geq 0\}$. It is easy to see $X_0 \neq \varnothing$ because $C^0 \times C_\gamma \times C^0 \times \{0\} \subset X_0$, where 0 represents 0 function in C_γ.

In X_0, since $P(t) \equiv 0$ for all $t \geq 0$, system (2.7) becomes (3.7) for all positive times. Since $S(0) > 0$, by Theorem 3.2 in [35] and $P(t) \equiv 0$,

$$(R(t), S(t), M(t), P(t)) \to E_S = (R_S, \overline{S}, 0, 0)$$

as $t \to \infty$. This implies that E_S, viewed as an element of X, attracts all orbits starting in X_0.

We also need to show $\{E_S\}$ is compact, invariant, uniformly weakly ρ-repelling, isolated in X and acyclic. The proof of first two properties is trivial.

Suppose $\{E_S\}$ is not a uniformly weak ρ-repeller, that is, for any $\epsilon > 0$ there exists some $x_0 \in X$ and $T_0 > 0$ such that $\rho(x_0) > 0$ and $\|\Phi(t, x_0) - E_S\|_D < \epsilon$

when $t > T_0$. In particular, since $PRN > 1$, we can define

$$\epsilon_0 = \frac{1}{2} \min \left\{ \frac{kB\overline{S} - (D + k\overline{S})}{k(1+B)}, \overline{S} \right\} > 0,$$

and assume this assertion holds for ϵ_0.

Since $|S(t) - \overline{S}| = |S_t(0) - \overline{S}| \leq \|S_t - \overline{S}\|_\gamma \leq \|\Phi(t, x_0) - E_S\|_D$, we claim $|S(t) - \overline{S}| < \epsilon_0$ when $t > T_0$. Without loss of generality, after a time-shift, we can assume this inequality holds for all $t > 0$. And consequently,

$$(\overline{S} - \epsilon_0)\widehat{P}(\lambda) < \widehat{SP}(\lambda) < (\overline{S} + \epsilon_0)\widehat{P}(\lambda).$$

Now we apply these inequalities to (3.10) and obtain

$$(D + \lambda)\widehat{P}(\lambda) \geq \left(-k(\overline{S} + \epsilon_0) + k(\overline{S} - \epsilon_0) \int_0^\infty b(\tau)e^{-(\lambda+D)\tau} d\nu(\tau) \right) \widehat{P}(\lambda).$$

Since $P(t) > 0$ for $t > 0$, $\widehat{P}(\lambda)$ is positive and finite for $\lambda > 0$ so we conclude that

$$(D + \lambda) \geq -k(\overline{S} + \epsilon_0) + k(\overline{S} - \epsilon_0) \int_0^\infty b(\tau)e^{-(\lambda+D)\tau} d\nu(\tau).$$

Letting $\lambda \to 0$ we find that

$$D + k\overline{S} - kB\overline{S} \geq -k(1+B)\epsilon_0 > kB\overline{S} - (D + k\overline{S}),$$

which is clearly a contradiction. Therefore, $\{E_S\}$ is a uniformly weak ρ-repeller.

Now we show $\{E_S\}$ is isolated in X and acyclic in X_0. It is easy to see in X_0, (2.7) reduces to the ODEs (3.7) and E_S is asymptotically stable for (3.7). Thus $\{E_S\}$ is acyclic in X_0 and isolated in X_0. By Lemma 8.18 in [33], since $\{E_S\}$ is a uniformly weak repeller and is isolated in X_0, it is isolated in X.

By Theorem A.3.1, Φ is uniformly weakly ρ-persistent. To show the uniform persistence, we apply Theorem A.3.2. Note K_D is a compact attractor which attracts all bounded sets, so the first two conditions of Theorem A.3.2 are satisfied.

For the last condition, by formal solution (2.10), $P(0) > 0$ implies $P(t) > 0$ for all positive t, thus $\rho(\Phi(t, x))$ cannot be 0 provided $\rho(x) > 0$. Hence by Theorem A.3.2, Φ is uniformly ρ-persistent. □

Since phage P persists, it is reasonable to expect that infected bacteria species I persists. Though I is not considered as a component of the phase space $\mathcal{B}_D^+$, we can still use (2.5) to show its persistence.

Corollary 3.3.2. *Infected bacteria I persists uniformly if $PRN > 1$ and $S(0), P(0) > 0$.*

Proof. Note $S_\infty > 0$ and $P_\infty > 0$, we can assume $S(t) > \frac{1}{2} S_\infty$ and $P(t) > \frac{1}{2} P_\infty$ for all $t \geq 0$ after a possible time-shift. Thus by (2.5),

$$I(t) \geq \frac{1}{4} \int_0^\infty \mathfrak{F}(s) e^{-Ds} S_\infty P_\infty ds > 0,$$

it hence persists uniformly. □

As shown in [34], if $PRN < 1$, Phage go extinct. The following theorem shows a similar result for (2.7).

Theorem 3.3.3. *If $PRN < 1$, $P(t) \to 0$ as $t \to \infty$ and all trajectories with $S(0) > 0$ are attracted by $\{E_S\}$.*

Proof. By Lemma 3.2.4, $S^\infty \leq \overline{S}$. So for any $\epsilon > 0$, there exists a $T_0 > 0$ such that for all $t > T_0$, $S(t) < \overline{S} + \epsilon$. Thus we can assume $S(t) < \overline{S} + \epsilon$ for all $t \geq 0$ after a time-shift.

Note $\lambda \geq 0$ and $\widehat{P}(\lambda) \geq 0$ imply that $e^{-(\lambda+D)\tau} \leq e^{-D\tau}$ and thus by (3.10),

$$D\widehat{P}(\lambda) \leq (\lambda + D)\widehat{P}(\lambda) \leq P(0) + kC_0 + k(B-1)\widehat{SP}(\lambda).$$

We divide this proof into 2 cases: $k(B-1) \leq 0$ and $k(B-1) > 0$.

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If $k(B-1) \leq 0$, $D\widehat{P}(\lambda) \leq P(0) + kC_0$ so $\widehat{P}(\lambda)$ is bounded for $\lambda \geq 0$.

If $k(B-1) > 0$, $\widehat{SP}(\lambda) \leq (\overline{S} + \epsilon)\widehat{P}(\lambda)$ and consequently,

$$\left(D - k(B-1)(\overline{S}+\epsilon)\right) \widehat{P}(\lambda) \leq P(0) + kC_0$$

Since $PRN < 1$, we can pick ϵ small enough to make $D - k(B-1)(\overline{S}+\epsilon) > 0$.

Therefore, in both cases, $\widehat{P}(\lambda)$ is uniformly bounded by a positive constant for $\lambda \geq 0$. Let $\lambda \to 0$ and applying the monotone convergence theorem to get $\widehat{P}(0) = \int_0^\infty P(t)dt < \infty$. Since $P'(t)$ is bounded, $P(t)$ is uniformly continuous and $P(t) \to 0$ as $t \to \infty$.

The last assertion is a direct consequence of Lemma 3.2.1. $\qquad\square$

We can get an extinction result of I in this case.

Corollary 3.3.4. *Infected bacteria I goes extinct if $PRN < 1$.*

Proof. Consider the differential equation of I an apply the fluctuation method to it to obtain

$$0 \leq -DI^\infty + kS^\infty P^\infty = -DI^\infty,$$

because $P^\infty = 0$, by the non-negativity of I, $I^\infty = 0$. $\qquad\square$

All results regarding the persistence and extinction of Phage P and infected bacteria I are presented above. For (2.7), $PRN = 1$ is still a sharp threshold for the persistence and extinction of Phage P. Smith and Thieme [34] proved the similar statement for the model without resistant species M, and in [34] for the infection-age model (1.9).

It is not difficult to see that the persistence and extinction of P is irreverent to resistant bacteria M, the persistence theorem 3.3.1 holds as long as Lemma 3.2.1 is true, which is guaranteed by assumption (**F2**). And the extinction result, i.e.

Theorem 3.3.3 is valid provided Lemma 3.2.4 holds. Note that the upper bound in Lemma 3.2.4 is $\overline{S}$, which is exactly the bacteria density in the definition of $PRN = PRN(\overline{S})$. And one can imagine that if S does not persist, e.g. when the inequality in assumption (**F2**) is reversed, P will be eventually washed out because Phage cannot reproduce enough baby Phage without a host. For more details and discussion on (**F2**), please see Section 6.1.

3.4   Persistence of Resistant Bacteria

In this section we will show the conditional persistence of M. It is very clear from [35] that in a chemostat where phage species P is absent, the bacteria species with the lowest break-even value will be the solo survivor, all other species will vanish. This result has been generalized in different manners, e.g. non-monotone uptake functions and different removal rates for each bacteria species, for more details, please see Section 1.2.

Nevertheless, experimental observations such as in Levin, Stewart and Chao [26] have confirmed that the coexistence of different bacteria species is possible when a phage species specialized on attacking the superior bacteria is introduced into the chemostat. As the persistence of S is always true, the coexistence of both bacteria species is equivalent to the persistence of M.

The first statement of this section is a sufficient condition for the persistence of M. This is again an application of the topological approach Theorem A.3.1, with uniformly weak persistence proved, the uniform persistence follows almost automatically by Thoeorem A.3.2.

Theorem 3.4.1. *The resistant bacteria M persists uniformly if one of the following holds:*

   1. The initial value of susceptible bacteria $S(0) = 0$, or

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2. $PRN > 1$, $MRN > 1$, $S(0) > 0$, $P(0) > 0$ and E_{SP} is asymptotically stable and attracts all solutions with $S(0) > 0$, $P(0) > 0$ for system (2.7) with $M(0) = 0$.

Proof. If $S(0) = 0$, $S(t) = 0$ for all $t \geq 0$ and $P(t) \to 0$, thus system (2.7) reduces to

$$R'(t) = D(R_0 - R(t)) - f_M(R(t))M(t),$$

$$M'(t) = (f_M(R(t)) - D)M(t),$$

By Theorem 3.2 in [35], all trajectories with $M(0) > 0$ converge to $(R_M, \overline{M})$. Thus M persists uniformly.

Now we assume $S(0) > 0, P(0) > 0, PRN > 1, MRN > 1$, and that E_{SP} attracts all solutions with $S(0) > 0, P(0) > 0$ and $M(0) = 0$. Then, by (2.8) and (2.10), it is easy to see $S(t), P(t) > 0$ for all $t > 0$.

Let $X = \{x \in \mathscr{B}_D^+ : \pi_S(x)(0) > 0, \pi_P(x)(0) > 0\}$. By Theorem 3.2.3 and Theorem 3.3.1, S and P persist uniformly, and by Theorem 2.3.6, Φ has a compact attractor of bounded sets in $\mathscr{B}_D^+$, it indicates assumption (**C**) in Theorem A.3.1 is satisfied.

Define $\rho : X \to [0, \infty)$ as $\rho(x) = \pi_M(x) = M(0)$. Let $X_0 = \{x \in X : \rho(\Phi(t, x)) = 0, \forall t \geq 0\} = \{x \in X : M(t) = 0, t \geq 0\}$.

By assumption, E_{SP} attracts all solutions in X_0. $\{E_{SP}\}$ is clearly compact, invariant and acyclic in X_0.

Moreover, $\{E_{SP}\}$ is uniformly weakly ρ-repelling. Assume $\{E_{SP}\}$ is not uniformly ρ-repelling, for any $\epsilon > 0$ fixed, there exists some $x_0 \in X$ such that $\rho(x) > 0$ and

$$\limsup_{t \to \infty} \|\Phi(t, x_0) - E_{SP}\|_D < \epsilon.$$

Therefore, it is possible to find $T_0 > 0$ such that for all $t > T_0$, $|\pi_R(\Phi(t, x)) - R^*| \leq \|\Phi(t, x)) - E_{SP}\|_D < \epsilon$. However, note $MRN > 1$ implies $f_M(R^*) > D$ and choose

ϵ as

$$\epsilon = R^* - f_M^{-1}\left(\frac{f_M(R^*)+D}{2}\right),$$

then for all $t > T_0$, $\pi_R(\Phi(t,x)) > R^* - \epsilon = f_M^{-1}\left(\frac{f_M(R^*)+D}{2}\right)$, thus the formal solution of M, i.e. (2.9), yields

$$M(t) = M(T_0)\exp\left(\int_{T_0}^t f_M(R(s)) - D\, ds\right) > M(T_0)e^{\frac{f_M(R^*)-D}{2}},$$

which goes to ∞ when $t \to \infty$.

This is a contradiction because $M(t) = \rho(\Phi(t,x_0)) \le \|\Phi(t,x_0) - E_{SP}\|_D < \epsilon$ for all $t > T_0$.

Therefore, $\{E_{SP}\}$ is a uniformly weak ρ-repeller. As E_{SP} is asymptotically stable in X_0, it is isolated in X_0. Thus by Lemma 8.18 in [33], $\{E_{SP}\}$ is isolated in X.

And hence Theorem A.3.1 implies Φ is uniformly weak ρ-persistent. By the existence of compact attractor K_D and formal solution (2.9), all assumption of Theorem A.3.2 are satisfied and M is hence uniformly persistent. $\qquad \square$

Despite the assumption of Theorem 3.4.1 may be difficult to verify, there are a few results on the asymptotic stability of E_{SP} on similar models. For instance, in [32, Chapter 8] and [7], the authors studied model (1.7), the resistant bacteria M is absent and the delay term in differential equations of I and P contain only one single discrete delay (equivalent to (2.7) when $M(t) \equiv 0$ and $\eta(\tau)$ is a Dirac δ distribution). In [32], the author introduced the same concept PRN (involving delay parameter τ), which is similar to (3.1) but not identical. Then there exists a $\tau_c > 0$ such that $PRN = 1$ at $\tau = \tau_c$ and there exists τ_0, τ_1 such that $0 < \tau_0 < \tau_1 < \tau_c$, E_{SP} and E_{SP} is asymptotically stable if $PRN > 1$ and $0 \le \tau < \tau_0$ or $\tau_1 < \tau < \tau_c$.

For (2.7), since the differential equations of I and P involve infinite distributed delay terms, it seems impossible to solve it and prove a similar result without knowing the distribution function. However, as we will see later in Chapter 5, for a special case of (2.7), we are able to simulate and show the parameter range in which E_{SP} is locally asymptotically stable and M persists.

On the other hand, assume M persists, it is natural to expect P persists, because otherwise by Lemma 3.2.1, all trajectories with $S(0) > 0$ are attracted by E_S. Actually, the persistence of phage P will counter the fitness disadvantage of resistant bacteria M relative to susceptible bacteria S. This observation was phased in mathematical language by the following theorem.

Theorem 3.4.2. *Let $(R(t), S_t(\cdot), M(t), P_t(\cdot))$ be a solution of (2.7) with $S(0), M(0) > 0$ and suppose there exists some $\epsilon > 0$ and $T_0 > 0$ such that $M(t) > \epsilon$ for all $t > T_0$. Then*

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t f_S(R(s)) - f_M(R(s)) - kP(s)\,ds = 0.$$

Proof. Let $Y = \frac{S}{M}$, then

$$Y'(t) = (f_S(R(t)) - f_M(R(t)) - kP(t))Y(t),$$

Since $S_\infty > 0$ and $M > \epsilon$ when $t > T_0$, $Y(t)$ is bounded and $Y_\infty > 0$. Thus

$$(\ln Y(t))' = \frac{Y'(t)}{Y(t)} = f_S(R(t)) - f_M(R(t)) - kP(t).$$

And

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t (\ln Y(s))'\,ds = \lim_{t \to \infty} \frac{1}{t}(\ln Y(t) - \ln Y(0)) = 0,$$

because $|\ln Y(t)|$ is bounded. Consequently,

$$\lim_{t \to \infty} \frac{1}{t} \int_0^t f_S(R(s)) - f_M(R(s)) - kP(s)\,ds = 0$$

as claimed. $\square$

Note Theorem 3.4.2 holds for each given trajectory with $\liminf\limits_{t\to\infty} M(t) > 0$. Though it does not require the uniform persistence of M, it should be very clear that Theorem 3.4.2 applies to every trajectory with $S(0), M(0) > 0$ if M persists uniformly.

In this section we present a sufficient condition yet with a necessary condition for the persistence of M. For the sufficient condition, i.e. Theorem 3.4.1, the main assumption is that E_{SP} is locally asymptotically stable and attracts all trajectories in $\{M(t) \equiv 0\}$, it is independent from the formulation of the differential equation of P, hence it should apply to models in [34] and [7] if a resistant bacteria species were considered in their systems. Similarly, Theorem 3.4.2 should be able to be adapted for other models as well.

This chapter and the previous chapter contain analytic results on DDE model (2.7). So far we have proved the persistence of susceptible bacteria S, the persistence/extinction of phage P, we also give a sufficient condition for the persistence of M. A few analytic results on (2.7) are deferred to Chapter 6.

CHAPTER 4

GAMMA DISTRIBUTED DELAY AND THE ODE MODEL

In this chapter we will consider a special case of (2.7). By assuming the latent period of lysis obeys a Gamma distribution, we can reduce (2.7) into an ODE system.

Throughout this chapter the following one, we assume

$$b(\tau) = b$$

is a constant independent from the latent period and the distribution of latent period is

$$\eta(\tau) = \int_0^\tau g_m(s,a)ds = \int_0^\tau \frac{a^m s^{m-1}}{(m-1)!} e^{-as} ds, \tag{4.1}$$

where $m \in \mathbb{N}$ is the shape and $\frac{1}{a}$ is the scale of this Gamma distribution. Note when $m = 1$, the Gamma distribution is degenerate and coincide with exponential distribution. That is, the major part of infected bacteria are lysing immediately at the time of infection, and the number of lysis is an exponentially decreasing function of τ. However, as we see in experiments, there is an observable "average" latent time of lysis, and most infected bacteria lyse shortly before or after this average latent period. For instance, Ellis and Delbrück [13] claimed that at 37°C, the average latent time is about 30 minutes. Therefore, it is reasonable to assume $m \geq 2$. In this case, the mean of Gamma distribution is $\frac{m}{a}$, which also represents the average latent period.

Since this ODE model is a special case of (2.7), clearly all local stability and persistent result should still hold. But it is convenient to discuss a ODE version of these theorems briefly.

4.1 Formulation of the ODE Model

The main technique we used here is called the "linear chain trick" as discussed in [24, 32]. This procedure allows us to rewrite a DDE system consists of distributed delays into an ODE system, provided that the latent period obeys a Gamma distribution.

To perform this transformation, we introduce some new variables I_j for $1 \leq j \leq m$,

$$I_j(t) = \frac{k}{a} \int_0^\infty e^{-D\tau} g_j(\tau, a) S(t - \tau) P(t - \tau) d\tau, \tag{4.2}$$

note (4.2) also gives the initial values of I_j's.

It is easy to see

$$I_j(t) = k \frac{a^{j-1}}{(j-1)!} \int_0^\infty e^{-(a+D)\tau} \tau^{j-1} S(t - \tau) P(t - \tau) d\tau \qquad \text{(letting } u = t - \tau)$$

$$= k \frac{a^{j-1}}{(j-1)!} e^{-(a+D)t} \int_{-\infty}^t e^{(a+D)u} (t - u)^{j-1} S(u) P(u) du.$$

Therefore, we have

$$I_1'(t) = \frac{d}{dt} \left(k e^{-(a+D)t} \int_{-\infty}^t e^{(a+D)u} S(u) P(u) du \right)$$

$$= k S(t) P(t) - (a + D) I_1(t)$$

And for $2 \leq j \leq m$, we have

$$I_j't(t) = \frac{d}{dt} \left(k \frac{a^{j-1} e^{-(a+D)t}}{(j-1)!} \int_{-\infty}^t e^{(a+D)u} (t - u)^{j-1} S(u) P(u) du \right)$$

$$= k \frac{a^{j-1} e^{-(a+D)t}}{(j-1)!} \left(\frac{d}{dt} \int_{-\infty}^t e^{(a+D)u} (t - u)^{j-1} S(u) P(u) du \right) - (a + D) I_j(t)$$

$$= k \frac{a^{j-1} e^{-(a+D)t}}{(j-2)!} \int_{-\infty}^t e^{(a+D)u} (t - u)^{j-2} S(u) P(u) du - (a + D) I_j(t)$$

$$= a I_{j-1}(t) - (a + D) I_j(t).$$

Thus any solution of (2.7) gives rise, via (4.2), to a solution of

$$R'(t) = D(R_0 - R(t)) - f_S(R(t))S(t) - f_M(R(t))M(t),$$

$$S'(t) = (f_S(R(t)) - D)S(t) - kS(t)P(t),$$

$$M'(t) = (f_M(R(t)) - D)M(t),$$

$$I_1'(t) = kS(t)P(t) - (a+D)I_1(t),$$

$$I_j'(t) = aI_{j-1}(t) - (a+D)I_j(t), \qquad 2 \le j \le m,$$

$$P'(t) = -DP(t) - kS(t)P(t) + abI_m(t),$$

(4.3)

and

$$I'(t) = -DI(t) + kS(t)P(t) - aI_m(t). \tag{4.4}$$

Since $I(t)$ is not involved by any equation in (4.3) and can be solved by an integration, we consider only (4.3) hereafter.

To be more precise, suppose $x = (R(0), S_0(\cdot), M(0), P_0(\cdot)) \in \mathscr{B}_D^+$ is the initial data of (2.7) and let $\Phi(t,x) = (R(t), S_t(\cdot), M(t), P(t))$ be the solution through x, then $(R(t), S_t(0), M(t), I_1(t), \dots, I_m(t), P_t(0))$ is a solution of (4.3) with the initial condition $(R(0), S_0(0), M(0), I_1(0), \dots, I_m(0), P_0(0))$, where each $I_j(0)$ is given by (4.2).

And by Proposition 7.3 of [32], if $(R(t), S(t), M(t), I_1(t), \dots, I_m(t), P(t))$ is a bounded solution of (4.3) on $\mathbb{R}$, then $(R(t), S_t(\cdot), M(t), P_t(\cdot))$ is a bounded solution of (2.7) provided the distribution of $\eta(\tau)$ is given by (4.1) and $b(\tau) = b$ is a constant.

As direct corollaries of theorems in Section 2.3, all basic properties such as positivity and boundedness still hold for (4.3). We simply make the following assertions.

Theorem 4.1.1. *All solutions of (4.3) remain non-negative provided non-negative initial values.*

Theorem 4.1.2. *System (4.3) is dissipative.*

Proof. Let

$$Y = R + S + M + \frac{b}{(b-1)} \sum_{j=1}^{m} I_j + \frac{1}{b-1} P,$$

then $Y' = -D(R_0 - Y)$, thus (4.3) is dissipative. □

Since b is now a constant, Theorem 4.1.2 not only shows the dissipativity, but also proves that $Y(t) \to R_0$ as $t \to \infty$.

4.2 Compact Attractor and Equivalency

In this section we will investigate the compact attractor of (4.3). Similar to (2.7), ODE system (4.3) has a compact attractor which attracts all bounded sets in the state space. And by considering each total trajectory in this attactor, we can establish a connection between compact attractors of (4.3) and (2.7).

Since (4.3) is an ODE system, we choose $\mathbb{R}_+^{m+4}$ as the state space and let Ψ be the semiflow induced by (4.3). We also assume $\mathbb{R}_+^{m+4}$ is equipped with the maximum norm and we use $|\cdot|$ to represent this norm. To show the existence of the compact global attractor, we employ the following theorem:

Theorem 4.2.1 (Theorem 2.30 in [33]). *If a semiflow is point-dissipative, asymptotically smooth, and eventually bounded on every bounded set in its state space, then there exists a compact attractor of bounded sets (compact global attractor).*

Thus as a consequence, we have

Corollary 4.2.2. *The semiflow Ψ induced by (4.3) has a compact global attractor K_O, it attracts all bounded sets in $\mathbb{R}_+^{m+4}$.*

Proof. The point-dissipativity follows from Theorem 4.1.2.

To show Ψ is asymptotically smooth, let W be an arbitrary forward invariant bounded closed set in $\mathbb{R}_+^{m+4}$, then it is compact and sequentially compact. Hence for any $\{t_j\}_{j=1}^\infty \subset \mathbb{R}_+$ with $t_j \to \infty$ as $t \to \infty$, and any $\{y_j\}_{j=1}^\infty \subset W$, by the forward invariance of W, $\Psi(t_j, y_j) \in W$ for all $j \in \mathbb{N}$. Therefore, the sequential compactness implies $\{\Psi(t_j, y_j)\}_{j=1}^\infty$ has a convergent subsequence and Ψ is thus asymptotically smooth.

And lastly, the eventual boundedness of Ψ on bounded sets is a direct corollary of Theorem 4.1.2.

Therefore, Ψ has a compact attractor K_O which attracts all bounded sets in $\mathbb{R}_+^{m+4}$. $\qquad\square$

The following theorem is taken from [33]:

Theorem 4.2.3 (Proposition 3.24 in [33]). *The compact global attractor consists of points such that there exists a bounded total trajectory through this point.*

Now let's explore the connection between K_O and K_D. We defined projection maps π_i for $i \in \{R, S, M, P\}$ from $\mathscr{B}_D^+$ to each of its components in Section 3.2. Now we define $\tilde{\pi}_j : \mathbb{R}_+^{m+4} \to \mathbb{R}_+$ for $j \in \{R, S, M, I_1, \ldots, I_m, P\}$ as the projection map from $\mathbb{R}_+^{m+4}$ to the corresponding subspace.

We define a map $\iota : K_O \to K_D$. For each $y = (R, S, M, I_1, \ldots, I_m, P) \in K_O$, let $\psi(t)$ be the total trajectory through y, then by Theorem 4.2.3, $\psi(t)$ is bounded in $\mathbb{R}_+^{m+4}$. Write $S^-(s) = \tilde{\pi}_S(\psi(s))$ and $P^-(s) = \tilde{\pi}_P(\psi(s))$ for all $s \leq 0$, then $S^-(\cdot), P^-(\cdot) \in C_\gamma$ because ψ is bounded in $\mathbb{R}_+^{m+4}$. Define

$$\iota(y) = (R, S^-(\cdot), M, P^-(\cdot)) \in \mathscr{B}_D^+.$$

Then we have the following lemma:

Lemma 4.2.4. *The map ι defined above is a one-to-one and onto map from K_O to K_D.*

Proof. To show $\iota(y) \in K_D$, by Theorem 4.2.3, it suffices to show there exists a bounded total trajectory through $\iota(y)$. Let $\phi(t) = \iota(\psi(t))$, then by Proposition 7.3 in [32], $\phi(t)$ is a total trajectory of (2.7) through $\iota(y)$. Moreover, $\phi(t)$ is bounded in $\mathscr{B}_D^+$ because $\psi(t)$ is bounded in $\mathbb{R}_+^{m+4}$. Therefore, $\iota(y) \in K_D$ for $y \in K_O$.

And ι is injective, let y_1, y_2 be distinct points in K_O, then at least one component of y_1 and y_2 are different. If $\tilde{\pi}_i(y_1) \neq \tilde{\pi}_i(y_2)$ for $i \in \{R, S, M, P\}$, then clearly $\iota(y_1) \neq \iota(y_2)$. Otherwise, if $\tilde{\pi}_{I_j}(y_1) \neq \tilde{\pi}_{I_j}(y_2)$ for some $1 \leq j \leq m$, by (2.6), either $S_1^-(\cdot) \neq S_2^-(\cdot)$ or $P_1^-(\cdot) \neq P_2^-(\cdot)$ or both. Therefore, $y_1 \neq y_2$ implies $\iota(y_1) \neq \iota(y_2)$.

ι is also an onto map. For each $x = (R, S(\cdot), M, P(\cdot)) \in K_D$, let $\phi(t)$ be the total trajectory through x, then it gives rise to a solution of (4.3) via (4.2). Let $y = (R, S(0), M, I_1(0), \ldots, I_m(0), P(0)) \in \mathbb{R}_+^{m+4}$ where $I_j(0)$ are calculated by (4.2). Also let $\psi(t)$ be the total trajectory through y, then $\psi(t)$ is bounded by Theorem 2.3.7. Thus $\psi(t) \subset K_O$ and $y \in K_O$. By the definition of ι, $\iota(y) = x$. $\qquad\square$

Note from the last paragraph in the proof of Lemma 4.2.4, we can define an inverse map of ι, call it ι^{-1}. The inverse map $\iota^{-1} : K_D \to K_O$ is defined as

$$\iota^{-1}(x) = (\pi_R(x), \pi_S(x)(0), \pi_M(x), I_1(0), \ldots, I_m(0), \pi_P(x)(0)),$$

where $I_j(0)$'s are obtained by (4.2).

Theorem 4.2.5. *The map $\iota : K_O \to K_D$ is a homeomorphism.*

Proof. It suffices to that ι^{-1} is continuous and Lipschitz.

The continuity of ι^{-1} is easier to prove. Since K_D is bounded in $\mathscr{B}_D^+$, we can choose $L > 0$ such that $\|K_D\|_D < L$. For any $\epsilon > 0$, let $\delta = \min\{\frac{\epsilon}{2kL}, \frac{1}{2}\epsilon\}$. Then

for $x_1 = (R_1, S_1(\cdot), M_1, P_1(\cdot))$ and $x_2 = (R_2, S_2(\cdot), M_2, P_2(\cdot))$ in K_D with $\|x_1 - x_2\|_D$ we have

$$\max \{|R_1 - R_2|, |S_1(0) - S_2(0)|, |M_1 - M_2|, |P_1(0) - P_2(0)|\} \leq \delta < \epsilon.$$

And for I_j's, we write $I_{j,i}$ as the I_j calculated by (4.2) for x_i ($i = 1, 2$), then

$$|I_{j,1}(0) - I_{j,2}(0)| \leq k \int_0^\infty e^{-D\tau} g_j(\tau, a) |S_1(-\tau) P_1(-\tau) - S_2(-\tau) P_2(-\tau)| d\tau$$

$$\leq k \int_0^\infty e^{-(D-2\gamma)} g_j(\tau, a) \left(\|S_1\|_\gamma \|P_1 - P_2\|_\gamma + \|P_2\|_\gamma \|S_1 - S_2\|_\gamma \right) d\tau$$

$$\leq 2k \delta L \int_0^\infty e^{-D-2\gamma} g_j(\tau, a) d\tau < 2k \delta L \leq \epsilon.$$

Therefore, since $\mathbb{R}^{m+4}_+$ takes the maximum norm, we have $|\iota^{-1}(x_1) - \iota^{-1}(x_2)| < \epsilon$ if $\|x_1 - x_2\|_D < \delta$.

Note the argument above also implies that

$$|\iota^{-1}(x_1) - \iota^{-1}(x_2)| < \max\{2kL, 2\} \|x_1 - x_2\|_D,$$

therefore ι^{-1} is Lipschitz. □

4.3 Equilibria and their Local Stability

As a special case of (2.7), ODE system (4.3) always has the following trivial, phage-free equilibria:

$$E_0 = (R_0, 0, \ldots, 0), \ E_S = (R_S, \overline{S}, 0, \ldots, 0), \ E_M = (R_M, 0, \overline{M}, 0, \ldots, 0).$$

And not surprisingly, both E_0 and E_M are unstable.

Similar to (2.7), the local stability of E_S is again determined by the Phage Reproduction Number (PRN). Since $b(\tau) = b$ is a constant, the average number of new phage eventually released by an infected bacterium B is given by the

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following formula:

$$B = \int_0^\infty e^{-D\tau} b\, d\nu(\tau) = b \int_0^\infty e^{-D\tau} g_m(\tau, a)\, d\tau$$

$$= b \left(-\frac{1}{a+D} e^{-(a+D)\tau} \frac{a^m \tau^{m-1}}{(m-1)!} \Big|_{\tau=0}^{\infty} + \frac{a}{a+D} \int_0^\infty e^{-(a+D)\tau} \frac{a^{m-1}\tau^{m-2}}{(m-2)!}\, d\tau \right)$$

$$= b \left(\frac{a}{a+D} \int_0^\infty e^{-D\tau} g_{m-1}(\tau, a)\, d\tau \right) = \cdots = \frac{a^{m-1}b}{(a+D)^{m-1}} \int_0^\infty e^{-D\tau} g_1(\tau, a)\, d\tau$$

$$= \frac{a^{m-1}b}{(a+D)^{m-1}} \int_0^\infty a e^{-(a+D)\tau}\, d\tau = \frac{a^m b}{(a+D)^m}.$$

So PRN can be written as

$$PRN = PRN(\overline{S}) = \frac{a^m b k \overline{S}}{(a+D)^m (D + k\overline{S})}. \tag{4.5}$$

Similar to Lemma 3.2.1, we have the following assertion on the local stability of E_S. Since (4.3) is an ODE system, we can analyze the polynomial characteristic equation as treating usual ODE systems.

Theorem 4.3.1. *The boundary equilibrium E_S of (4.3) is locally asymptotically stable if $PRN < 1$ and is unstable if $PRN > 1$.*

Proof. Computing the Jacobian matrix at E_S gives that

$$J = \begin{pmatrix} J_1 & * \\ 0 & J_2 \end{pmatrix},$$

where J_1 is a 3×3 matrix:

$$J_1 = \begin{pmatrix} -D - f_S'(R_S)\overline{S} & -D & -f_M(R_S) \\ f_S'(R_S)\overline{S} & 0 & 0 \\ 0 & 0 & f_M(R_S) - D \end{pmatrix},$$

and J_2 is a $(m+1) \times (m+1)$ matrix:

$$J_2 = \begin{pmatrix} -(a+D) & 0 & 0 & \dots & 0 & k\overline{S} \\ a & -(a+D) & 0 & \dots & 0 & 0 \\ 0 & a & -(a+D) & \dots & 0 & 0 \\ \vdots & 0 & \ddots & \ddots & 0 & \vdots \\ 0 & \dots & 0 & a & -(a+D) & 0 \\ 0 & \dots & \dots & 0 & ab & -D-k\overline{S} \end{pmatrix}.$$

Eigenvalues of J_1 are $\lambda = -D$, $\lambda = f_2(R_1) - D < 0$ and $\lambda = -f_1'(R_1)\overline{S} < 0$.

Thus the characteristic equation of E_S is $\overline{\theta}_S(\lambda) = 0$, where

$$\overline{\theta}_S(\lambda) = (\lambda+D)(\lambda - f_M(R_S) + D)(\lambda + f_S'(R_S)\overline{S})$$
$$\left[(\lambda+a+D)^m(\lambda+D+k\overline{S}) - a^m bk\overline{S} \right]. \tag{4.6}$$

The constant term is $(a+D)^m(D+k\overline{S}) - a^m bk\overline{S}$, which has the same sign as $PRN - 1$.

Note that if $PRN > 1$, $\overline{\theta}_S(0) < 0$ because the constant term is negative and $\overline{\theta}_S(\lambda) \to \infty$ as $\lambda \to \infty$, hence $\overline{\theta}_S(\lambda) = 0$ has a positive real root, and consequently E_S is unstable.

If $PRN < 1$, J_2 is an irreducible matrix with non-negative off-diagonal entries, so by theorem A.5 in [35], $s(J_2) := \max\{\Re\lambda : \overline{\theta}_S(\lambda) = 0\}$ is a root of $\overline{\theta}_S(\lambda) = 0$. However, by Descarte's rule of signs, as the constant term is now positive, $\overline{\theta}_S(\lambda) = 0$ has no positive real roots and 0 is not a root, thus $s(J_2) < 0$ and real parts of all eigenvalues of J_2 are less than or equal to $s(J_2)$, hence E_S is locally asymptotically stable when $PRN < 1$. □

Besides phage-free equilibria shown above, (4.3) has another two equilibria, namely,

$$E_{SP} = (R^*, S^*, 0, I_1^*, \dots, I_m^*) \text{ and } E_{SMP} = (R_M, S^*, M^\#, I_1^\#, \dots, I_m^\#, P^\#).$$

The susceptible bacteria concentration at E_{SP} is the level at which $PRN(S^*) = 1$, which can be interpreted as the lowest S concentration to support the phage at a steady state. $0 < R^* < R_0$ is the unique solution of $DR^* + f_S(R^*)S^* = DR_0$, and $kP^* = f_S(R^*) - D$. Each I_j^* for $1 \leq j \leq m$ can be solved accordingly. The uniqueness of R^* is proved in Theorem 4.3.2. For (4.3), we have

$$S^* = \frac{D}{k}\frac{(a+D)^m}{a^m b - (a+D)^m}, \quad I_j^* = \frac{a^{j-1}}{(a+D)^j}kS^*P^*, \quad P^* = \frac{f_S(R^*) - D}{k}.$$

For E_{SMP}, the S remains the same, while the R component is exactly the break-even value of M. $P^\#$ and $I_j^\#$'s have similar formulas as in E_{SP} except for R^* is replaced by R_M. To be more precise, we have

$$M^\# = \overline{M} - \frac{f_S(R_M)}{D}S^*, \quad I_j^\# = \frac{a^{j-1}}{(a+D)^j}kS^*P^\#, \quad P^\# = \frac{f_S(R_M) - D}{k}.$$

Similar to corresponding equilibria of (2.7), the existence of these equilibria are conditional.

Theorem 4.3.2. *E_{SP} is a non-negative equilibrium of (4.3) if and only if $PRN \geq 1$. E_{SMP} is a non-negative equilibrium if and only if $MRN \geq 1$.*

Proof. Let's consider E_{SP} first. Assume $PRN \geq 1$, then

$$a^m b \geq (a+D)^m\left(1 + \frac{D}{k\overline{S}}\right) > (a+D)^m,$$

hence $S^* > 0$. And recall $D(R_0 - R^*) = f_S(R^*)S^*$. Let $h_L(R) = D(R_0 - R)$ and $h_R(R) = f_S(R)S^*$. Obviously both functions are continuous. Moreover, $h_L(R)$ is a strictly decreasing function with $h_L(0) = DR_0$ and $h_L(R_0) = 0$. And $h_R(R)$ is a strictly increasing function, we have $h_R(0) = 0$ by **(F1)** and $h_R(R_0) = f_S(R_0)S^* > 0$. Therefore, there exists a unique $R^* \in (0, R_0)$. In particular, if $PRN \geq 1$,

$$h_R(R_S) = DS^* = \frac{D^2\overline{S}(a+D)^m}{a^m b k\overline{S} - (a+D)^m k\overline{S}} = \frac{D^2\overline{S}}{PRN(D + k\overline{S}) - k\overline{S}} \leq D\overline{S} = h_L(R_S),$$

thus $R^* \in (R_S, R_0)$ and consequently $P^* \geq 0$. The non-negativity of I_j^* hence follows.

On the other hand, note $h_R(R_S) \leq h_L(R_S)$ only if $PRN \geq 1$, so $PRN \geq 1$ is a necessary condition for $P^* \geq 0$.

For E_{SMP}, assume $MRN \geq 1$. Then $f_M(R^*) \geq D = f_M(R_M)$. By the monotonicity of f_M, it is equivalent to $R^* \geq R_M$. Clearly it implies $R^* > R_S$ and hence $P^\# > 0$. Also in this case, by using the same $h_L(R)$ and $h_R(R)$, it is easy to conclude $PRN > 1$, so $S^* > 0$ and

$$M^\# \geq R_0 - R^* - \frac{f_S(R^*)}{D} S^* = 0.$$

The non-negativity of $I_j^\#$'s are trivial.

Conversely, suppose E_{SMP} is non-negative, then $M^\# \geq 0$ implies $h_L(R_M) \geq f_S(R_M)S^*$, thus $R^* \geq R_M$ follows and consequently $MRN \geq 1$ is a necessary condition. $\qquad\square$

We can summarize the existence conditions and local stabilities of equilibria of (4.3) by the Table 3.

Table 3.Equilibria and local stability of ODE model (4.3)

Equilibrium	Existence Condition	Stability
$E_R = (R_0, 0, \ldots, 0)$	always exists	unstable by (**F1**)
$E_S = (R_S, \overline{S}, 0, \ldots, 0)$	always exists	see Theorem 4.3.1
$E_M = (R_M, 0, \overline{M}, 0, \ldots, 0)$	always exists	unstable by (**F2**)
$E_{SP} = (R^*, S^*, 0, I_1^*, \ldots, I_m^*, P^*)$	$PRN \geq 1$	Corollary 4.4.4
$E_{SMP} = (R_M, S^*, M^\#, I_1^\#, \ldots, I_m^\#, P^\#)$	$MRN \geq 1$	unknown

4.4 Bifurcation Analysis

In this section we choose b as a bifurcation parameter and assume all other parameter values are fixed. By varying b, we can investigate local stability changes of E_{SP} and E_{SMP}.

Note PRN for system (4.3) is given by (4.5), hence it is an increasing function on b. When $b > 1$ is small, $PRN < 1$ and E_{SP} does not exists. There exists a unique b^* such that $PRN = 1$ and E_{SP} appears at $b = b^*$.

The following theorem states that E_S undergoes a transcritical bifurcation and loses its stability to E_{SP} at this critical value b^*.

Theorem 4.4.1. *Let*
$$b^* = \frac{(a+D)^m(D+k\overline{S})}{a^m b k \overline{S}},$$
then E_S undergoes a transcritical bifurcation at $b = b^*$. As b increases and exceeds b^*, E_S becomes unstable and E_{SP} becomes a non-negative equilibrium and gains the stability.

Proof. Let $F(b, \mathbf{x}) : \mathbb{R}_+ \times \mathbb{R}_+^{m+4}$ denote the vector field of (4.3) with bifurcation parameter b.

When $b = b^*$, E_S and E_{SP} coincide and 0 is a simple root of characteristic equation (4.6). The right and left eigenvectors associated with the 0 eigenvalue are
$$\mathbf{v}_R = (\frac{k}{f_S'(R_S)}, -\frac{k(D+f_S'(R_S))}{f_S'(R_S)}, 0, \frac{k\overline{S}}{a+D}, \frac{ak\overline{S}}{(a+D)^2}, \dots, \frac{a^{m-1}k\overline{S}}{(a+D)^m}, 1)^T,$$
$$\mathbf{v}_L = (0, 0, 0, \left(\frac{a}{a+D}\right)^m b^*, \left(\frac{a}{a+D}\right)^{m-1} b^*, \dots, \frac{a}{a+D} b^*, 1),$$
respectively.

A calculation shows that
$$\frac{\partial^2 F}{\partial b \partial \mathbf{x}}\bigg|_{(E_S, b^*)} = \begin{pmatrix} 0 & 0 \\ 0 & \frac{\partial J_2}{\partial b} \end{pmatrix},$$

the $(m+1, m)$ entry of $\frac{\partial J_2}{\partial b}$ is 1 and all others vanish. Thus

$$\mathbf{v}_L \left(\left. \frac{\partial^2 F}{\partial b \partial \mathbf{x}} \right|_{(E_S, b^*)} \right) \mathbf{v}_R = \frac{a^m b^* k \overline{S}}{(a+D)^m} = D + k \overline{S} \neq 0.$$

Write $\mathbf{v}_R = (\eta_1, \eta_2, \eta_3, \xi_1, \xi_2, \ldots, \xi_m, 1)$, the second derivative of the vector field at (E_S, b^*) with respect to the direction $(\mathbf{v}_R, \mathbf{v}_R)$ is

$$D_{\mathbf{x}}^2 F(E_S, b^*)(\mathbf{v}_R, \mathbf{v}_R) = \frac{d}{ds} \begin{pmatrix} * \\ * \\ * \\ -(a+D)\eta_1 + k(\overline{S} + s\eta_2) \\ a\xi_1 - (a+D)\xi_2 \\ \vdots \\ a\xi_{m-1} - (a+D)\xi_m \\ ab^*\xi_m - (D + k(\overline{S} + s\eta_2)) \end{pmatrix} = \begin{pmatrix} * \\ * \\ * \\ k\eta_2 \\ 0 \\ \vdots \\ 0 \\ -k\eta_2 \end{pmatrix}.$$

So $\mathbf{v}_L[D_{\mathbf{x}}^2 F(E_S, b^*)(\mathbf{v}_R, \mathbf{v}_R)] = -\frac{D}{\overline{S}} \frac{k(D + f_S'(R_S))}{f_S'(R_S)} \neq 0.$

According to Theorem 4.3.1 in Guckenheimer and Holmes [17], (4.3) undergoes a transcritical bifurcation when $b = b^*$.

Now let's turn to the stability analysis of E_S. Since $\lambda = 0$ is a simple root of (4.6), the implicit function theorem applies. There exists a function $\xi(b)$ such that $\theta_S(\xi(b), b) = 0$ when b is close enough to b^*.

The calculation shows that

$$\left. \frac{\partial \theta_S}{\partial \lambda} \right|_{(0, b^*)} = D f_S'(R_S) \overline{S} (D - f_M(R_S)) \left((m(D + k\overline{S}) + a + D)(a+D)^{m-1} \right) > 0,$$

$$\left. \frac{\partial \theta_S}{\partial b} \right|_{(0, b^*)} = -a^m k \overline{S} < 0,$$

hence $\xi'(b_1) = - \left(\left. \frac{\partial \theta_S}{\partial \lambda} \right|_{(0, b^*)} \right) \left(\left. \frac{\partial \theta_S}{\partial b} \right|_{(0, b^*)} \right) > 0$. That is, $\theta_S(\lambda)$ has a positive real root when $b > b^*$ but close enough, and E_S loses the stability at $b = b^*$.

A similar argument shows that E_{SP} gains the stability. The characteristic equation of E_{SP} is

$$\theta_{SP}(\lambda) = (\lambda + D)(\lambda - f_M(R^*) + D)\left[(\lambda + a + D)^m \theta_{SP,1}(\lambda) - a^m bkS^* \theta_{SP,2}(\lambda)\right],$$

(4.7)

where

$$\theta_{SP,1}(\lambda) = \lambda^2 + (D + f_S'(R^*)S^* + kS^*)\lambda + f_S'(R^*)S^*(f_S(R^*) + kS^*) - k^2 S^* P^*,$$

$$\theta_{SP,2}(\lambda) = \lambda - kP^* + f_S'(R^*)S^*.$$

Taking the partial derivatives shows that

$$\left.\frac{\partial \theta_{SP}}{\partial \lambda}\right|_{(0,b^*)} = D(D - f_M(R_S))(a + D)^{m-1}((m(D + k\bar{S}) + (a + D)f_S'(R_S)\bar{S})) > 0,$$

$$\left.\frac{\partial \theta_{SP}}{\partial b}\right|_{(0,b^*)} = D(D - f_M(R_S))(a + D)^m \left(D\left.\frac{dP^*}{db}\right|_{b=b^*}\right) > 0.$$

Therefore, there exists a function $\eta(b)$ such that $\theta_{SP}(\eta(b), b) = 0$ for b close enough to b^* and $\eta'(b^*) < 0$. Namely, $\theta_{SP}(\lambda)$ has a negative real root if $b - b^* > 0$ but small. And all other roots have negative real parts by the continuous dependence. Thus E_{SP} gains the stability after this transcritical bifurcation. $\square$

The bifurcation analysis for E_{SP} is more complicated. From the characteristic equation (4.7), it is easy to see when $R^* > R_M$, or equivalently, $MRN > 1$, E_{SP} is unstable because $\lambda = f_M(R^*) - D > 0$ is a positive real root. However, when $MRN < 1$, the local stability of E_{SP} is determined by the bracket factor in $\theta_{SP}(\lambda)$. We will investigate roots of this factor by using Rouché's theorem. To apply this theorem, we first introduce a new polynomial $\theta_{SP}^\infty(\lambda)$, it is obtained by letting $b \to \infty$ in the bracket term of $\theta_{SP}(\lambda)$. Then we show $\theta_{SP}^\infty(\lambda)$ has roots with positive real parts, thus Rouché's theorem implies at least one root of $\theta_{SP}(\lambda)$ has positive real parts when b is large enough. And by the continuous dependence of

roots on parameters, $\theta_{SP}(\lambda)$ has a pair of purely imaginary root at some critical value $b = b_b$. This idea is carried out rigorously by the following theorems.

Lemma 4.4.2. *Let $\theta_{SP}^\infty(\lambda)$ be defined as*

$$\theta_{SP}^\infty(\lambda) = (\lambda + a + D)^m(\lambda^2 + D\lambda) + D(a + D)^m(f_1(R_0) - D - \lambda),$$

then it has a pair of conjugate complex roots with positive real parts and all other roots have negative real parts.

Proof. We first show that $\theta_{SP}^\infty(\lambda) = 0$ has at least one pair of complex roots with positive real parts.

A simple calculation shows that the linear term of $\theta_{SP}^\infty(\lambda)$ vanishes, that is, the coefficient of λ is 0. And the constant term is not 0, hence 0 is a not a root of $\theta_{SP}^\infty(\lambda)$. Note all other coefficients are strictly positive, by Descartes' rule of signs, since there is no sign changes between coefficients, $\theta_{SP}^\infty(\lambda) = 0$ has no positive real roots. And it is easy to verify 0 is not a root.

Since every real coefficient polynomial can be written as a product of irreducible quadratic terms and linear terms, we can formally factorize θ_{SP}^∞ as

$$\theta_{SP}^\infty(\lambda) = \prod_{i=1}^{p}(\lambda + a_i)\prod_{j=1}^{q}(\lambda^2 + b_j\lambda + c_j), \tag{4.8}$$

where $p, q \in \mathbb{Z}_+$ and $a_i, b_j, c_j \in \mathbb{R}$. Note if any $a_i = 0$ or $c_j = 0$, 0 will be a root of $\theta_{SP}^\infty(\lambda)$, hence all a_i's and c_j' are non-zero.

Suppose any $a_i < 0$, $\lambda = -a_i > 0$ is a positive real root of $\theta_{SP}^\infty(\lambda)$, which contradicts the conclusion of Descartes' rule of signs.

Thus hereafter we assume $a_i > 0$ for all $1 \le i \le p$.

If any $c_j < 0$, the discriminant of the corresponding quadratic term is

$$b_j^2 - 4c_j > 0,$$

thus this term can be further factorized as the product of two real linear terms, which contradiction the irreducibility of quadratic terms. Hence all c_j's must be positive.

In (4.8), we can calculate the coefficient of λ and it gives

$$\left(\prod_{j=1}^{q} c_j\right)\left[\sum_{i=1}^{p}\frac{\prod_{l=1}^{p} a_l}{a_i}+\sum_{j=1}^{q}\frac{b_j}{c_j}\right],$$

and it equals 0 because the coefficient of λ in $\theta_{SP}^{\infty}(\lambda)$ vanishes.

Since all a_i's are positive, the first term in the bracket is strictly positive. And consequently, the second term is strictly negative. Since all c_j's are positive, there exists at least one j_0 such that $b_{j_0} < 0$, and two roots of the corresponding quadratic term $\lambda^2 + b_{j_0}\lambda + c_{j_0}$ are

$$\lambda_{1,2} = \frac{-b_{j_0} \pm \sqrt{b_{j_0}^2 - 4c_{j_0}}}{2},$$

since this is an irreducible quadratic term, the discriminant is strict negative and real part of $\lambda_{1,2}$ is $-\frac{b_{j_0}}{2} > 0$.

Thus $\theta_{SP}^{\infty}(\lambda)$ has at least one pair of complex roots with positive real parts.

Now we show that $\theta_{SP}^{\infty}(\lambda)$ has at most one two roots with positive real parts. Let's start from

$$\widetilde{\theta}_{SP}^{\infty}(\lambda) = (\lambda + a + D)^m (\lambda + D) = a_{m+1}\lambda^{m+1} + a_m\lambda^m + \ldots a_1\lambda + a_0,$$

then its Routh-Hurwitz table can be written as

$$
\begin{array}{ccccccc}
a_{m+1} & a_{m-1} & a_{m-3} & \cdots & a_5 & a_3 & a_1 \\[4pt]
a_m & a_{m-2} & a_{m-4} & \cdots & a_4 & a_2 & a_0 \\[4pt]
\xi_{3,1} & \xi_{3,2} & \xi_{3,3} & \cdots & \xi_{3,\frac{m}{2}-1} & \xi_{3,\frac{m}{2}} & \\[4pt]
\xi_{4,1} & \xi_{4,2} & \xi_{4,3} & \cdots & \xi_{4,\frac{m}{2}-1} & \xi_{4,\frac{m}{2}} & \\[4pt]
\vdots & \vdots & \vdots & \iddots & & & \\[4pt]
\xi_{m-2,1} & \xi_{m-2,2} & 0 & & & & \\[4pt]
\xi_{m-1,1} & \xi_{m-1,2} & 0 & & & & \\[4pt]
\xi_{m,1} & 0 & & & & & \\[4pt]
\xi_{m+1,1} & 0 & & & & &
\end{array}
$$

Since all roots of $\widetilde{\theta}^{\infty}_{SP}(\lambda)$ are real and strictly negative, there is no sign change in the first column of this table.

Similarly, note $\theta^{\infty}_{SP}(\lambda)$ can be written as

$$
\theta^{\infty}_{SP}(\lambda) = a_{m+1}\lambda^{m+2} + a_m\lambda^{m+1} + \cdots + a_1\lambda^2 + a_{-1}.
$$

Its Routh-Hurwitz table is (the star superscript means this entry is different from the above table for $\widetilde{\theta}_{SP}^{\infty}(\lambda)$):

a_{m+1}	a_{m-1}	a_{m-3}	$\cdots$	a_5	a_3	a_1	a_{-1}
a_m	a_{m-2}	a_{m-4}	$\cdots$	a_4	a_2	0	0
$\xi_{3,1}$	$\xi_{3,2}$	$\xi_{3,3}$	$\cdots$	$\xi_{3,\frac{m}{2}-1}$	$\xi_{3,\frac{m}{2}}^{*}$	a_{-1}	
$\xi_{4,1}$	$\xi_{4,2}$	$\xi_{4,3}$	$\cdots$	$\xi_{4,\frac{m}{2}-1}$	$\xi_{4,\frac{m}{2}}^{*}$	0	
$\vdots$	$\vdots$	$\vdots$	$\cdot^{\cdot^{\cdot}}$				
$\xi_{m-2,1}$	$\xi_{m-2,2}^{*}$	a_{-1}					
$\xi_{m-1,1}$	$\xi_{m-1,2}^{*}$	0					
$\xi_{m,1}^{*}$	a_{-1}						
$\xi_{m+1,1}^{*}$	0						
a_{-1}							

Note the only changes in the first column are $\xi_{m,1}^{*}$, $\xi_{m+1,1}^{*}$, and adding a_{-1}, hence there are at most three sign changes. Namely, $\theta_{SP}^{\infty}(\lambda)$ has at most three roots with positive real parts. Similarly, if assume m is odd, we can deduce that $\theta_{SP}^{\infty}(\lambda)$ has at most two roots with positive real parts.

However, as shown above, $\theta_{SP}^{\infty}(\lambda)$ has no positive real roots and at least one pair of complex roots with positive real parts, so the only possibility is $\theta_{SP}^{\infty}(\lambda)$ has exactly one pair of complex roots with positive real parts. $\qquad\square$

And now we can apply Rouché's theorem and conclude that $\theta_{SP}(\lambda)$ has purely imaginary roots at some critical value $b = b_h$.

Theorem 4.4.3. *There exists a unique $b_h > b^*$ such that the bracket term in $\theta_{SP}(\lambda)$, i.e.,*

$$\theta_{SP}^{0}(\lambda) = (\lambda + a + D)^{m}\theta_{SP,1}(\lambda) - a^{m}bkS^{*}\theta_{SP,2}(\lambda) \qquad (4.9)$$

has a pair of purely imaginary roots at $b = b_h$.

Proof. We first show (4.9) has at least one root lies in the open right half-plane for large b.

By the previous lemma, we know that there exists z_0 with $\Re z_0 > 0$ such that $\theta_{SP}^\infty(z_0) = 0$. Pick $\delta > 0$ small enough such that $K = \{z \in \mathbb{C} : |z - z_0| < \delta\}$ lies in the open right half-plane and $\theta_{SP}^\infty(z) \neq 0$ on ∂K. By the compactness of ∂K, there exists $z_{\min} \in \partial K$ such that $|\theta_{SP}^\infty(z_{\min})| = \min\{|\theta_{SP}^\infty(z)| : z \in \partial K\} > 0$.

Define the difference between $\theta_{SP}^\infty(\lambda)$ and $\theta_{SP}^0(\lambda)$ as

$$\theta_{SP}^\#(\lambda) = (\lambda + a + D)^m((f_S'(R^*)S^* + kS^*)\lambda + f_S'(R^*)S^*(f_S(R^*) + kS^*))$$
$$- (a + D)^m D f_S'(R^*)S^* - (a + D)^m kS^*(\lambda - kP^* + f_S'(R^*)S^*),$$

then $\theta_{SP}^0(\lambda) = \theta_{SP}^\infty(\lambda) + \theta_{SP}^\#(\lambda)$.

As $b \to \infty$, $S^* \to 0$, $R^* \to R_0$ and every term is bounded, hence for every $\epsilon > 0$, we can choose $b_\epsilon > b^*$ such that for all $b > b_\epsilon$,

$$f_S'(R^*)S^* + kS^* < \epsilon,$$

$$|f_S'(R^*)S^*(f_S(R^*) + kS^*)| < \epsilon,$$

$$(a + D)^m D f_S'(R^*)S^* < \epsilon,$$

$$(a + D)^m kS^* < \epsilon,$$

$$|(a + D)^m kS^*(-kP^* + f_S'(R^*)S^*)| < \epsilon.$$

Thus

$$|\theta_{SP}^\#(z)| < \epsilon|(z + a + D)^m|(|z| + 1) + \varepsilon(|z| + 2).$$

And there exists $z_\epsilon \in \partial K$ such that

$$|\theta_{SP}^\#(z)| \leq \epsilon|(z_\epsilon + a + D)^m|(|z_\epsilon| + 1) + \epsilon(|z_\epsilon| + 2),$$

for all $z \in \partial K$.

By choosing ϵ small enough, we can obtain that

$$|\theta_{SP}^\#(z)| < |\theta_{SP}^\infty(z_{\min})| < |\theta_{SP}^\infty(z)|$$

on ∂K. Therefore, by applying Rouché's theorem, $\theta^0_{SP}(\lambda)$ and $\theta^\infty_{SP}(\lambda)$ have the same number of roots in K. That is, for $b > b^\#$, $\theta_{SP}(\lambda)$ has at least one root with positive part.

Note for any $b > b^*$, 0 is not a root of $\theta^0_{SP}(\lambda)$ because its constant term is

$$f'_S(R^*)S^*P^* + DkP^* > 0.$$

Therefore, by the continuous dependence on b, at some b in $(b^*, b^\#)$, $\theta^0_{SP}(\lambda)$ has a root with 0 real part. And its imaginary part is non-zero because 0 is not a root for $\theta^0_{SP}(\lambda)$ when $b > b^*$. Namely, it is a purely imaginary root.

Define

$$b_h = \min\{b > b^* : \theta^0_{SP})(\lambda) = 0 \text{ has a pair of purely imaginary roots}\},$$

then all roots of $\theta^0_{SP}(\lambda)$ have negative real parts and the proof is complete. □

Note Theorem 4.4.3 studies only $\theta^0_{SP}(\lambda)$, i.e., the bracket factor of $\theta_{SP}(\lambda)$. If we define
$$b_M = \left(\frac{a+D}{a}\right)^m \left(\frac{1}{k}\frac{f_S(R_M)}{M} + 1\right),$$
when b increases and exceeds b_M, E_{SP} will have a positive real root $\lambda = f_M(R^*) - D$, hence it is no longer stable. By taking this factor into account, we have the following corollary:

Corollary 4.4.4. E_{SP} *is locally asymptotically stable for all* $b \in (b^*, \min\{b_h, b_M\})$.

Proof. Note

$$\theta_{SP}(\lambda) = (\lambda + D)(\lambda - f_M(R^*) + D)\theta^0_{SP}(\lambda),$$

and by Theorem 4.4.3 and the definition of b_M, all roots of $\theta_{SP}(\lambda)$ have negative real parts when $b \in (b^*, \min\{b_h, b_M\})$. □

Ideally, we want to show that E_{SP} undergoes a Hopf bifurcation at $b = b_h$ if $b_h < b_M$, nevertheless, due the computational difficulty, whether E_{SP} undergoes a supercritical Hopf bifurcation is still left open. But we can briefly illustrate the outline of this idea here. As it has been proved above, $\theta_{SP}(\lambda)$ has purely imaginary roots $\lambda = \pm i\omega_0$ at $b = b_h$, assume $\lambda = \mu + i\omega$, then

$$\Re\theta_{SP}(\mu + i\omega, 0)|_{(0,\omega_0,b_h)} = 0,$$

$$\Im\theta_{SP}(\mu + i\omega, 0)|_{(0,\omega_0,b_h)} = 0,$$

Since $\theta_{SP}(\lambda)$ is an analytic function, its derivatives satisfy Cauchy-Riemann equation, hence

$$\left| \frac{\partial \theta_{SP}}{\partial \lambda} \right|_{(0,\omega_0,b_h)} = \begin{vmatrix} \frac{\partial \Re\theta_{SP}}{\partial \mu} & \frac{\partial \Re\theta_{SP}}{\partial \omega} \\ -\frac{\partial \Re\theta_{SP}}{\partial \omega} & \frac{\partial \Re\theta_{SP}}{\partial \mu} \end{vmatrix} = \left(\frac{\partial \Re\theta_{SP}}{\partial \mu} \right)^2 + \left(\frac{\partial \Re\theta_{SP}}{\partial \omega} \right)^2 > 0,$$

and the implicit function theorem applies. And consequently,

$$\begin{pmatrix} \frac{d\mu}{db} \\ \frac{d\omega}{db} \end{pmatrix} \Bigg|_{(0,\omega_0,b_h)} = -\left(\frac{\partial \theta_{SP}}{\partial \lambda} \right)^{-1} \begin{pmatrix} \frac{\partial \Re\theta_{SP}}{\partial b} \\ \frac{\partial \Im\theta_{SP}}{\partial b} \end{pmatrix} \Bigg|_{(0,\omega_0,b_h)}$$

$$= \frac{-1}{\left(\frac{\partial \Re\theta_{SP}}{\partial \mu} \right)^2 + \left(\frac{\partial \Re\theta_{SP}}{\partial \omega} \right)^2} \begin{pmatrix} \frac{\partial \Re\theta_{SP}}{\partial \mu} & -\frac{\partial \Re\theta_{SP}}{\partial \omega} \\ \frac{\partial \Re\theta_{SP}}{\partial \omega} & \frac{\partial \Re\theta_{SP}}{\partial \mu} \end{pmatrix} \begin{pmatrix} \frac{\partial \Re\theta_{SP}}{\partial b} \\ \frac{\partial \Im\theta_{SP}}{\partial b} \end{pmatrix} \Bigg|_{(0,\omega_0,b_h)}$$

$$= \frac{-1}{\left(\frac{\partial \Re\theta_{SP}}{\partial \mu} \right)^2 + \left(\frac{\partial \Re\theta_{SP}}{\partial \omega} \right)^2} \begin{pmatrix} \frac{\partial \Re\theta_{SP}}{\partial \mu}\frac{\partial \Re\theta_{SP}}{\partial b} - \frac{\partial \Re\theta_{SP}}{\partial \omega}\frac{\partial \Im\theta_{SP}}{\partial b} \\ \frac{\partial \Re\theta_{SP}}{\partial \omega}\frac{\partial \Re\theta_{SP}}{\partial b} + \frac{\partial \Re\theta_{SP}}{\partial \mu}\frac{\partial \Im\theta_{SP}}{\partial b} \end{pmatrix} \Bigg|_{(0,\omega_0,b_h)}.$$

Therefore, if we can show

$$\frac{\partial \Re\theta_{SP}}{\partial \mu}\frac{\partial \Re\theta_{SP}}{\partial b} - \frac{\partial \Re\theta_{SP}}{\partial \omega}\frac{\partial \Im\theta_{SP}}{\partial b} \Bigg|_{(0,\omega_0,b_h)} < 0, \qquad (4.10)$$

then E_{SP} undergoes a supercritical Hopf bifurcation at $b = b_h$. And if (4.10) is true for every $b > b^*$ such that $\theta_{SP}^0(\lambda)$ has a pair of purely imaginary roots, then

geometrically, every pair of purely imaginary roots cross the imaginary axis from left to right. As $\theta_{SP}^{\infty}(\lambda)$ has only one pair of complex roots with positive real parts, we claim that b_h is the unique critical value such that $\theta_{SP}^{0}(\lambda)$ has a pair of purely imaginary roots.

Note that in (4.10), to study $\frac{\partial \Re \theta_{SP}}{\partial b}$ and $\frac{\partial \Im \theta_{SP}}{\partial b}$, we also need more assumptions on $f_S(R)$. To be more precise, since $f_S'(R^*)$ varies as b increases, we need to know the sign of $f_S''(R^*)$. Apparently letting f_S be a concave function is a reasonable choice, however, it seems showing (4.10) is still very difficult with this additional assumption.

In section 5.3, we are able to perform a numerical simulation and observe the local stability of E_{SP}. By choosing different parameter values, we can see that E_{SP} may undergo a Hopf bifurcation at some $b_h < b_M$ or loses its stability to E_{SMP} if $b_h > b_M$. For more details, please see Figure 3 and Figure 4.

4.5   Persistence Results

Due to the nature that (4.3) is a special case of (2.7), all persistence and extinction results proved in Chapter 3 should apply to (4.3) without any difficulties.

However, since (4.3) is an ODE system and $b(\tau)$ is assumed to be a constant b, there are a few remarks that worth to be emphasize here.

The first fact is that since $b(\tau)$ is a constant, the conclusion of Theorem 2.3.4 can be improved:

Theorem 4.5.1. *Let*

$$Y := R + S + M + \frac{b}{b-1}\sum_{j=1}^{m}I_j + \frac{1}{b-1}P,$$

then $Y \to R_0$ as $t \to \infty$.

Theorem 4.5.1 together with Corollary 4.2.2 imply that K_O is a subset of the the hyperplane $\{y \in \mathbb{R}_+^{m+4} : Y = R_0\}$.

For persistence results, we can apply the corresponding theorem to this special case. Or by using the same argument and the following remarks, we can prove it directly.

For susceptible bacteria S, note Lemma 3.2.1 still holds for (4.3) because it is independent from the differential equation of P and I. And Lemma 3.2.2 is true by replacing $\frac{D}{Bk}$ with $\frac{D}{(b-1)k}$, it is because by replacing (3.8) with

$$\left(\frac{b}{b-1}\sum_{i=1}^{m}I_j + \frac{1}{b-1}P\right)'(t) = -D\left(\frac{b}{b-1}\sum_{i=1}^{m}I_j + \frac{1}{b-1}P\right)(t) + kS(t)P(t),$$

we can obtain that

$$0 \le ((b-1)kS^\infty - D)\left(\frac{b}{b-1}\sum_{i=1}^{m}I_j + \frac{1}{b-1}P\right)^\infty$$

by using the fluctuation argument (and possibly after a time-shift). So the argument of Lemma 3.2.2 will work for (4.3) after this treatment.

The persistence and extinction of phages P as well as I_j's are determined by PRN. However, (3.10) should be updated accordingly. Notice

$$(\lambda + a + D)\widehat{I_1}(\lambda) = I_1(0) + k\widehat{SP}(\lambda),$$

$$(\lambda + a + D)\widehat{I_j}(\lambda) = I_j(0) + a\widehat{I_{j-1}}(\lambda), \qquad 2 \le j \le m,$$

$$(\lambda + D)\widehat{P}(\lambda) = P(0) - k\widehat{SP}(\lambda) + ab\widehat{I_m}(\lambda).$$

Since $\lambda \ge 0$,

$$\widehat{I_m}(\lambda) = \frac{I_m(0) + a\widehat{I_{m-1}}(\lambda)}{\lambda + a + D} \le \frac{a}{a+D}\widehat{I_{m-1}} + \frac{I_m(0)}{a+D}$$

$$\le \cdots \le \frac{a^{m-1}}{(a+D)^m}\widehat{SP}(\lambda) + \sum_{j=1}^{m}\frac{a^{m-j}}{(a+D)^{m-j+1}}I_j(0).$$

Thus by replacing (3.10) with

$$(\lambda + D)\widehat{P} \le P(0) + \left[\left(\frac{a}{a+D}\right)^m b - 1\right]k\widehat{SP}(\lambda) + \sum_{j=1}^{m}\frac{a^{m-j}}{(a+D)^{m-j+1}}I_j(0),$$

Theorem 3.3.1 and 3.3.3 can be proved for (4.3) by using the same idea (the phase space is $\mathbb{R}^{m+4}_+$ instead of $\mathscr{B}^+_D$).

And for the persistence of M, the same argument can be used for (4.3) with slight modification on phase space. However, sufficient conditions for the locally asymptotic stability of E_{SP} seem to be easier to verify.

In this chapter we introduced a new model (4.3) as a special case of (2.7). By using "linear chain trick", we can reduce a system involving infinite distributed delay terms (Gamma distribution) into a system consists of ordinary differential equations. Solutions of (2.7) give rise to solutions of (4.3) and vice versa. Not surprisingly, all standard results, such as positivity and boundedness of solutions, apply to (4.3). In particular, we also proved the equivalency between compact global attractors of (2.7) and (4.3). Since all asymptotic behaviors of trajectories are reflected by the attractor, this equivalency serves an essential role in this research. And lastly, it is not difficult to give similar proofs of persistence and extinction of species for (4.3) as in Chapter 3.

In the following chapter we will take the advantage of (4.3) being an ODE system, so that we can run numerical simulations with a bunch of ODE software to analyze local stabilities of equilibria as well as compact global attractors.

CHAPTER 5

SIMULATION

In this chapter we will present some simulation results and observations. Since (2.7) is a complicated model which involves infinite delay terms, it is very difficult to simulate and plot bifurcation diagrams for (2.7). Thus in this chapter we will mainly focus on (4.3).

For ODE system (4.3), we investigate local stability of E_{SP} and E_{SMP}. As mentioned before, stability of these two equilibria are still not clearly known yet due to the computational difficulty, however, since characteristic equations of E_{SP} and E_{SMP} are polynomials hence it is much easier to locate purely imaginary roots as well as roots with positive real parts.

And later we will show bifurcation diagrams in two different scenarios, as well as trajectories for each parameter value set. For both parameter value sets, E_{SP} are unstable and there exist periodic orbits bifurcated from E_{SP} in the subspace $\{M \equiv 0\}$. However, one example showed that this periodic orbit is attracting all orbits starting with $M(0) > 0$, and the other one is more interesting because we observe that there exists another stable period orbit in $\{M > 0\}$ and attracts all orbit with positive $M(0)$.

To perform the simulation, we further simplify (4.3) by adopting the following assumption:

F3. $f_M(R) = (1 - \varepsilon)f_S(R)$ and both functions are of Michaelis-Menten type.

The parameter ε can be consider as the cost of a bacteria to become resistant to the phage infection.

The main tool we used for simulation is Mathematica and XPP-AUTO, some figures are enhanced by Inkscape (adding labels and legends). The detailed technique and algorithm will be explained in the corresponding sections.

5.1   Parameter Evaluation

Though the abstract chemostat has a simple structure, the practical device in the laboratory is still very complicated and consists of numerous subsystems. However, biologists and technicians are able to measure different types of quantitative values during the experiment and determine parameter values.

For example, Bohannan and Lenski [8] studied the bacteria-phage interaction with different concentration of glucose in the input flows. Not only did they performed a series of experiments, they also presented different mathematical models inherited from Levin, Stewart and Chao [26] and other research projects. For the simulation purpose, [8] also listed important parameter values either from the authors' observation or previous studies. Those parameters are experimental data so we will adopt them and run a simulation on (4.3) accordingly.

In [8], the authors took the yield constant of bacteria species into account, as mentioned before, we can assume yields constants are 1 by rescaling parameters and variables. The following table is a quick summary of parameter values we adopt from [8] and other references:

Since models studied in [8] involve a single discrete delay, $\tau = 0.5$h is assumed to be a constant. However, for (4.3), the mean of Gamma distribution $g_m(s, a)$ is $\frac{m}{a}$ and it represents the average latent period, we assume $m = 5$ and $a = 10$, so that the average delay is 0.5h for (4.3) too.

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Table 4.List of Parameter Values and Response Functions for Simulation

Parameter	Unit	Value	Scaled Value	Source
R_0	mg/L	0.178212	0.178212	[29]
D	h^{-1}	0.2	0.2	[8]
k	ml/h	3×10^{-7}	0.15	[8, 25]
τ	h	0.5	0.5	[13]
$f_S(R)$		$\frac{0.7726}{0.0727+R}$	$\frac{0.7726}{0.0727+R}$	[8, 39]

5.2   Equilibria and Local Stability

In this section we will investigate local stability of E_{SP} and E_{SMP}. We use numerical methods to locate purely imaginary roots for characteristic equations of E_{SP} and E_{SMP}.

We take b and ε as two varying parameters and assume all others are fixed. Recall that $f_M(R) = (1 - \varepsilon)f_S(R)$ as assumed in (**F3**).

To investigate stability of E_{SP} and E_{SMP}, as well as existence and stability of periodic solutions, we present Figure 1 and Figure 2 below. Both Figures are plotted in the ε-b parameter space, E_{SP} is shown by a pentagram and E_{SMP} is represented by a triangle. A solid symbol (pentagram or triangle) means a locally asymptotically stable equilibrium while a hollow symbol stands for an unstable equilibrium. Circles are periodic orbits, a solid circle represents a stable period orbit and the dashed line indicates an unstable period orbit.

Notice that Figure 2 is a continuation of Figure 1 for large ε but their scales are different. In order to display the dynamics for large ε more clearly, the horizontal scale is expanded.

Now let's turn to details of Figure 1 and Figure 2.

The horizontal line $\mathbf{T}_1$ at the very bottom of both figures is where $PRN = 1$. Since PRN is independent from $f_M(R)$ hence independent from ε, $\mathbf{T}_1$ is hor-
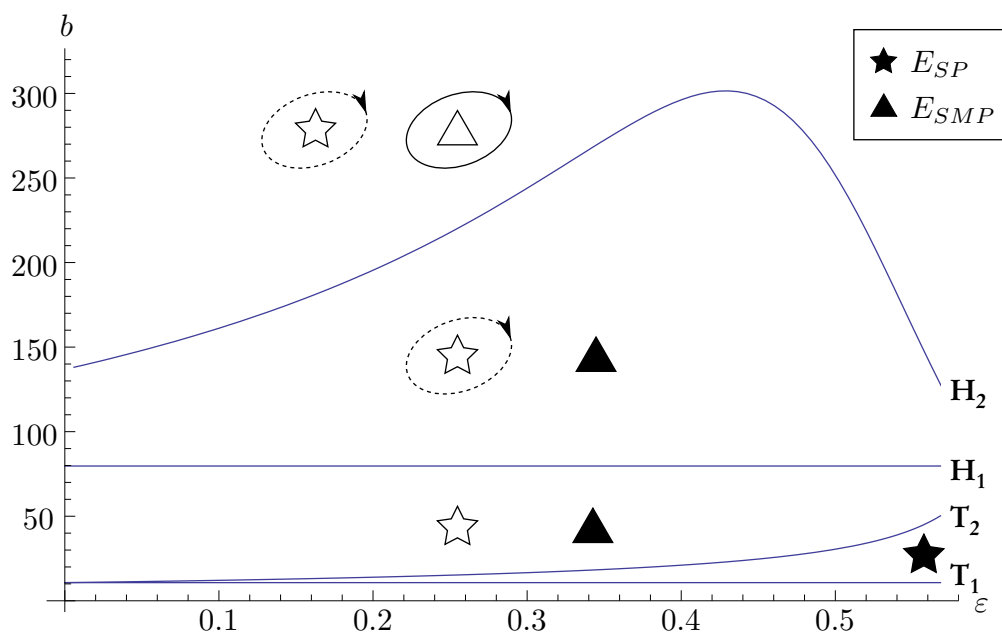
Figure 1.Equilibria, periodic orbits, and their stability in ε-b parameter space (small ε).
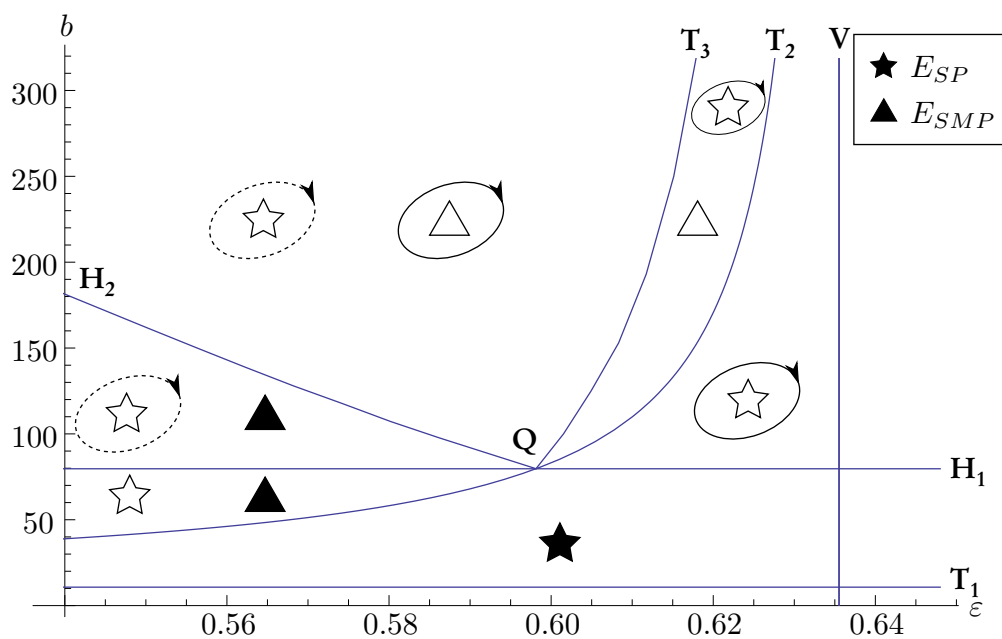
Figure 2.Equilibria, periodic orbits, and their stability in ε-b parameter space (blow-up of large ε).

izontal. $\mathbf{T_1}$ is solved explicitly from the equation $PRN = 1$. If b is below $\mathbf{T_1}$, neither E_{SP} nor E_{SMP} is a non-negative equilibrium, by Theorem 3.3.3 and Theorem 3.2.1, E_S attracts all orbits with $S(0) > 0$. For b beyond $\mathbf{T_1}$, E_{SP} exists and is stable in the region immediately above it.

The other horizontal line above $PRN = 1$ is $\mathbf{H_1}$, it is the line along which a periodic orbit bifurcates from E_{SP} in the $\{M \equiv 0\}$ subspace, since the only factor in the characteristic equation (4.7) which contains f_M is $\lambda - f_M(R^*) + D$, varying ε may affect the stability of E_{SP} but no purely imaginary roots are associated to this factor. Thus $\mathbf{H_1}$ is again horizontal. $\mathbf{H_1}$ is computed numerically by Mathematica by searching a smallest b_h such that (4.7) has a pair of purely imaginary root. The existence of such b_h is guaranteed by Theorem 4.4.3.

The vertical line $\mathbf{V}$ in Figure 2 is the maximal value of ε, which is solved analytically by setting $(1 - \varepsilon)f_S(R_0) = D$, if ε exceeds this value, $f_M(R_0) < D$ and consequently M goes extinct.

The increasing curve $\mathbf{T_2}$ represents $MRN = 1$, since ε matters, this is no longer a horizontal line. $\mathbf{T_2}$ is determined analytically by setting $MRN = 1$, to be more precise, by solving

$$\frac{(1 - \varepsilon)f_S(R^*)}{D} = 1.$$

In Figure 1, when b is increasing and crosses $\mathbf{T_2}$ at any fixed ε, the system undergoes a transcritical bifurcation, E_{SP} loses stability and E_{SMP} becomes stable. However, in Figure 2, the dynamics become more complicated. $\mathbf{T_2}$ intersects $\mathbf{H_1}$ at a critical point $\mathbf{Q} = (\varepsilon_c, b_c)$, at which E_{SMP} becomes non-negative and a periodic orbit appears in $\{M \equiv 0\}$ spaces as a result of Hopf bifurcation. Note at $\mathbf{Q}$, characteristic equation of E_{SP} and E_{SP} coincide, it has a pair of purely imaginary roots and a zero root. This is an apparent fold-Hopf bifurcation, however, the normal form is degenerated so we cannot analyze the dynamics near $\mathbf{Q}$ rigorously.

E_{SMP} may undergo a Hopf bifurcation as well. This curve is shown in Figure 1 as $\mathbf{H_2}$, and remarkably, it meets $\mathbf{H_1}$ and $\mathbf{T_2}$ at $\mathbf{Q}$ in Figure 2. This line is obtained numerically by using Mathematica. We find out the characteristic equation associated with E_{SMP} and try to find the smallest b such that this equation has a pair of purely imaginary roots.

If $\varepsilon \in (0, \varepsilon_c)$ is fixed and b is increased, according to Figure 1 and the left half of Figure 2, bifurcation and exchanges of stability occurs as follows: $E_S \to E_{SP} \to E_{SMP} \to POM$, where POM denotes a stable periodic orbit with positive M component bifurcating from E_{SMP}. Note the unstable periodic orbit from unstable E_{SP} is ignored.

If $\varepsilon > \varepsilon_c$ but less than the maximal value, suppose ε is fixed and b is increasing, bifurcations and stability exchanges occur as $E_S \to E_{SP} \to E_{SMP} \to PO \to POM$, where PO is a stable periodic orbit with $M = 0$ bifurcating from E_{SP}. The stability switch $PO \to POM$ leads us to the last curve, i.e. $\mathbf{T_3}$, in Figure 2, it is where PO becomes unstable to the "invasion of M" and a periodic orbit with (possible very small) M-component bifurcates from PO. This bifurcation occurs as the Floquet exponent of PO,

$$\frac{1}{T} \int_0^T (1 - \varepsilon) f_S(R(t)) - D \, dt,$$

changes sign. This "lift-off" bifurcation is studied for a food chain model in [35, Section 3.6]. $\mathbf{T_3}$ itself is solved numerically by studying the sign of the integral above using Mathematica. Interestingly, this curve in parameter space also meets other curves (except for $PRN = 1$) at $\mathbf{Q}$.

All curves and lines described above partition ε-b parameter space into open regions. In each region, numerical simulations suggest that there exists a

unique attrator of positive initial data. This attractor may be E_{SP} (solid penta-gram), E_{SMP} (solid triangle), or stable periodic orbits.

Notable among these regions is the very large one in Figure 1 and the left half of Figure 2 where E_{SMP} is stable. Above it, for large values of b, a stable pe-riodic orbit with $M > 0$ exists. For this oscillatory region, the boundary consists of two curves: Hopf bifurcation curve $\mathbf{H_2}$ of E_{SMP} and the "lift-off" bifurcation curve $\mathbf{T_3}$ where the stable periodic orbit merges with the periodic orbit in the $\{M \equiv 0\}$ subspace.

As one expects, when the cost of resistance is large, namely, ε is close to the vertical line $\mathbf{V}$, the region where E_{SP} is stable is larger. And for b beyond the Hopf bifurcation line $\mathbf{H_1}$ of E_{SP}, there is a large region in which a periodic orbit is stable in $\{M \equiv 0\}$.

As we will see in the next section, the oscillatory solutions may oscillate quite strongly. In other words, the absolute value of S or P can be extremely small in parts of the cycle. Technically S and P can persist in the mathematical sense as proved in Theorem 3.2.3 and Theorem 3.3.1. However, in laboratory experiments, there is a large chance that one of them or both will be completely washed out over long periods due to demographic stochasticity.

But for the region in which E_{SMP} is stable, we may regard it as the most stable region of existence of susceptible bacteria S, resistant bacteria M and phages P. A notable fact is that this region reaches maximum height (for b) at an inter-mediate cost of resistance.

5.3   Bifurcation Diagrams and Attractors

As we have seen in the previous section, the local stability of E_{SP} and E_{SMP}, as well as existence and stability of periodic orbits, can be significantly different depend-ing on the choice of (ε, b) in the parameter space. In this section we will fix two ε

values as "samples" and vary b to explore the stability switch between equilibria and periodic orbits. In particular, we will illustrate two possible paths of stability exchanges: $E_S \to E_{SP} \to E_{SMP} \to POM$ and $E_S \to E_{SP} \to PO \to POM$.

All bifurcation diagrams and trajectories are solved by XPP-AUTO and enhanced by Inkscape.

Our first "sample" is when $\varepsilon = 0.2$, the bifurcation diagram is shown by Figure 3. Four diagrams shown in Figure 3 are bifurcation diagram of R, S, M, and P, respectively. Burst size b is plotted on the horizontal axis. It is worth to point out that the vertical scale of P diagram is different from the other three. In Figure 3, thick lines are locally asymptotically stable equilibria, thin lines are unstable equilibria. For periodic orbits, hollow circles are unstable ones and solid circles represent stable periodic orbits.
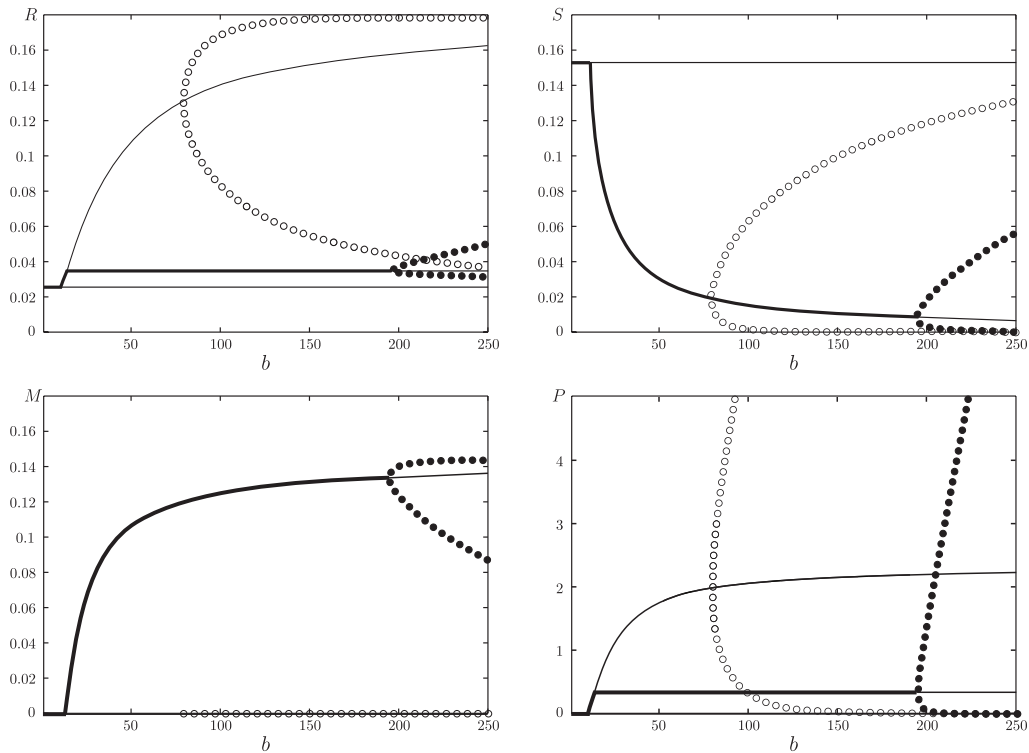

Figure 3.Bifurcation diagram with cost of resistance fixed at $\varepsilon = 0.2$.

Let's start from the left ($b = 0$) in Figure 3 where b is small, then $PRN < 1$ and E_S is (globally) stable. The available nutrient level is low because without phage P, S is superior to M and it consumes as much resource as possible. From the diagram of R in Figure 3, we can observe that E_{SP} is stable when b is approximately between 10 and 14. This coincides with what we see from Figure 1, the vertical length of the stable window of E_{SP} is short at $\varepsilon = 0.2$. For larger b, E_{SMP} becomes a positive equilibrium and it is stable. However E_{SP} and E_{SMP} are not distinguishable from the S diagram because E_{SP} and E_{SMP} share the same S-component, namely S^*. Another bifurcation occurs at $b \approx 80$ in the $\{M \equiv 0\}$ subspace, an unstable periodic orbit bifurcates from E_{SP} and lies entirely in this subspace. The only diagram in which this periodic orbit is not significantly observable is the M diagram (shown as hollow circle on the horizontal axis). At about $b \approx 190$, E_{SMP} undergoes a Hopf bifurcation resulting a stable periodic orbit. This periodic orbit is represented by solid circles in all four diagram. It should be noted that although in S and P diagram it seems this periodic orbit is touching the horizontal axis, it is actually bounded away from the axis. Recall that the uniform persistence means there exists a lower bound such that for all positive initial values, the limit inferior is bounded away from 0 by a fixed constant. However, this constant could be extremely small.

We infer from Figure 3 that if the cost of resistance is low, the chemostat is dominated by bacteria. Approximately, for b bigger than 14, the majority of bacteria is resistant species M and the minority is susceptible species S. The combined density of two species is essentially at the same level of bacteria as in the phage-free system. The total bacterial densities are controlled by nutrient levels. In this case, the nutrient is reduced to a very low level and phages are scarce.

The second "sample" is more interesting. Now we pick $\varepsilon = 0.61$ and obtain Figure 4. Besides all notations used in Figure 3, in Figure 4 we use dashed line to indicate an equilibrium with some negative components and dot-dashed line for periodic orbits with negative components. Actually the only negative component we take into account is the M component, hence the bottom half of M diagram illustrates the dynamics for $M < 0$.
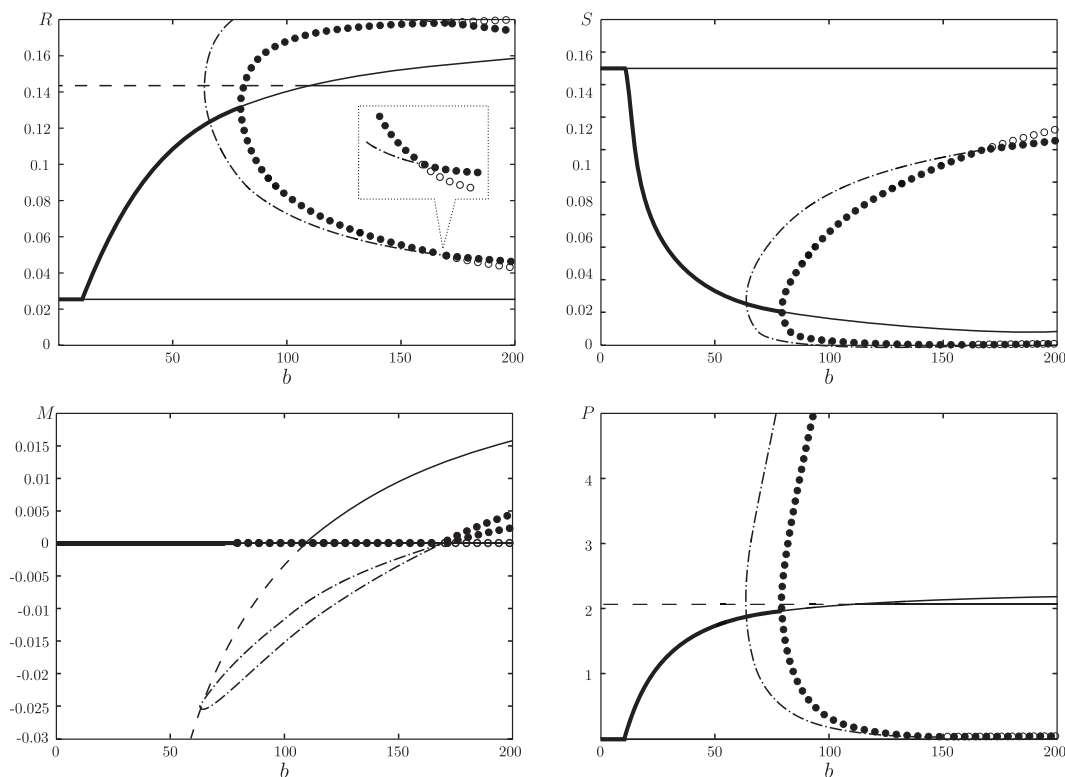

Figure 4. Bifurcation diagram with cost of resistance fixed at $\varepsilon = 0.61$.

In Figure 4, we again start from the left. For small b, since $PRN < 1$, E_S is (globally) asymptotically stable. As b increases, E_{SP} becomes a stable equilibrium. At $b \approx 80$, E_{SP} undergoes a Hopf bifurcation and a stable periodic orbit occurs in the $\{M \equiv 0\}$ subspace, this orbit is not only stable in $\{M \equiv 0\}$, it is also stable to the "invasion" of M. The R diagram is the best one to observe this stability switch because E_{SP} and E_{SMP} share the same S component and $M \equiv 0$ for both

E_{SP} and the periodic orbit. And at $b \approx 110$, E_{SMP} becomes a positive equilibrium (represented by the rising curve in the M diagram). An interesting observation is at $b \approx 170$, this periodic orbit in $\{M \equiv 0\}$ loses stability and a new periodic orbit arises from it with positive M component becomes stable. This is similar to the "lift-off" bifurcation as discussed in [35, Section 3.6]. It is not a small amplitude orbit. It occurs as the Floquet multiplier associated with the differential equation of M becomes unity as b is varied. For super-threshold values of $b > 170$, this periodic orbit has small but positive M values, while for sub-threshold $b < 170$, the periodic orbit has negative M values.

To trace this negative M-value periodic orbit, we first locate E_{SMP} with negative M-values, it is represented by the dashed line in Figure 4 and find a Hopf bifurcation point at $b \approx 60$, then run the simulation along the periodic orbit (shown as dot-dash lines). It is easy to observe that this negative M-value periodic orbit coincides with the one in $\{M \equiv 0\}$ hyperplane when $b \approx 170$, hence it shrinks into a point in the M diagram.

In order to clarify this lift-off bifurcation phenomena, we did another two simulations at the sub-threshold value $b = 150$ and super-threshold value $b = 200$, respectively. Both simulations assume the following initial data:

$$R(0) = 0.1, \ S(0) = 0.1, \ M(0) = 0.005, \ I_1(0) = \cdots = I_5(0) = 0.001, \ P(0) = 1.$$

At sub-threshold $b = 150$, the simulation is shown by Figure 5, the only non-negative periodic orbit lies in the $\{M \equiv 0\}$ hyperplane. Also the last figure in Figure 5 depicts $M(t)$ converging to 0 as the solution approaches the periodic orbit in the $M = 0$ hyperplane.

At super-threshold $b = 200$, there are two periodic orbits, one lies in $\{M \equiv 0\}$ and the other one has small but positive M-component. These are shown
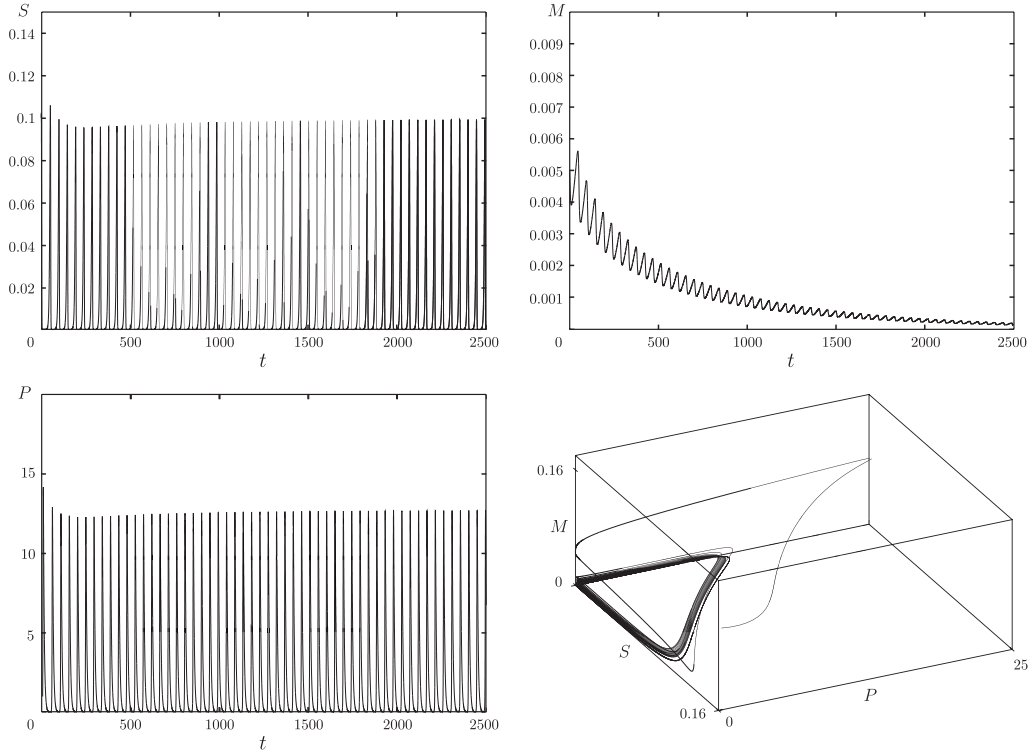
Figure 5.Numerical simulation at $(\varepsilon, b) = (0.61, 150)$.

in Figure 6. The one with positive M-component is stable and the other one is unstable (though stable in $\{M \equiv 0\}$). The simulation shows the solution with $M(0) > 0$ is attracted by the stable periodic orbit.

We infer from Figure 4 that at high cost of resistance, bacteria are controlled by a much more numerous phage population, resistant bacteria M are non-existent or rare depending on virulence, namely b, resource is high and goes unused, and strong predator-prey oscillations may be present.

In this chapter we have shown some simulation results. As we can see, there are mainly two scenarios depending on the cost of resistance ε. For small ε, stability exchanges follow the path $E_S \rightarrow E_{SP} \rightarrow E_{SMP} \rightarrow POM$ and there is large region in which E_{SMP} is locally asymptotically stable.
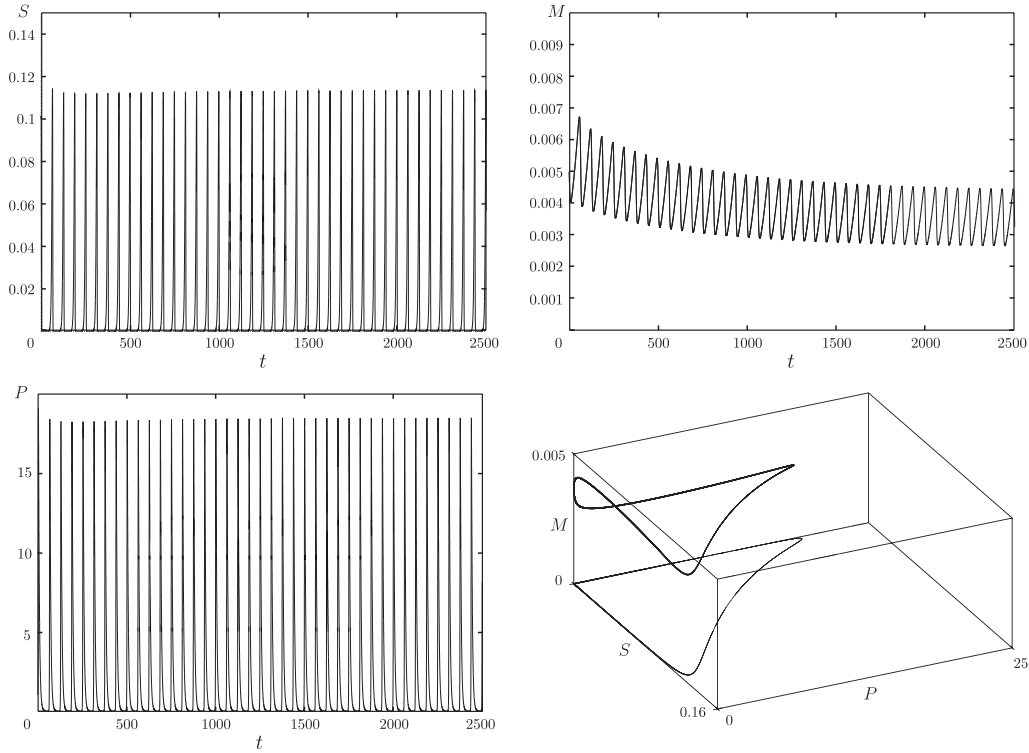
Figure 6.Numerical simulation at $(\varepsilon, b) = (0.61, 200)$.

And the more interesting case is when $\varepsilon > \varepsilon_c$, i.e., to the right of critical point Q, the stability switch is much more complicated, a "lift-off" bifurcation is involved. The periodic orbit POM is stable only if the the Floquet exponent of PO becomes positive.

It is clear that the appearance of E_{SMP} as a positive equilibrium is associated with $MRN > 1$. However, as we can see in the right half of Figure 4, the simulation suggests M does not persist even if $MRN > 1$. This is further confirmed by Figure 5 at sub-threshold value $b = 150$, E_{SMP} is a positive equilibrium but trajectories with $M(0) > 0$ is attracted by a periodic orbit in the $\{M \equiv 0\}$ hyperplane. Hence $MRN > 1$ is not a sufficient condition for M persistence but a positive Floquet exponent might be.

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CHAPTER 6

GENERALIZATION AND DISCUSSION

In system (2.7), there are one susceptible bacteria species, one resistant bacteria species, and one phage species. The key assumption (**F2**) guarantees that susceptible bacteria S is the superior competitor for the nutrient. In this chapter we will explore what if (**F2**) fails to hold.

By comparing persistence results on S and P in Chapter 3 to those claimed in [34], we noted the persistence of S and P is not affected by the resistant bacteria species. Therefore, it appears that the conclusion of Section 3.2 and 3.3 may still hold after introducing more inferior resistant bacteria species.

6.1   Alternative Assumptions on Response Functions

In this section we will exam alternative assumptions on response functions. In Chapter 2, we assumed respones functions $f_S(R)$ and $f_M(R)$ satisfy (**F1**)–(**F2**). Assumption (**F1**) is essential for our model, because it can be easily shown that if the break-even value of a bacteria species is greater than the concentration of the nutrient in the input flow, this particular species will be eventually washed out. We present a short mathematical proof here:

Lemma 6.1.1. *If $f_i(R_0) < D$, for $i \in \{S, M\}$, this bacteria species vanishes.*

Proof. We use simple differential inequalities to prove this assertion. Without loss of generality, we assume $f_S(R_0) < D$.

Note
$$R'(t) \leq -DR(t) + DR_0,$$

hence $R^\infty \leq R_0$. And since $f_S(R_0) < D$, by the continuity and monotonicity of f_S, there exists $\epsilon > 0$ such that $f_S(R) < D$ for all $R \in [0, R_0 + \epsilon)$. In particular,

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there exists $T > 0$ such that for all $t > T$, $R(t) < R_0 + \epsilon$, therefore,

$$S'(t) \leq (f_S(R_0 + \epsilon) - D)S(t),$$

for all $t > T$. And consequently $S(t) \to 0$ in this case. $\qquad\square$

As for (**F2**), it is observed in Bohannan and Lenski [9] that the resistant bacteria is usually a mutant species of susceptible ones. This mutation generally reduces the fitness. Thus we choose (**F2**) in Chapter 2 as a basic assumption for system (2.7). Nevertheless, if M does not loss any fitness due to the mutation, or more generally, if M is a completely different species which is resistant to this particular phage P and is superior to S, we may consider the following alternative assumptions on the relation between $f_S(R)$ and $f_M(R)$:

F2a. $f_M(R) = f_S(R)$, $0 \leq R \leq R_0$.

F2b. $f_S(R) < f_M(R)$, $0 < R \leq R_0$.

The second case is easier to analyze. Intuitively, if M is superior to S and phage P attacks only S, the only possibility is the extinction of both S and P. As the solo survivor in the chemostat, M consumes as much nutrient as it could and the system is attracted by a steady state. This intuitive observation is confirmed by the following theorem.

Theorem 6.1.2. *In (2.7), suppose (F2b) is true, all trajectories with $M(0) > 0$ is attracted by E_M.*

Proof. First we introduce a new variable $Y = S + I + \frac{1}{b_0}P$, then

$$Y'(t) = f_S(R(t))S(t) - DY(t) - \frac{1}{b_0}kS(t)P(t) +$$

$$\int_0^\infty \left(\frac{b(\tau)}{b_0} - 1\right)e^{-D\tau}S(t-\tau)P(t-\tau)d\tau$$

$$\leq (f_S(R(t)) - D)Y(t),$$

so

$$\left(\frac{Y}{M}\right)'(t) \leq \left[f_S(R(t)) - f_M(R(t))\right]\left(\frac{Y}{M}\right)(t),$$

and consequently,

$$\left(\frac{Y}{M}\right)(t) = \left(\frac{Y}{M}\right)(t_0)\exp\left(\int_{t_0}^t f_S(R(s)) - f_M(R(s))ds\right),$$

for all $t > t_0 \geq 0$.

On the other hand, note by the fluctuation argument,

$$0 \geq DR_0 - DR_\infty - f_S(R_\infty)S^\infty - f_M(R_\infty)M^\infty.$$

Suppose $R_\infty = 0$, then $0 \geq DR_0$ leads to a contradiction. Therefore, $R_\infty > 0$. As we have proved in Lemma 6.1.1, $R^\infty \leq R_0$, thus there exists $t_0 > 0$ such that for all $t \geq t_0$, $R(t) \in [\frac{1}{2}R_\infty, R_0 + 1]$, since $f_S(R) - f_M(R)$ is strictly negative and continuous on $[\frac{1}{2}R_\infty, R_0 + 1]$, it attains its maximum on this interval, which is again strictly negative. Thus there exists $\delta > 0$ such that $f_S(R(t)) - f_M(R(t)) < -\delta$ for all $t \geq t_0$. Hence

$$\left(\frac{Y}{M}\right)(t) \leq \left(\frac{Y}{M}\right)(t_0)e^{-\delta(t-t_0)} \to 0.$$

By Lemma 2.3.3, all components are non-negative provided non-negative initial data, thus S, I, and P vanish.

In the ODE system consisting of R and M:

$$R'(t) = -DR(t) + DR_0 - f_S(R(t))S(t) - f_M(R(t))M(t),$$

$$M'(t) = (f_M(R(t)) - D)M(t),$$

(6.1)

by considering $S(t)$ as a function depending on time, we can treat this system as a non-autonomous system with the following limit equation:

$$R'(t) = -DR(t) + DR_0 - f_M(R(t))M(t),$$
$$M'(t) = (f_M(R(t)) - D)M(t),$$

(6.2)

By abusing the notation, clearly all trajectories are attracted by E_0 or E_M, however, since $M(0) > 0$, no trajectories of (6.1) can be attracted by E_0, thus every trajectory with $M(0) > 0$ converges to E_M. □

The theorem above solves the problem when (**F2b**) is true. Now let's proceed to (**F2a**), it turns out this is a more interesting case. Since this is a degenerated case, there is a line of equilibria, we prove that every trajectory is attracted by a point on this line, and the uniform persistence of M is obtained provided that $PRN > 1$. However, a counterexamples shows the uniform persistence of S does not hold.

To simplify the proof, we state an auxiliary lemma first.

Lemma 6.1.3. *Suppose $h(t)$ is a non-negative and continuously differentiable function on $[0, \infty)$ and $|h'(t)|$ is bounded, then $h^\infty > 0$ implies $\int_0^\infty h(s)ds = \infty$.*

Proof. Since $h^\infty > 0$, there exists some $\delta > 0$ such that $h^\infty > \delta$. Also, by the boundedness of $|h'(t)|$, we can choose $L > 0$ such that $|h'(t)| < L$. Let $d = \frac{\delta}{L}$.

Pick a sequence $\{t_k\}_{k=1}^\infty$ such that $t_1 > d$, $h(t_k) > \delta$, and $t_k - t_{k-1} > 2d$. For each t_k, define $t_k^L = t_k - d$ and $t_k^R = t_k + d$, then

$$\int_0^\infty h(t)dt \geq \sum_{k=1}^\infty \int_{t_k^L}^{t_k^R} h(t)dt \geq \sum_{k=1}^\infty d\delta = \infty,$$

and the proof is complete. □

Now we state the following theorem:

Theorem 6.1.4. *Suppose (F2a) is true, then (2.7) has a line of equilibria:*

$$L = \{(\overline{R}, S, M, 0) : S + M = R_0 - \overline{R}, S \geq 0, M \geq 0\},$$

where $\overline{R} = f_S^{-1}(D) = f_M^{-1}(D)$.

Every trajectory with $S(0) + M(0) > 0$ *is attracted by an equilibrium point on L. In particular,*

$$\lim_{t \to \infty} P(t) = 0$$

for every trajectory.

Moreover, if $PRN > 1$ *and* $P(0) > 0$, $M(0) > 0$, *then M persists uniformly, that is, we have* $M(\infty) := \lim_{t \to \infty} M(t)$ *exists and*

$$M(\infty) \geq R_0 - \overline{R} - S^* > 0.$$

Proof. Since $f_S(R)$ and $f_M(R)$ are identical, write $f(R)$ as the uptake function. Now let $Y = I + \frac{1}{b_0}P$. We divide the proof into a few steps below.

Step 1: Both I and P converge to 0.

Suppose that $P^\infty > 0$, so $\int_0^\infty P(s)ds = \infty$ by Lemma 6.1.3. Formal solutions of $S(t)$ and $M(t)$, i.e. (2.8) and (2.9), imply that

$$S(t) = \frac{S(0)}{M(0)}M(t)\exp\left(-k\int_0^t P(s)ds\right). \tag{6.3}$$

By the boundedness of $M(t)$, we have $S(t) \to 0$. Note

$$Y'(t) = -DY(t) + \frac{b_0 - 1}{b_0}kS(t)P(t)$$
$$+ k\int_0^\infty e^{-D\tau}\left(\frac{b(\tau)}{b_0} - 1\right)S(t-\tau)P(t-\tau)d\nu(\tau)$$
$$\leq -DY(t) + \frac{b_0 - 1}{b_0}kS(t)P(t).$$

By an application of fluctuation argument, we have $0 \leq -DY^\infty$, and by non-negativity of solutions, $Y^\infty = 0$. This contradiction shows that $P^\infty = 0$ and consequently, $I^\infty = 0$.

Step 2: Every solution with $S(0), M(0) > 0$ converges to a point on L.

We consider the following 2-dimensional non-autonomous system by taking $P(t)$ as a time-dependent function:

$$R'(t) = D(R_0 - R(t)) - f(R(t))(S + M)(t),$$
$$(S + M)'(t) = (f(R(t)) - D)(S + M)(t) - kS(t)P(t). \tag{6.4}$$

It is asymptotically autonomous and its limit equation is

$$R'(t) = D(R_0 - R(t)) - f(R(t))(S + M)(t),$$
$$(S + M)'(t) = (f(R(t)) - D)(S + M)(t). \tag{6.5}$$

This is a classical chemostat model, every solution of (6.5) converges to $E_0 = (R_0, 0)$ or $E^* = (\overline{R}, R_0 - \overline{R})$. In particular, E^* attracts all solutions with $S(0) > 0, M(0) > 0$. By Theorem A.4.2, every solution of (6.4) converges to an equilibrium of (6.5). However, no trajectory with $(S + M)(0) > 0$ converges to $(R_0, 0)$ because if so, there exists $T_0 > 0$ such that for all $t \geq T_0$, $R(t) > \frac{1}{2}(R_0 + \overline{R}) > \overline{R}$ and thus

$$(S + M)(t) = (S + M)(t_0) \exp\left(\int_{t_0}^{t} f(R(t)) - D \, ds\right)$$
$$> (S + M)(t_0) \exp\left(\int_{t_0}^{t} f\left(\frac{1}{2}(R_0 + \overline{R})\right) - D \, ds\right) \to \infty$$

as $t \to \infty$, which contradicts $(S + M)(t) \to 0$. So all solutions of (6.4) with $(S + M)(0) > 0$ are attracted by $(\overline{R}, R_0 - \overline{R})$.

Note
$$\frac{S(t)}{M(t)} = \frac{S(0)}{M(0)} \exp\left(-k \int_0^t P(s) ds\right),$$
the integral is an increasing function of t, thus it either diverges to ∞ or converges to a finite limit. In both cases,

$$\lim_{t \to \infty} \frac{S(t)}{M(t)} = \frac{S(0)}{M(0)} \lim_{t \to \infty} \exp\left(-k \int_0^t P(s) ds\right)$$

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exists. Together with $\lim\limits_{t\to\infty}(S+M)(t)=R_0-\overline{R}$, both $\lim\limits_{t\to\infty}S(t)$ and $\lim\limits_{t\to\infty}M(t)$ exist.

Therefore, every solution of (2.7) with $S(0)>0,M(0)>0$ is attracted by a point on L.

Step 3: $S^\diamond := \lim\limits_{t\to\infty}S(t)>0$ and $M^\diamond := \lim\limits_{t\to\infty}M(t)>0$.

Suppose $M^\diamond=0$, then $S^\diamond=R_0-\overline{R}$. By (6.3) and non-negativity of $P(t)$, we have $S^\diamond \le \frac{S(0)}{M(0)}M^\diamond=0$, which forms a contradiction. Thus $M^\diamond>0$.

Now suppose $S^\diamond=0$, note $\frac{1}{b_0}P(t)\le Y(t)$, thus

$$Y'(t)\le -DY(t)+\frac{b_0-1}{b_0}kS(t)P(t)\le -DY(t)+(b_0-1)kS(t)Y(t).$$

Since $S(t)\to 0$, we can assume $S(t)<\frac{D}{2(b_0-1)k}$ after a time-shift, thus $Y'(t)\le -\frac{D}{2}Y(t)$, and consequently,

$$\int_0^\infty P(s)ds \le b_0\int_0^\infty Y(s)ds \le b_0\int_0^\infty Y(0)e^{-\frac{D}{2}s}ds = \frac{2b_0}{D}Y(0).$$

Since the integral of P is a finite number, by taking the limit of both sides of (6.3), $S^\diamond > \frac{S(0)}{M(0)}M^\diamond\exp(-\frac{2k}{Db_0}Y(0))>0$, which contradicts the assumption that $S^\diamond=0$.

Step 4: S does not persist uniformly. If $PRN>1$ and $P(0),M(0)>0$, M persists uniformly.

For any $\epsilon>0$, without loss of generality, assume $\epsilon<R_0-\overline{R}$. Let $S(0)=\epsilon$ and $M(0)=R_0-\overline{R}-\epsilon$, $P(0)>0$, then by (6.3), since the integral of P is strictly positive, $\frac{S^\diamond}{M^\diamond}<\frac{S(0)}{M(0)}$. However, $S^\diamond+M^\diamond=S(0)+M(0)=R_0-\overline{R}$, so $S^\diamond<S(0)=\epsilon$. Therefore, for any $\epsilon>0$, we can always find a trajectory such that $S^\diamond<\epsilon$.

By Laplace transform (3.10),

$$(\lambda+D)\widehat{P}(\lambda)\ge -k\widehat{SP}(\lambda)+k\widehat{SP}(\lambda)\int_0^\infty b(\tau)e^{-(\lambda+D)\tau}d\nu(\tau).$$

Since $S(t)\to S^\diamond$, for any $\epsilon>0$, we can assume $S(t)>S^\diamond-\epsilon$ after a possible time-shift. Therefore,

$$(\lambda+D)\widehat{P}(\lambda)\ge k(S^\diamond-\epsilon)\widehat{P}(\lambda)\left(\int_0^\infty b(\tau)e^{-(\lambda+D)\tau}d\nu(\tau)-1\right).$$

By taking $\lambda \to 0$, and dividing both sides by $\widehat{P}(0) > 0$, we have $D \geq k(B-1)(S^\diamond - \epsilon)$. Since this inequality holds for any $\epsilon > 0$, we let $\epsilon \to 0$ and get

$$D \geq k(B-1)S^\diamond. \tag{6.6}$$

And (6.6) is exactly $S^\diamond \leq S^*$. Therefore, $M^\diamond \geq R_0 - \overline{R} - S^*$. Note $R_0 - \overline{R} - S^* > 0$ if and only if $PRN > 1$ and the proof is complete. $\qquad\square$

In this section we considered two possible alternates of (**F2**). The latter case (**F2b**) seems to be trivial, it is not difficult to imagine that an inferior competitor suffering from a disease will eventually be washed out.

However, the first case leads to an interesting conclusion. It is usually difficult to analyze local stability of a line of equilibira. But fortunately, we are able to show some definite results on trajectories with positive initial data. As proved in Theorem 6.1.4, every such trajectory is attracted by a unique equilibrium point on L, no trajectory will wander between two or more points on L. Yet another observation is that, though phage P will eventually be washed out, the phage reproduction number PRN still plays an important role. With $PRN > 1$ and $P(0) > 0$, we have shown that $M(\infty)$ is bounded away from 0 uniformly by a constant. Nevertheless, the uniform persistence of S is no longer true. For any small ϵ, we can always find a trajectory such that the limit of its S component is less than ϵ (but strictly positive).

6.2   Generalizations

In this section we will discuss some possible generalizations on the current model. The first possible generalization is to consider more resistant species. If we consider the following system:

$$R'(t) = D(R_0 - R(t)) - f_S(R(t))S(t) - \sum_{j=1}^{n} f_{M_j}(R(t))M_j(t),$$

$$S'(t) = (f_S(R(t)) - D)S(t) - kS(t)P(t),$$

$$M_j'(t) = (f_{M_j}(R(t)) - D)M_j(t), \qquad 1 \leq j \leq n, \qquad (6.7)$$

$$I'(t) = -DI(t) + kS(t)P(t) - k\int_0^\infty e^{-D\tau}S(t-\tau)P(t-\tau)d\nu(\tau),$$

$$P'(t) = -DP(t) - kS(t)P(t) + k\int_0^\infty b(\tau)e^{-D\tau}S(t-\tau)P(t-\tau)d\nu(\tau).$$

And assume all $f_S(R)$ and $f_{M_j}(R)$'s are continuously differentiable increasing functions, together with the following hypothesis:

F1*. $f_{M_j}(R) = f_S(R)$, $0 \leq R \leq R_0$ and $1 \leq j \leq n$.

F2*. $f_{M_1}(R) < f_{M_2}(R) < \cdots < f_{M_n}(R) < f_S(R)$, $0 < R \leq R_0$ and $1 \leq j \leq n$.

Note (**F2***) is a very strong assumption, it actually implies that M_n is the only possible resistant species which could persist provided positive initial data. This is easy to see from formal solutions of M_j's, we have

$$\left(\frac{M_i}{M_j}\right)(t) = \left(\frac{M_i}{M_j}\right)(0)\exp\left(\int_0^t f_{M_i}(R(s)) - f_{M_j}(R(s))ds\right), \qquad (6.8)$$

as before, we can show that all solutions are eventually bounded. To be more precise, it is possible to prove similar results as stated in Lemma 2.3.4 and Theorem 2.3.7. Moreover, it is not difficult to show $R(t)$ is attracted by an interval $[\frac{1}{2}R_\infty, R_0 + 1]$, which is bounded away from 0. Therefore, if $i < j$, (6.8) implies $\frac{M_i}{M_j}(t) \to 0$ as $t \to \infty$, and by the boundedness each M_j, obviously $M_i(t) \to 0$ follows. That is, all M_j's for $1 \leq j \leq n-1$ will be washed out.

Therefore, with a careful analysis, system (6.7) should be able to be handled by the same framework as presented in previous chapters of this dissertation. All persistence and extinction results should still be valid.

In Levin, Stewart and Chao [26], the authors formulated a general model (1.3), we generalize their idea here by using distributed delay to replace the discrete delay used in [26].

We assume there are n bacteria species and l phage species together with $n \times l$ infected bacteria species.

Besides assuming each normal bacterium utilize the nutrient, we also allow infected bacteria to consume nutrient. And phages not only binding themselves to healthy bacteria, they also try to attack infected bacteria.

To simplify the notation, we assume the bacteria species are

$$S(t) = (S_1(t), S_2(t), \ldots, S_n(t))^T,$$

and uptake functions forms a vector $f(R(t)) = (f_{S_i}(R(t)))_{1 \leq i \leq n}$. Phage species is

$$P(t) = (P_1(t), P_2(t), \ldots, P_l(t))^T.$$

The adsorption rate is given by the matrix $k = (k_{ij})_{n \times l}$. Note $k_{ij} = 0$ means S_i is resistant to P_j.

All infected bacteria is given by a matrix

$$I(t) = \left(I_{ij}(t) \right)_{n \times l},$$

where I_{ij} represents the concentration of S_i infected by P_j. Since infected bacteria now consume nutrients, their uptake functions are $g(R(t)) = (g_{I_{ji}}(R(t)))_{l \times n}$. We also allow phage to bind themselves to infected bacteria, thus the second adsorption rate matrix is $\widetilde{k} = (\widetilde{k}_{ij})_{n \times l}$.

Since this system now involves multiple bacteria species and phage, the average number of baby phage from an infected bacterium cell vary. We use $b(\tau) = (b_{ij}(\tau))_{n \times l}$ to represent the average phage particles released from I_{ij} at an infection age τ. Also, the lysis distribution $v(\tau) = (v_{ij}(\tau))_{n \times l}$.

Moreover, for a matrix $A(t,\tau) = (A_{ij}(t,\tau))_{n\times l}$, we introduce a new notation here as

$$\langle A, \nu \rangle := \left(\int_0^\infty A_{ij}(t,\tau) d\nu_{ij} \right)_{n\times l}.$$

Last but not least, let $\mathrm{diag} : \mathbb{R}^n \to \mathcal{M}(n,n)$, where $\mathcal{M}(n,n)$ is the space of real $n \times n$ matrices, be the map mapping a vector to a diagonal matrix such that for any $V \in \mathbb{R}^n$, $\mathrm{diag}(V)_{ii} = V_i$. Conversely, let $\mathrm{diag}^{-1} : \mathcal{M}(n,n) \to \mathcal{M}(n,1) \cong \mathbb{R}^n$ be defined as $\mathrm{diag}^{-1}(W)_i = W_{ii}$ for all $W \in \mathcal{M}(n \times n)$.

Now we are ready to present the general model as in [26].

$$R'(t) = D(R_0 - R(t)) - f(R(t)) \cdot S(t) - \mathrm{tr}(g(R(t)) \cdot I(t)),$$

$$S'(t) = -DS(t) + \mathrm{diag}(f(R(t))) \cdot S(t) - \mathrm{diag}(S(t)) \cdot k \cdot P,$$

$$I'(t) = -DI(t) + \mathrm{diag}(S(t)) \cdot k \cdot \mathrm{diag}(P(t))$$
$$\qquad - \left\langle e^{-D\tau} \mathrm{diag}(S(t-\tau)) \cdot k \cdot \mathrm{diag}(P(t-\tau)), \nu \right\rangle, \tag{6.9}$$

$$P'(t) = -DP(t) - \mathrm{diag}(P(t)) \cdot k^T \cdot S(t) - \mathrm{diag}^{-1}\left(I^T(t) \cdot \widetilde{k} \cdot \mathrm{diag}(P(t)) \right)$$
$$\qquad + \mathrm{diag}^{-1} \left\langle e^{-D\tau} b^T \cdot \mathrm{diag}(S(t-\tau)) \cdot k \cdot \mathrm{diag}(P(t-\tau)), \nu \right\rangle.$$

Clearly, system (6.9) models a more realistic scenario because in natural environments, there are usually more than one bacteria species and more than one phage species, and they may coexist by sharing the same resources. But unfortunately, due to the complicated nature of this system, it is impossible for us to give a rigorous analysis at this moment.

CHAPTER 7

CONCLUSIONS

In this research we studied a chemostat model (2.7) with infinite distributed delay terms. The model formulates the phage-bacteria interaction in a chemostat. This model is inspired by (1.5) in [26] and is an elaboration on the model (1.8) in [34].

The main difference between this model and previous models such as (1.4), (1.6), (1.7), and (1.8) is that (2.7) contains a resistant bacteria species. Therefore we can study whether assertion (**O1**)–(**O2**) are true and investigate the persistence condition for resist bacteria species M. A similar model (1.10) was previously studied by Beretta, Sakakibara and Takeuchi in [6, 5]. The difference between (2.7) and (1.10) is that the latter was formulated by DDEs with a single discrete delay. And the conclusion of [6, 5] does not include persistence analysis.

Therefore, to the best of our knowledge, (2.7) is the first DDE model formulating interaction between a susceptible bacteria species, a resistant bacteria species, and phage with infinite distributed delay terms. The main conclusions of this dissertation can be summarized as below:

First we formulated a DDE model (2.7). And by using abstract results developed in [18, 21], we proved the existence, uniqueness, and continuous dependence on parameters and initial data for solutions of (2.7). We also proved positivity and boundedness of its solutions. By introducing the phage space $\mathscr{B}_D^+$, we are able to define the semiflow induced by (2.7). And it also allows us to show the existence of a compact global attractor (the compact attractor attracts all bounded sets).

We defined a Phage Reproduction Number PRN and found that E_S is globally asymptotically stable if $PRN < 1$ (Theorem 3.3.3 and Lemma 3.2.1).

Moreover, P goes extinct if $PRN < 1$ (Theorem 3.3.3). For $PRN > 1$, we showed P persists uniformly by Theorem 3.3.1. These results confirms that the sharp criteria for the persistence/extinction of phage P obtained in Smith and Thieme [34] is not affected by the resistant bacteria M.

And for persistence of M, a necessary condition is given by Theorem 3.4.2. And a sufficient condition is proved in Theorem 3.4.1. It is not optimal and may be difficult to verify, however, the numerical simulation suggests the persistence of M is true for a large set of parameter values.

Other analytical results on (2.7) are shown in Chapter 6, by changing (**F2**), we have another two cases in which the resistant bacteria persists. In particular, Theorem 6.1.4 shows that if M is as good as S in the competition of nutrient, it persists provided $PRN > 1$.

We also investigated a special case of (2.7), i.e., when $\eta(\tau)$ is a Gamma distribution. An ODE model (4.3) was obtained. We proved (4.3) has a compact global attractor and there is a homeomorphism between attractors of (2.7) and (4.3). Some analytical bifurcation analysis of (4.3) was presented in Section 4.4.

Numerical simulations were reported in Chapter 5. We studied the local stability of E_{SP} and E_{SMP} in the (ε, b) parameter space. It shows that there is a large region in which E_{SMP} is stable. And for all large b, there exists a stable period orbit with positive M component. This is later confirmed by bifurcation diagrams Figure 3 and Figure 4. In particular, two simulations Figure 5 and Figure 6 suggest $MRN > 1$ is not a sufficient condition for the persistence of M, but a positive Floquet exponent might be.

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APPENDIX A
TOOL BOX

In this appendix we will state some tools and technique used in this dissertation.

All theorems, statements or assertions in this appendix are adopted from other books and papers. These results include:

1. The fundamental framework of phase space of functional differential equations (FDEs) developed by Hale and Kato [18] and Hino, Murakami and Naito [21].

2. The linerized stability framework for FDEs with delays studied by Ruess and Summers [30].

3. General persistence theory studied by Smith and Thieme [33].

4. Asymptotically autonomous ODE studied by Thieme [36].

Since different author prefers different notations and terminology, in this appendix we may change some symbols or restate their theorems in a proper sense. However, all credits should go to the original authors. For details, proofs, and comments, please refer to the corresponding book or paper.

A.1 Phase space of FDEs with infinite delays

All following definitions and theorems are adopted from [18, 21, 19].

For an abstract FDE

$$\dot{x}(t) = F(x_t), \tag{A.1}$$

where $x_t(s) = x(t+s)$ for all $s \in (-\infty, 0]$, a phase space $\mathscr{B}$ is a Banach space with a semi-norm $\|\cdot\|_{\mathscr{B}}$ consisting of functions mapping $(-\infty, 0]$ into $\mathbb{R}^n$. Phase space $\mathscr{B}$ should satisfy the following admissible axioms:

B1. There exists a positive constant H and functions $K, N : \mathbb{R}_+ \to \mathbb{R}_+$ with K continuous and N locally bounded, such that for any $\sigma \in \mathbb{R}$ and $A > 0$, if $\varphi : (-\infty, \sigma + A) \to \mathbb{R}^n$, $\varphi_\sigma \in \mathscr{B}$ and φ is continuous on $[\sigma, \sigma + a)$, then for every $t \in [\sigma, \sigma + a)$, the following conditions hold:

    a) $\varphi_t \in \mathscr{B}$.

    b) $|\varphi(t)| \leq H\|\varphi_t\|_{\mathscr{B}}$.

    c) $\|\varphi_t\|_{\mathscr{B}} \leq K(t - \sigma)\sup\{|\varphi(s)| : \sigma \leq s \leq t\} + N(t - \sigma)\|\varphi_\sigma\|_{\mathscr{B}}$.

B2. For the exact function φ in (**B1**), φ_t is a $\mathscr{B}$-valued continuous function for $t \in [\sigma, \sigma + A)$.

Suppose $\Omega \subset \mathbb{R} \times \mathscr{B}$ is an open set, $F : \Omega \to \mathbb{R}^n$ is a continuous function. By [18], a solution of (A.1) on an interval $I \subset \mathbb{R}$ is a function

$$x : \bigcup_{t \in I} (-\infty, t] \to \mathbb{R}^n$$

such that $(t, x_t) \in \Omega$ for all $t \in I$, $x(t)$ is continuously differentiable and satisfies (A.1), where $x(t) = x_t(0)$. For any given $(\sigma, \phi) \in \Omega$, say x is a solution of (A.1) through (σ, ϕ) if there exists some $A > \sigma$ such that x is solution of (A.1) on $[\sigma, A]$ and $x_\sigma = \phi$.

The following theorems are adopted from [18]:

Theorem A.1.1 (Theorem 2.1 in [18]). *For any $(\sigma, \phi) \in \Omega$, there exists a solution of* (A.1) *through (σ, ϕ).*

Theorem A.1.2 (Theorem 2.2 in [18]). *If F is locally Lipschitz, i.e., there exists a constant $\widetilde{L} > 0$ such that $|F(\varphi_1) - F(\varphi_2)| \leq \widetilde{L} \|\varphi_1 - \varphi_2\|_{\mathscr{B}}$ in a neighborhood of (σ, φ), then there exists a unique solution of* (A.1) *through (σ, φ).*

Theorem A.1.3 (Theorem 2.5 in [18]). *Suppose x is the locally unique solution of* (A.1) *through (σ, φ) defined on $[\sigma, \sigma + A]$ for some $A > 0$. For any $\varepsilon > 0$, there exists a $\delta > 0$ such that if $(\sigma', \varphi') \in \Omega$, $|\sigma' - \sigma| < \delta$, and $\|\varphi' - \varphi\|_{\mathscr{B}} < \delta$, then $\|\widetilde{x}_t(\sigma', \varphi') - x_t(\sigma, \varphi)\|_{\mathscr{B}} < \varepsilon$ for all $t \in [\max\{\sigma, \sigma'\}, \sigma + A]$, where $\widetilde{x}$ is the solution of* (A.1) *through (σ', φ').*

Theorem A.1.4 (Theorem 2.6 in [18]). *Suppose x is the locally unique solution of* (A.1) *through (σ, φ) defined on $[\sigma, \sigma + A]$, where $A > 0$ is a constant or $A = \infty$. Consider functional differential equation $\dot{x}(t) = \widetilde{F}(\mu, x_t)$, where $\widetilde{F}(\mu, x_t) : \mathbb{R} \times \mathscr{B}_D \to \mathbb{R}^5$ is continuously differentiable and $\widetilde{F}(0, x_t) = F(x_t)$, let the locally unique solution through (μ, σ, φ) be $\widetilde{x}(\mu; \sigma, \varphi)$. Then for each $\varepsilon > 0$, there exists $\delta > 0$ such that $|\widetilde{x}(\mu; \sigma, \varphi) - x|_{\mathscr{B}} < \varepsilon$ if $|\mu| < \delta$.*

And solutions extend to the maximal interval of existence:

Theorem A.1.5 (Theorem 2.4 in [18]). *Suppose x is a non-continuable solution of* (A.1) *on $[0, A)$, if F takes closed bounded sets of $\Omega = \mathbb{R} \times \mathscr{B}$ into bounded sets, then for any closed bounded set W in Ω, there exists some $t_W > 0$ such that $(t, x_t) \notin W$ for $t_W \leq t < A$.*

And for the existence of compact global attractor, the authors claimed another two admissible conditions are needed:

B3. $\mathscr{B}$ is complete.

B4. If $\{\varphi_n\} \subset \mathscr{B}$ converges to some φ uniformly on any compact subset of $(-\infty, 0]$ and $\{\varphi_n\}$ is Cauchy in $\mathscr{B}$ with respect the to seminorm $\|\cdot\|_{\mathscr{B}}$, then $\varphi \in \mathscr{B}$ and $\|\varphi_n - \varphi\|_{\mathscr{B}} \to 0$ as $n \to \infty$.

And the following theorem is true:

Theorem A.1.6 (Theorem 9.1 in [19, Chap 12]). *Suppose that $\mathscr{B}$ satisfies **(B1)** – **(B4)** and $K(t)$ is bounded for $t \geq 0$ and $N(t) \to 0$ as $t \to \infty$. If Φ_D is point dissipative and positive orbits of bounded sets are bounded, then there is a (non-empty) compact global attractor for* (A.1).

A.2 Linearized Stability Framework for FDEs with delays

Ruess and Summers [30] studied the relation between the local stability of an equilibrium of a non-linear FDE and its linearized reduction. The authors developed a framework and proposed a few assumptions, under which their main results Theorem A.2.1 will hold.

The authors considered a fairly general FDE:

$$
\begin{aligned}
x'(t) &= -\alpha x(t) - Ax(t) + F(x_t), \qquad t \geq 0, \\
x|_t &= \varphi \in \mathscr{B},
\end{aligned}
\tag{A.2}
$$

where α is a real constant, $A : D(A) \subset \mathscr{X} \to \mathscr{X}$ is an accretive operator in a Banach space $\mathscr{X}$. And $\mathscr{B}$ is an admissible function space of initial data $\varphi : (-\infty, 0] \to \mathscr{X}$. And $F : \widehat{\mathscr{B}} \to X$ is a Lipschitz continuous mapping from a subset $\widehat{\mathscr{B}}$ of $\mathscr{B}$ to $\mathscr{X}$.

The phase space $\mathscr{B}$ should satisfy all admissible axioms **(B1)**–**(B4)** and the following additional assumptions:

R1. The followings are true:

  a) $\widehat{\mathscr{X}}$ is a closed subset of X;

  b) $\widehat{\mathscr{B}}$ is a closed and convex subset of $\mathscr{B}$;

  c) $A : D(A) \subset \mathscr{X} \to \mathscr{X}$ is an accretive operator.

  d) $F : \widehat{\mathscr{B}} \to \mathscr{X}$ is Lipschitz continuous with Lipschitz constant $L_F \geq 0$.

  e) $\alpha \in \mathbb{R}$ and assume $\zeta = \max\{0, L_F - \alpha\}$.

R2. If $x \in \widehat{\mathscr{X}}$, $\psi \in \widehat{\mathscr{B}}$, $\lambda > 0$ with $\zeta\lambda < 1$ and φ_x is the solution to

$$
\begin{aligned}
\varphi &= \lambda\varphi' + \psi, \\
\varphi(0) &= x,
\end{aligned}
\tag{A.3}
$$

  then $\varphi_x \in \widehat{\mathscr{B}}$.

R3. If $x \in \widehat{\mathcal{X}}$, $\psi \in \widehat{\mathcal{B}}$, and $\lambda > 0$ with $\zeta \lambda < 1$, then

$$\frac{1}{1+\lambda\alpha}(\psi(0) + \lambda F(\varphi_x)) \in (\text{Id} + \frac{\lambda}{1+\lambda\alpha}A)(D(A) \cap \widehat{\mathcal{X}}),$$

for every $x \in \hat{\mathcal{X}}$.

Suppose φ_e is an equilibrium for (A.2), consider the following linearized system:

$$x'(t) = -\alpha x(t) - Ax(t) + F'_{\varphi_e}(x_t), \qquad t \geq 0,$$
$$x|_t = \varphi \in \mathcal{B}, \tag{A.4}$$

where F'_{φ_e} is the Fréchet derivative of F at φ_e. The the following theorem is true.

Theorem A.2.1 (Corollary 2.5 in [30]). *If the zero equilibrium of* (A.4) *is exponentially asymptotically stable, then* φ_e *is an exponentially asymptotically stable equilibrium of* (A.2).

A.3 General Persistence Theory

Most definitions and results in this section are adopted from [33].

Let $\Theta : \mathbb{R}_+ \times X \to X$ be a semiflow and $\rho : X \to \mathbb{R}_+$ be a function, then Θ is called "uniformly ρ-persistent" if there exists some $\epsilon > 0$ such that

$$\liminf_{t\to\infty} \rho(\Theta(t,x)) > \epsilon,$$

for all $x \in X$ such that $\rho(x) > 0$. Similarly, Θ is called "uniformly weakly ρ-persistent" if there exists some $\epsilon' > 0$ such that

$$\limsup_{t\to\infty} \rho(\Theta(t,x)) > \epsilon',$$

for all $x \in X$ such that $\rho(x) > 0$.

Usually a persistent function ρ is taken as the projection from a point $x \in X$ to one of its components. For instance, in (2.7), the phase space is $X = \mathcal{B}_D^+$ and and semiflow induced by this equation is Φ. We define $\rho : \mathcal{B}_D^+ \to \mathbb{R}_+$ as $\rho(x) = S(0)$ for every $x(R, S(\cdot), M, P(\cdot)) \in \mathcal{B}_D^+$, then we say S persists uniformly if Φ is uniformly ρ-persistent. Similarly, we can define uniform persistence and uniformly weak persistence for each variable in (2.7).

The following theorem is usually called the "topological approach of uniformly weak persistence" or "acyclic theorem", it gives the sufficient and necessary conditions for the uniformly weak persistence.

Theorem A.3.1 (Theorem 8.20 in [33]). *Let $\Omega \subset \cup_{i=1}^{k} M_i$ where each $M_i \subset X_0$ is compact, invariant, and isolated in X_0, $M_i \cap M_j = \varnothing$ if $i \neq j$, and $\{M_1, M_2, \ldots, M_k\}$ is acyclic. Then Θ is uniformly weakly ρ-persistent if and only if each M_i is uniformly weakly ρ-repelling.*

To apply Theorem A.3.1, the phase space X should satisfy the following hypothesis:

C. There exists a set $U \subset X$ and some $c > 0$ such that $\Phi_t(x) \to U$ as $t \to \infty$ for all $x \in X$ and $U \cap \{\rho \leq c\}$ has compact closure in X.

In Theorem A.3.1, $X_0 = \{x \in X : \rho(\Theta(t,x)) = 0, \ \forall t \geq 0\}$ and $\Omega = \cup_{x \in X_0} \omega(x)$, where $\omega(x)$ is the ω-limit set of x. For sets $V_1, V_2 \subset X_0$, write $V_1 \mapsto V_2$ if there exists some total trajectory ϕ in X_0 such that $\phi(0) \notin V_1 \cup V_2$ but $\phi(-t) \to V_1$ and $\phi(t) \to V_2$ as $t \to \infty$. $\{V_1, V_2, \ldots, V_k\}$ is call cyclic if, after possibly renumbering, $V_1 \mapsto V_2$, $V_2 \mapsto V_3$, $\ldots$, $V_j \mapsto V_1$ for some $j \in \{2, 3, \ldots, k\}$. It is called acyclic if it is not cyclic.

Moreover, a set V_0 is called isolated if there exists a neighborhood W_0 of V_0 such that every compact invariant set in W_0 is a subset of V_0. V is said to be weakly ρ-repelling in X if there exists no $x \in X$ such that $\rho(x) > 0$ but $\Theta(t,x) \to V$ as $t \to \infty$. And it is called uniformly weakly ρ-repelling if there exists some $\epsilon > 0$ such that

$$\limsup_{t \to \infty} d(\Theta(t,x), V) > \epsilon,$$

whenever $x \in X$ and $\rho(x) > 0$.

From the uniformly weak persistence, we can show the uniform persistence by the following theorem:

Theorem A.3.2 (Theorem 4.13 in [33]). *Let Θ be a semiflow with time-set $\mathbb{R}_+$ such that there exists a non-empty subset U of X with the following properties:*

1. *For every $x \in X$, $\rho(x) > 0$, $\Theta(t,x) \to U$ as $t \to \infty$.*

2. *If $0 < \varepsilon_1 < \varepsilon_2 < \infty$, then $U \cup \{\varepsilon_1 \leq \rho \leq \varepsilon_2\}$ is compact.*

3. *There are no $x \in U$, $r, s > 0$ such that $\rho(x) > 0$, $\rho(\Phi(t,x)) = 0$ and $\rho(\Phi(t + s, x)) > 0$.*

Then Θ is uniformly ρ-persistent if it is uniformly weakly ρ-persistent.

In most times, showing the uniformly weak persistence is more difficult then applying theorem A.3.2.

And the last but not least, a very handy tool regarding the $\limsup$ and $\liminf$ is called "fluctuation method". For a bounded function f on $\mathbb{R}$, we write

$$f^{\infty} := \limsup_{t \to \infty} f(t) \text{ and } f_{\infty} := \liminf_{t \to \infty} f(t).$$

With these notations, for a bounded and continuously differentiable function f, we have:

Lemma A.3.3 (Fluctuation Lemma, Proposition A.33 in [37]). *There are two sequences $s_n, t_n \to \infty$ with the following properties:*

$$f(s_n) \to f_{\infty}, \ f'(s_n) \to 0, f(t_n) \to f^{\infty}, \ f'(t_n) \to 0,$$

for $n \to \infty$.

A.4   Asymptotically Autonomous Systems

The following results are adopted from Thieme [36].

For two ordinary differential equations in $\mathbb{R}^n$:

$$\dot{x} = F_1(t, x), \tag{A.5}$$
$$\dot{y} = F_2(y), \tag{A.6}$$

where F_1 and F_2 are continuous functions and locally Lipschitz in x. We say (A.5) is "asymptotically autonomous" with limit equation (A.6) if $F_1(t, x) \to F_2(x)$ as $t \to \infty$, locally uniformly in $x \in \mathbb{R}^n$.

The similar concept applies to semiflows too. Assume (X, d) is a metric space, $\Theta_1 : \Delta \times X \to X$, $\Delta = \{(t, s); 0 \le s \le t < \infty\}$ is a non-autonomous continuous semiflow. Assume more that $\Theta_2 : [0, \infty) \times X \to X$ is an autonomous continuous semiflow. Then Θ_1 is said to be "asymptotically autonomous" with limit-semiflow Θ_2 if and only if

$$\Theta_1(t_j + s_j, s_j, x_j) \to \Theta_2(t, x), \ j \to \infty$$

for any three sequences $t_j \to t$, $s_j \to \infty$, $x_j \to x$ as $j \to \infty$, with $x, x_j \in X$, $0 \le t, t_j < \infty$ and $s_j \ge 0$.

The author claimed in [36] that if Θ_1 and Θ_2 are semiflows induced by (A.5) and (A.6), respectively, then Θ_1 is asymptotically autonomous with limit system Θ_2 if (A.5) is asymptotically autonomous with limit equation (A.6).

The following result on the asymptotic behavior of solutions of (A.5) is also proved in [36]:

Theorem A.4.1 (Theorem 2.5 in [36]). *ω-Θ_1-limit sets of points (s, x) with pre-compact (forward) orbits are non-empty, compact, and connected. Further they attract the orbits, i.e., $d(\Theta_1(t, s, x), \omega_{\Theta_1}(s, x)) \to 0$ as $t \to \infty$.*

Finally they are invariant under the limit-semiflow Θ_2, in particular any point y of $\omega_{\Theta_1}(s, x)$ lies on an entire Θ_2-orbit in $\omega_{\Theta_1}(s, x)$.

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And a stronger result, i.e. Theorem A.4.2, was proved if the following hypothesis is satisfied:

E. The equilibria of Θ_2 are isolated compact Θ-invariant subsets of X. Further the ω-Θ_2-limit set of any pre-compact Θ_2-orbit consists of a Θ_2-equilibrium.

Theorem A.4.2 (Corollary 4.3 in [36]). *Let (E) hold and assume that there is no Θ_2-cyclical chain of Θ_2-equilibria. Then any pre-compact forward Φ-orbit converges towards a Θ-equilibrium for $t \to \infty$.*

For the definition of cyclicity, please see APPENDIX A.3.