CRM Master Research Projects

CENTRE DE RECERCA MATEMÀTICA

Mathematical Modeling and Analysis of the Interaction of Populations of Bacteria and Bacteriophages within Chicken Intestine

Author: Sundus Zafar

Advisor: Àngel Calsina Ballest

Universitat Autònoma
de Barcelona

MATHEMATICAL MODELING AND ANALYSIS OF THE INTERACTION OF POPULATIONS OF BACTERIA AND BACTERIOPHAGES WITHIN CHICKEN INTESTINE

Author: Sundus Zafar
Date: September, 2009
Advisor: Dr. Angel Calsina Ballesta

Abstract

Intestinal infections in poultry chickens can not only cause damage to the animals who interact with them by any means but they are also a threat to human health as chickens are a part of our food chain. This work is a study of such infections which are caused by Salmonella bacteria in chickens and their therapy with bacteriophages. We introduce a mathematical model which is a time dependent convection model to discuss the dynamics of bacterial infections and their treatment with bacteriophages within a single host. We analyze the model in one spacial dimension within the intestine of chickens by considering only the convection term. We discuss that organism remains infected due to constant stationary behavior of bacteria within the intestine when there are no bacteriophages and also observe a constant stationary behavior of bacteriophages which make the organism infection free when administered to organism with food. We explain that death of infections also depends on certain parameters which can happen without any treatment. Stability analysis with respect to x variable show that none of these constant stationary states of the model are stable. Solutions of the model for variations of burst size b, adsorption coefficients κ and $\bar{\kappa}$, growth rate α and detachment rate μ and velocity v show that dynamics is sensitive to all of them.

To my Family.

Acknowledgments

All my thanks is to Allah almighty, the most gracious and the most merciful, who give me the strength, patience, knowledge and opportunity for this accomplishment.

I then like to thank Mathematics department, UAB; for giving me the chance to write my thesis here, and CRM for their financial support for my thesis under the program of Financial Grants for Master Project.

I am greatly thankful to my thesis advisor Dr. Angel Calsina Ballesta for his support and encouragement throughout my work. I highly appreciate his interest and help in achieving my target. His supervision led me to a better understanding of the subject and enhanced my research capabilities.

I would like to thank my family and friends in my home country, Pakistan, their love and encouragement always stayed with me in my work.

I deeply appreciate my husband for his love, support, help and encouragement throughout my work, which I always want to stay with me and I would like to thank my son whose birth made me more strong, patient, organized, a keen observer and a hard worker for managing my thesis work as well as to look after him and the households. They both have a big contribution in accomplishment of my work.

Contents

Chapter 1

Introduction

This work is a part of a collaboration of Mathematics department and CRM with department of Genetics and Microbiology, UAB; on therapy of different type of bacteria with bacteriophages. It is aimed to study the use of bacteriophages to fight against Salmonella bacteria within intestine of chickens.

Salmonella has the potential to cause a bacterial infection in chickens which is not very dangerous for them but it is harmful to the health of other organisms who interact with them by any means. These infections can create a serious illness in humans also when they pass in them with food through chickens. Due to rising levels of multidrug resistant pathogenic bacteria, the use of antibiotics to treat bacterial infections is becoming compromised, it is necessary to develop some alternative methods. Therefore the interest in phage(virus) therapy has increased because of the food safety issues and the emergence of these multidrug resistant pathogenic bacteria.

Bacteriophages are viruses that are obligate intracellular parasites, which multiply inside bacteria by making use of some or all of the host biosynthetic machinery (i.e., viruses that infect bacteria.). They were discovered by Twort in 1915 during first World War and independently by Felix d'Herelle in 1917, see [8] and [9]. They gave the idea of using Bacteriophages as a method of treatment of bacterial infections. They observed that broth cultures of certain intestinal bacteria could be dissolved by addition of a bacteria-free filtrate obtained from sewage. The lysis of the bacterial cells was said to be brought about by a virus which meant a "filterable poison" ("virus" is Latin for "poison").Probably every known bacterium is subject to infection by one or more viruses or "Bacteriophages" as they are known ("phage" for short, from Gr. "phagein" meaning "to eat" or "to nibble"), see [3]. It's structure can be seen in the following figure 1.1.

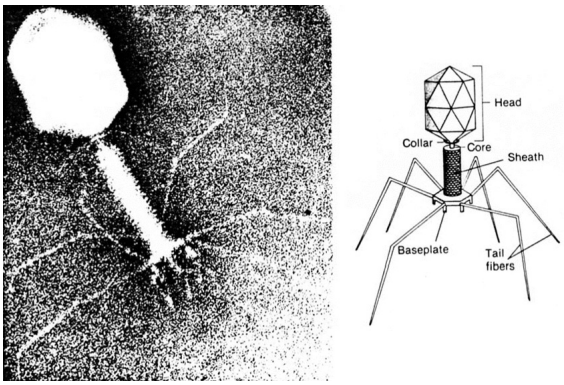

Figure 1.1: Left: Electron Micrograph of bacteriophage, Right: Model of phage . The phage possesses DNA contained within an icosahedral head. The tail consists of a hollow core through which the DNA is injected into the host cell. The tail fibers are involved with recognition of specific viral "receptors" on the bacterial cell surface, see [3].

Like most viruses, Bacteriophages typically carry only the genetic information needed for replication of their nucleic acid and synthesis of their protein coats. They may contain different materials but they

all contain nucleic acid and protein. Depending upon the phage, the nucleic acid can be either DNA or RNA but not both and it can exist in various forms, see [2]. The nucleic acids of phages often contain unusual or modified bases. These modified bases protect phage nucleic acid from nucleases that break down host nucleic acids during phage infection. A Bacteriophage can only infect certain bacteria bearing receptors that they can bind to, these receptors are on the bacteria for other purposes and phage have evolved to use these receptors for infection, which in turn determines the phage's host range. As phage virions do not move independently, they must rely on random encounters with the right receptors when in solution (blood, lymphatic circulation, irrigation, soil water etc.). This explains the modeling of these infections by means of Law of mass action. After making contact with the appropriate receptor, the phage then injects genetic material through the bacterial membrane. When the phage has gotten through the bacterial envelope, the nucleic acid from the head passes through the hollow tail and enters the bacterial cell. Usually, the only phage component that actually enters the cell is the nucleic acid. The remainder of the phage remains on the outside of the bacterium, this process is called *adsorption*. The virus nucleic acid uses the host cell's machinery to make large amounts of viral components. After many copies of viral components are made, they are assembled into complete viruses. The phage then directs production of an enzyme that breaks down the bacteria cell wall and allows fluid to enter. The cell eventually becomes filled with viruses (typically 100-200 is the burst size) and liquid, and bursts or lyses; as the host cells are ultimately killed by lysis, this type of viral infection is referred to as *lytic infection*, see [1] and [3]. It can be seen in the following figure 1.2.

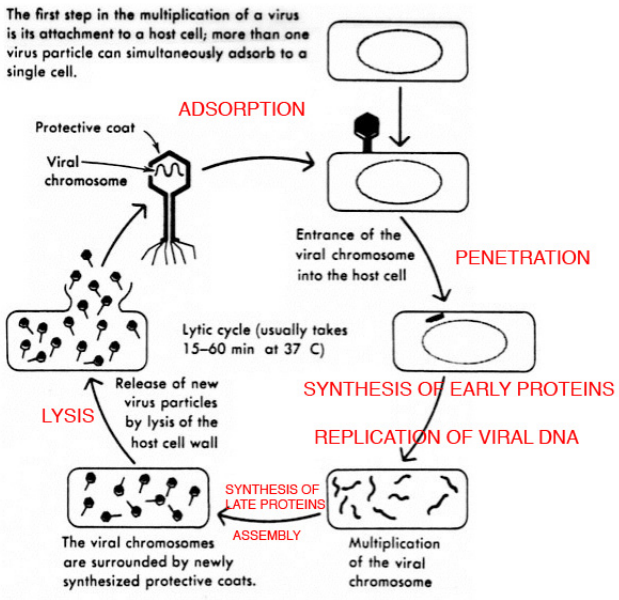

Figure 1.2: The lytic cycle of a bacterial virus, e.g. Bacteriophage, see [3].

Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections. Phage therapy is an alternative to antibiotics being developed for clinical use by research groups in Eastern Europe and the U.S. Several studies have shown that the bacteriophages may be useful in reducing the number of *Escherichia coli* O157, *Campylobacter*, *Listeria* and *Salmonella* contaminating the surface of food. Studies have also recently sought to utilize bacteriophages to treat airsacculitis in chickens and infections of fish. Several studies have investigated the use of bacteriophages to reduce *Salmonella* loads in the poultry intestine; however its application is resulted in modest success. Therefore in this work we will study the interaction of bacteriophages with *Salmonella* bacteria in order to cure the bacterial infections within chicken intestine by bacteriophages. An important benefit of phage therapy is derived from the observation that bacteriophages are much more specific than most antibiotics that are in clinical use. Theoretically, phage therapy is harmless to the eucaryotic host undergoing therapy, and it should not affect the beneficial normal flora of the host. Phage therapy also has few, if any, side effects, as opposed

to drugs, and does not stress the liver. Since phages are self-replicating in their target bacterial cell, a single, small dose is theoretically efficacious. On the other hand, this specificity may also be disadvantageous because a specific phage will only kill a bacterium if it is a match to the specific subspecies. Thus, phage mixtures may be applied to improve the chances of success, or clinical samples can be taken and an appropriate phage can be identified and grown, see [3].

This research is aimed to study and to develop an understanding of intestinal infections in poultry chickens. In order to study such infections at population level, one needs to understand these infections on an individual level and determine some individual characteristics. We can study the dynamics of bacteriophages and bacteria and their interaction within host at individual level and carry it to their dynamics within host at population level. Thus in our research we aim to model the dynamics of interaction between bacteriophages and Salmonella in the intestine of a single infected host. We draw an understanding of their interaction in one spatial dimension that is the direction of flow of food in the intestine of the organism which is the source of bacteriophages and Salmonella bacteria to move and to get interacted in the intestine in that direction. First we construct a mathematical model which is a time dependent convection model of interactions of bacteriophages with Salmonella bacteria. We establish the conditions which give the stationary solutions of the model in the case when the bacteria will grow in the intestine and when they will die due to treatment or infections by bacteriophages. Secondly we investigate whether or not these stationary solutions are stable. We have addressed the above in two different cases; when there is no inflow of bacteriophages i.e. when the organism or host is not treated with phages and when the host is infected or treated with some dose of bacteriophages. We then make an analysis of parameters of the model to develop an understanding of their affect on dynamics in the model.

This research work is structured as follows. The model describing the infections of two types of bacteria in the intestine and their interaction with bacteriophages within the intestine is introduced in chapter 2, we discuss the idea of the model and make a numerical exploration of our model for two different cases drawing some biological interpretations in chapter 3, we establish the conditions for stationary solutions of the model in chapter 4, and carry out the stability analysis of the constant stationary solutions in the sense of their behavior with respect to the x variable in chapter 5, we observe the model parameters and analyzed them in chapter 6. In chapter 7 we present the conclusions, propose some facts related to infections which can be of interest to biologists and mathematicians. In chapter 8, we give the `Matlab` codes or programs used to find the solutions of the model and for other similar purposes.

Chapter 2

Mathematical Model

2.1 Introduction and motivation

We begin our study by writing the following system of ODE's;

$$\begin{aligned} \frac{dS}{dt} &= \alpha S - \kappa PS, \\ \frac{dI}{dt} &= \kappa PS - \frac{1}{T} I, \\ \frac{dP}{dt} &= -\kappa PS + \frac{b}{T} I. \end{aligned} \tag{2.1}$$

System (2.1) is a simple model for bacteriophage infections, in this model S is the density (i.e., number of bacteria per ml) of susceptible bacteria, I is the density of infected bacteria, and P is the density (number of viruses per ml) of viruses (phages). A bacterium becomes infected I when viruses P attack the susceptible bacteria S and successfully injects its genetic material through the bacterial membrane. The virus then starts replicating inside the bacterium. The infected bacterium does not replicate itself by division. After a latency time of average length of time equal to T, an infected bacterium will die by lysis; i.e., the bacterium explodes releasing b copies $(b > 1)$ of the virus, where b is called the burst size, which are then free to attack other susceptible bacteria.

Previously, Gourley and Kuang discussed the dynamics of marine bacteriophages in [7], they have proposed a delay reaction diffusion model in one spatial dimension, it can be seen as follows:

$$\frac{\partial S(x,t)}{\partial t} = D_s \frac{\partial^2 S(x,t)}{\partial x^2} + \alpha S(x,t)\left(1 - \frac{S(x,t)}{\gamma}\right) - \kappa S(x,t) P(x,t), \tag{2.2}$$

$$\begin{aligned} \frac{\partial P(x,t)}{\partial t} &= D_p \frac{\partial^2 P(x,t)}{\partial x^2} - \mu_p P(x,t) - mP^2(x,t) - KS(x,t)P(x,t) + \\ &\quad b \times \{\text{rate of death of infectives by lysis}\} \end{aligned}$$

On an infinite one-dimensional domain $-\infty < x < \infty$, in their work this model helps to discuss what types of diffusion are appropriate and derivation of the time-delay terms for the case when there is diffusion, importantly it discusses the movement of infectives during the period between infection and lysis, so when an infective dies by lysis it will release b copies of the virus into the water at a different location from where it originally became infected.

This model assumes that once a bacterium become infected by a virus, it no longer competes with susceptibles for resources.This assumption means that there is no need of differential equation for $I(t)$. On the right hand side, D_s and D_p are the diffusivities of the susceptibles and the phages. The second term in the S equation shows a logistic growth of susceptibles, the last term in the S and fourth term

in P equation reflect the loss of bacteria and phages due to infections, and the last term in P equation shows the fact that each time an infective dies by lysis, it releases b copies of the virus. The difficulty of writing this last term in mathematical form is due to the fact that, already discussed, that lysis occurs at a different place than infection.

On the other hand Boldin [5] discussed the persistence and spread of bacterial gastro intestinal infections in her recent work. Her work is focused on within host dynamics and present a model describing the dynamics of pathogens in the intestine of a single host. Her model offers an acceptable description of within-host dynamics of several other gastro-intestinal infections. It represents the intestine as a cylindrical, but not necessarily circular, tube of length L, of constant cross-sectional area A and of constant circumference C. It considers two types of bacteria: the ones attached to the wall of the intestine and free bacteria that move down the intestine. First it helps to establish the conditions that guarantee growth of pathogens in the intestine and specify when the pathogen population will not be able to persist and then secondly it investigates the convergence of pathogens to a stable pathogen distribution.

The work done by Viladrich in [10] and by Gallardo in [6] is also used as reference for the following model. In their work they have focused on interactions of bacteriophages and bacteria with constant latency period T for lysis.

2.2 Model for interaction of bacteria and bacteriophages within intestine

In this work, we have proposed a model of interaction between *Salmonella* bacteria infecting the intestine of chickens and their specific bacteriophages. Following the lines of Boldin [5] and adding the virus populations, we present a model describing the dynamics of bacteria (*Salmonella*) and virus (bacteriophages) in the intestine of a single host. We consider two types of susceptibles (bacteria) and viruses (phages), ones attached $\bar{S}$ and $\bar{P}$ at the wall of the intestine and the free bacteria S and phages P which move down in the intestine of the organism. We derive our model in a finite one dimensional domain $x = [0, L]$, which is the length of intestine in cm i.e. the intestine starts at $x = 0$ and ends at $x = L$, we consider a zero influx of bacteria and a constant influx of viruses (bacteriophages) P at the boundary $x = 0$ which we assume they are administered to the host mixed with the food.

The model we present discuss that for a given constant dose of bacteriophages P, how they affect the growth of susceptible bacteria, $\bar{S}$ at the wall and the free bacteria S in the intestine due to infections, and how much free phages P and free bacteria S at $x = L$ move out of the intestine and leave the organism. Like in Gourley and Kuang [7] we also assume that once a bacterium becomes infected by a virus, it no longer competes with susceptibles for resources therefore we do not need a differential equation for infectives I and we also neglect the latency period T. This avoids the need of an analysis like the one in the last term of P equation in (2.2). Similarly we consider the logistic growth of susceptibles $\bar{S}$ and S. According to our assumptions, we now impose the boundary conditions: $S(0, t) = 0$ and $P(0, t) = P_0$ and derive our model which is the following system of PDE's.

$$\frac{\partial S}{\partial t} + v\frac{\partial S}{\partial x} = \left(\alpha\left(1 - \frac{S}{U}\right) - (\kappa P + \bar{\kappa}\bar{P})\right) S - \lambda_1 S + \mu_1 \bar{S}, \tag{2.3}$$

$$\frac{\partial \bar{S}}{\partial t} = \left(\alpha\left(1 - \frac{\bar{S}}{\bar{U}}\right) - (\bar{\kappa} P + \bar{\bar{\kappa}}\bar{P})\right) \bar{S} + \lambda_1 S - \mu_1 \bar{S}, \tag{2.4}$$

$$\frac{\partial P}{\partial t} + v\frac{\partial P}{\partial x} = (b-1)\,\kappa S P + b\bar{\kappa}\bar{P}S - \bar{\kappa}\bar{S}P - \lambda_2 P + \mu_2 \bar{P}, \tag{2.5}$$

$$\frac{\partial \bar{P}}{\partial t} = (b-1)\,\bar{\bar{\kappa}}\bar{S}\bar{P} + b\bar{\kappa}\bar{S}P - \bar{\kappa}\bar{P}S + \lambda_2 P - \mu_2 \bar{P}, \tag{2.6}$$

where $S = S(x,t)$, $\bar{S} = \bar{S}(x,t)$, $P = P(x,t)$ and $\bar{P} = \bar{P}(x,t)$. Here we assume that the free bacteria S and viruses P move with constant velocity v i.e. the flow of food through which the free bacteria S and viruses P move in the intestine is steady. The rate at which the attached bacteria(viruses) detach from the wall is $\mu_1(\mu_2)$ and the rate at which the free bacteria(viruses) attach to the wall is $\lambda_1(\lambda_2)$, $U(\bar{U})$ is the carrying capacity of free(S)(attached$(\bar{S})$) bacteria and $\kappa(\bar{\kappa})$ the adsorption constant for free(attached) bacteria and viruses, whereas $\bar{\bar{\kappa}}$ is the transmission coefficient for attached bacteria $\bar{S}$ and attached viruses $\bar{P}$, b the burst size and α is the bacterial growth rate constant.

The first term on right hand side in (2.3) and (2.4) shows the logistic growth of attached and free bacteria $(\bar{S}, S)$ and the second term the loss of attached and free bacteria $(\bar{S}, S)$ due to infections, the rest gives the loss and gain of attached and free bacteria population due to detachment and attachment from the wall of intestine. Similarly in (2.5) and (2.6) the first three terms on right hand side show that each time an infective dies, it releases b copies of viruses thus giving the number of viruses produced at any time and the loss of viruses due to the infections, there we assume that a lysis of a free bacterium produce free phages whereas the attached ones produce the attached viruses. Finally the fourth and fifth terms give the loss and gain of viruses due to attachment and detachment from the wall of intestine. The terms on the left hand side of the system involve the time derivatives whereas (2.3) and (2.5) have the convection terms of S and P.

Chapter 3

Model Analysis

Instead of analyzing the model derived in previous section we will consider a simplified version of it, which seems rather realistic from the biological point of view. Indeed we will assume that there are no attached viruses $\bar{P}$ at the wall of the intestine and the infections of bacteria by bacteriophages happen due to the free phages P only. i.e. Only free viruses P can interact with the attached bacteria $\bar{S}$ and free bacteria S within the intestine of chickens. In particular lysis of attached bacteria will result in releasing free phages. This leaves us with the following system of PDE's:

$$\frac{\partial S}{\partial t} + v\frac{\partial S}{\partial x} = \left(\alpha\left(1 - \frac{S}{U}\right) - \kappa P\right) S - \lambda S + \mu\overline{S}, \tag{3.1}$$

$$\frac{\partial \overline{S}}{\partial t} = \left(\alpha\left(1 - \frac{\overline{S}}{\overline{U}}\right) - \overline{\kappa} P\right) \overline{S} + \lambda S - \mu\overline{S}, \tag{3.2}$$

$$\frac{\partial P}{\partial t} + v\frac{\partial P}{\partial x} = (b-1)\left(\kappa S + \bar{\kappa}\bar{S}\right)P. \tag{3.3}$$

We are interested in looking for the stationary solutions of the above model in a bounded one dimensional domain $[0, L]$, they are analytically discussed in next section. In this section we want to see how our model behaves for different values of P_0; that is how it behaves for the imposed boundary condition i.e. $P(0,t) = P_0$ which means there is a constant influx P_0 of bacteriophages P. With `Matlab` we will get some graphs which can help us to understand and analyze the affect of P_0 on attached bacteria $\bar{S}$ and free bacteria S population. As we are interested in stationary solutions of our model in the sense of their behavior with respect to the x variable, we ignore the time derivatives in our model i.e. we assume all the time derivatives to be equal to zero. However the time dependence is important and it can be taken under consideration for any future work on this model e.g. for addressing the stability of the steady states, etc.

We begin our work by making the time derivatives zero in (3.1), (3.2) and (3.3) i.e. by making $\frac{\partial S}{\partial t} = 0$, $\frac{\partial \overline{S}}{\partial t} = 0$ and $\frac{\partial P}{\partial t} = 0$ in the above model, we have the following system of ODE's:

$$\nu\frac{dS}{dx} = \left(\alpha\left(1 - \frac{S}{U}\right) - \kappa P\right) S - \lambda S + \mu\overline{S}, \tag{3.4}$$

$$0 = \left(\alpha\left(1 - \frac{\overline{S}}{\overline{U}}\right) - \overline{\kappa} P\right) \overline{S} + \lambda S - \mu\overline{S}, \tag{3.5}$$

$$\nu\frac{dP}{dx} = (b-1)\left(\kappa S + \bar{\kappa}\bar{S}\right)P. \tag{3.6}$$

From (3.5) which does not contain any derivative we can get an explicit formula for $\bar{S}$ in terms of S and P, which can be seen as follows:

$$\overline{S}(x) = \frac{\left[-\left(\overline{\kappa}P(x) + (\mu - \alpha)\right) \pm \sqrt{\left(\overline{\kappa}P(x) + (\mu - \alpha)\right)^2 + 4\frac{\alpha\lambda S(x)}{\overline{U}}}\right]}{2\frac{\alpha}{\overline{U}}}.$$

As $\overline{S}$ cannot be negative so we will consider only the positive part of the above parabola. i.e.

$$\overline{S}(x) = \frac{\left[-\left(\overline{\kappa}P(x) + (\mu - \alpha)\right) + \sqrt{\left(\overline{\kappa}P(x) + (\mu - \alpha)\right)^2 + 4\frac{\alpha\lambda S(x)}{\overline{U}}}\right]}{2\frac{\alpha}{\overline{U}}} =: G\left(S(x), P(x)\right). \tag{3.7}$$

Nevertheless, notice that for $S(0) \equiv 0, \bar{S} \equiv 0$ is always a solution. Hence for any non negative constant P, $(0, 0, P)$ is a (trivial) solution of the system of ODE's (3.4) - (3.6), i.e. a trivial stationary solution of our model of PDE'S (3.1) - (3.3).

By substituting the value of $\bar{S}$ from (3.7) in (3.4) and (3.6), we get the following system of equations.

$$\nu\frac{dS(x)}{dx} =: F\left(S(x), P(x)\right), \tag{3.8}$$

$$\nu\frac{dP(x)}{dx} =: H\left(S(x), P(x)\right), \tag{3.9}$$

where

$$F(S, P) = \left(\alpha\left(1 - \frac{S}{U}\right) - \kappa P\right)S - \lambda S + \mu G(S, P), \tag{3.10}$$

$$H(S, P) = (b - 1)\left(\kappa S + \bar{\kappa}G(S, P)\right)P. \tag{3.11}$$

We now consider the system of equations (3.8) and (3.9) as our model for the analysis purpose with initial conditions $S(0) = 0$ and $P(0) = P_0$ where $P_0 \geq 0$ is a constant, they are derived from the imposed boundary conditions in the original model.

We now investigate the above system in the following two different cases:

3.1 In the absence of free phages P

We first consider that the organism is not treated with bacteriophages P, i.e. $P(0) = P_0$ where $P_0 = 0$, following graphs show how the bacteria infect the organism in this case and on which parameters the infections depend.

Figure 3.1 below is a result of the case when there is no interaction of bacteriophages P with bacteria $\bar{S}$ and S, as the influx $P_0 = 0$. This clearly shows that the organism is not yet cured from bacterial infection, it can be seen through the increase in bacterial populations $\bar{S}$ and S in figure 3.1. We can also understand the process of attachment and detachment of bacteria from the wall of the intestine in this figure 3.1, which we have assumed in our model . The free bacteria population S starts at 0, this satisfies our initial condition $S(0) = 0$, then as they move along the intestine, the attached bacteria population $\bar{S}$ on the wall keep on adding in free bacteria population S because they keep on detaching from the wall as the food passes through the intestine and the free bacteria population keep on attaching at the wall. From the results of figure 3.1 we can see that free bacteria population S is greater than attached bacteria population $\bar{S}$, this clearly indicates that the detachment rate was higher than attachment as $\mu > \lambda$, also the free bacteria population is larger than it was expected as the carrying capacity $U = 8$, and the population of S is less than expected as the carrying capacity $\bar{U} = 10$ which is also the result of the case $\mu > \lambda$. We can also see that at length $x = 800$, both populations start showing stationary behavior, which gives the amount of attached bacteria population $\bar{S}$ which will remain inside the organism and amount of free bacteria population S that will move down the intestine and will leave the organism at the end of the intestine i.e. at $x = L$.

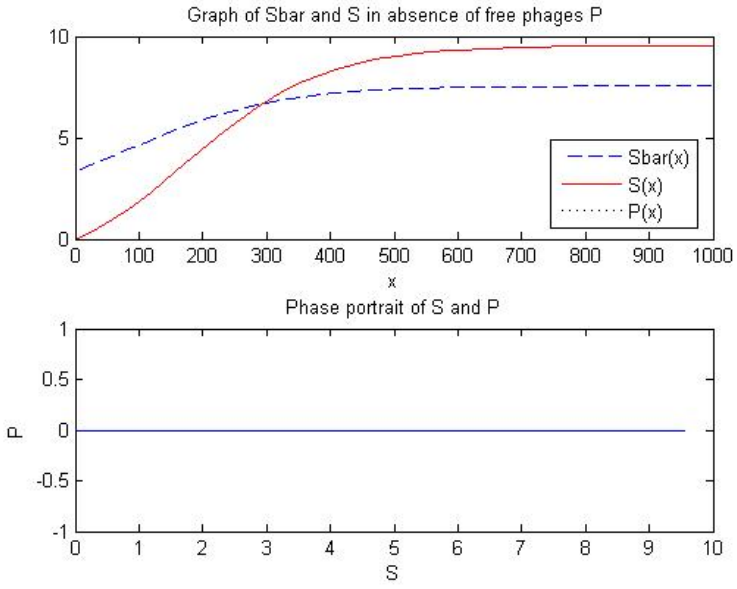

Figure 3.1: In this plot $\mu > \lambda$ where $P_0 = 0, \bar{U} = 10, U = 8, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

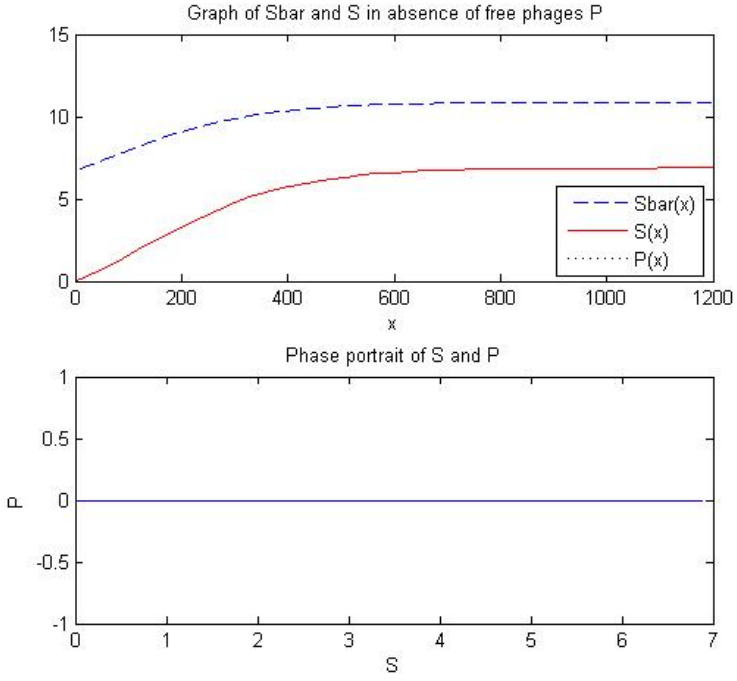

Figure 3.2: In this plot $\mu < \lambda$ where $P_0 = 0, \bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.01, \lambda = 0.02, b = 10, v = 5$.

In this figure 3.2, we have considered that $\mu < \lambda$ that is; the attachment rate is higher than the detachment rate, also $\bar{U} < U$ that is; the carrying capacity of attached bacteria population $\bar{S}$ is less than the carrying capacity of free bacteria population S, which can be clearly seen in figure 3.2. Due to high attachment rate λ the population of attached bacteria is increased than its carrying capacity $\bar{U}$ whereas because of low detachment rate μ the population of free bacteria is less than its carrying capacity U.Therefore less bacteria will leave the organism and their large population will remain inside the organism.

3.2 In the presence of free phages P

We now give a constant amount of dose of bacteriophages P to the organism, i.e. we now impose the initial condition $P(0) = P_0 > 0$, where P is equal to P_0 millions individuals per ml of solution. We want to see how this dose P_0 works on bacteria populations $\bar{S}$ and S. Below are some graphs which can help us to understand the situation;

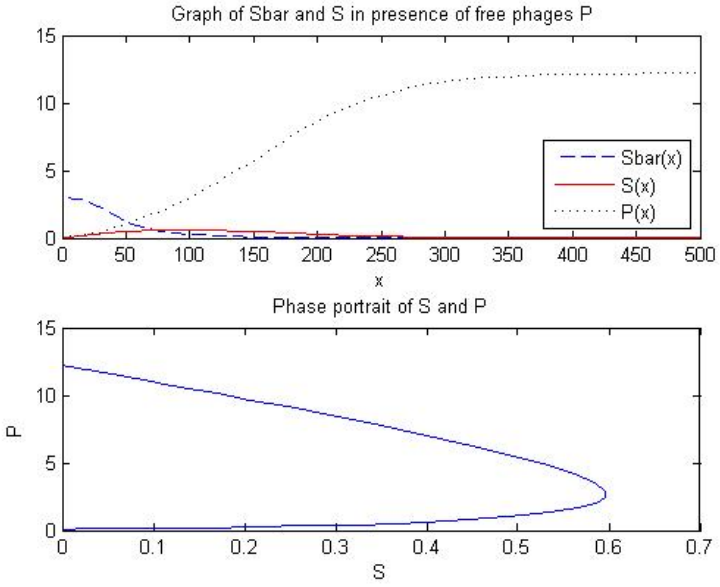

Figure 3.3: In this plot $P_0 = 0.1$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

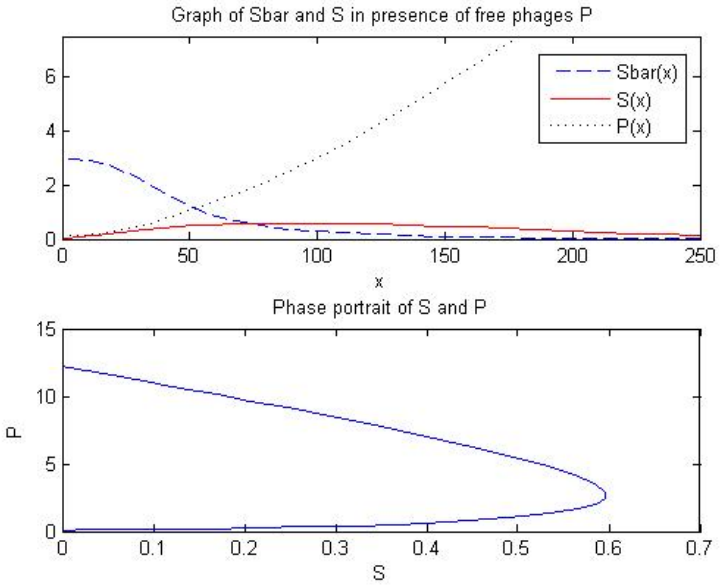

Figure 3.4: In this plot $P_0 = 0.1$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

Figure 3.4 is a close look of figure 3.3, it is a result of the case when we consider a constant intake of bacteriophages P in the organism. We see in the plot that due to the infections of attached bacteria population $\bar{S}$ and free bacteria population S by free phages P, both populations don't grow and increase,

they show a decreasing behavior along the intestine which can be observed by their negative slope. Also we can see that they decline before reaching their carrying capacity. As we have given a very small dose of free phages P so the infections of bacteria and viruses (bacteriophages) are very few in the beginning of the intestine, but once where the phages P start replicating their population grow very quickly and the number of infections increases, this can be seen through their rapid growth after they reach $x = 50$ in the intestine. Also both bacteria populations start to decline as attached bacteria population $\bar{S}$ reaches $x = 100$ and free bacteria population S reaches $x = 200$ in the intestine, because of infections and eventually in the middle of intestine at $x = 250$ all the bacteria are finished and only a certain amount of free phage population P move down the intestine and leave the organism, this can be seen in figure 3.3.

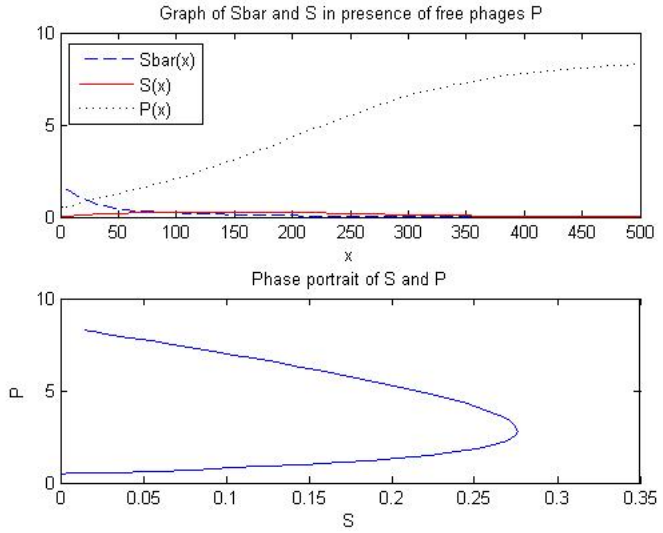

Figure 3.5: In this plot $P_0 = 0.5$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

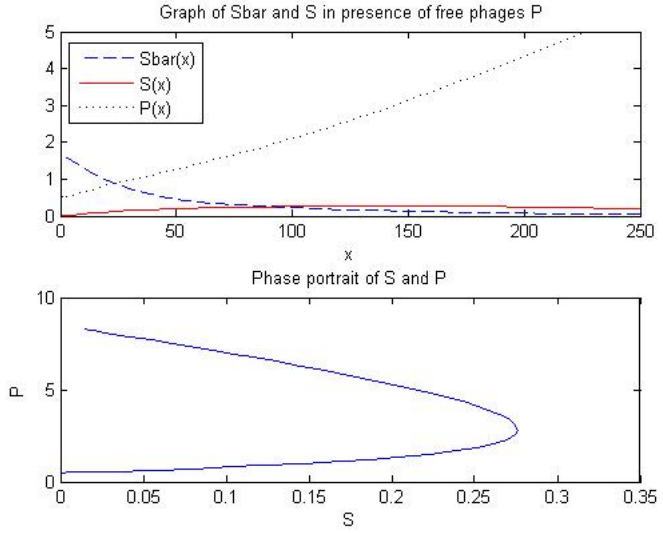

Figure 3.6: In this plot $P_0 = 0.5$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

Figure 3.6 is a close look of figure 3.5, in this we consider a constant intake P_0 of bacteriophages P, which is larger than the previous one i.e. $P_0 = 0.5$, to the organism. We see a clear effect of high dose of free phages P in the plot as both bacteria populations $\bar{S}$ and S die more quickly than in the

previous case, see figure 3.4, as we have given a large dose of phages P and the infections of bacteria and viruses (bacteriophages) are large so the phages P starts replicating from the beginning of intestine and their population grow very quickly and the infections keep on increasing, this can be seen through their rapid growth from the start. We can see the influence of high phage population P on attached bacteria population $\bar{S}$, it is lesser than the previous case from the beginning of intestine. Also both bacteria populations start declining as attached bacteria population $\bar{S}$ reaches $x = 150$ and free bacteria population S reaches $x = 200$ in the intestine, because of infections and eventually in the middle of the intestine at $x = 350$ all the bacteria are finished and only a certain amount of phage population P move down the intestine and leave the organism, this can be seen in figure 3.5.

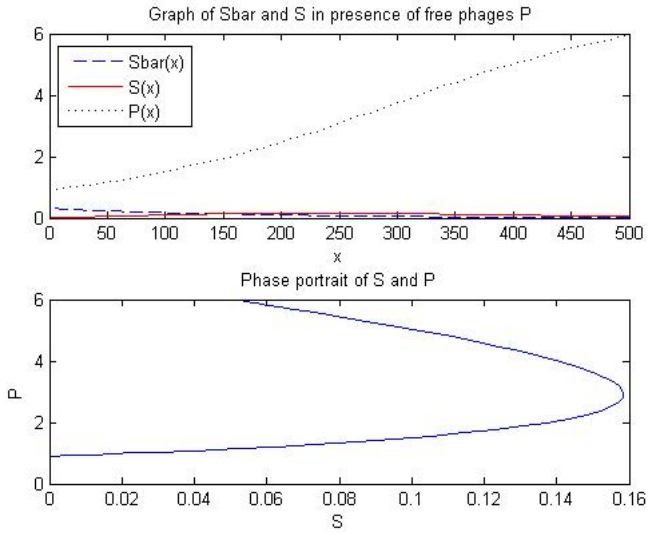

Figure 3.7: In this plot $P_0 = 0.9$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

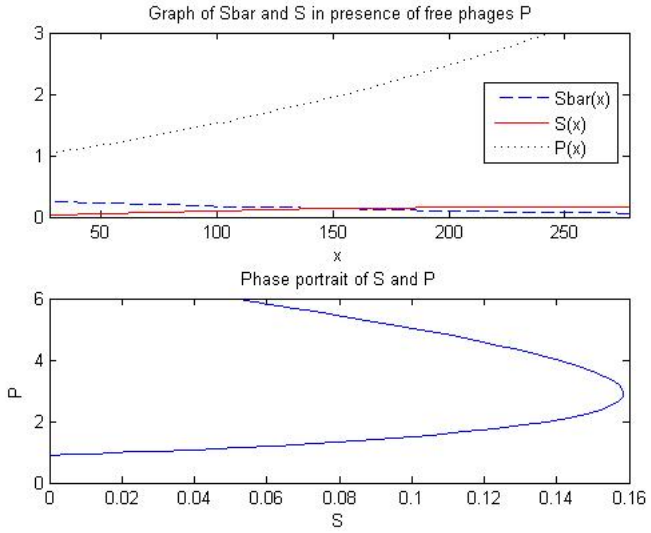

Figure 3.8: In this plot $P_0 = 0.9$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

Figure 3.8 is a close look of figure 3.7, in this we consider a constant intake P_0 of bacteriophages P, which is even larger than the previous one i.e. $P_0 = 0.9$, in the organism. We see a clear effect of high dose of free phages P in the plot as both bacteria populations $\bar{S}$ and S are very less now than the previous cases, see figure 3.8, as we have given a very high dose of phages P, the infections of bacteria by viruses (bacteriophages) are very large so the phages P start replicating from the beginning of the intestine and their population grow very quickly and the infections keep on increasing, this can be seen through their rapid growth after P reaches $x = 35$. Also both bacteria populations start declining as attached bacteria population $\bar{S}$ reaches $x = 150$ and free bacteria population S reaches $x = 250$ because of high infections and eventually near the end of intestine $x = 350$ all the bacteria are finished and only a certain amount of phage population P move down the intestine and leave the organism, this can be seen in figure 3.3.

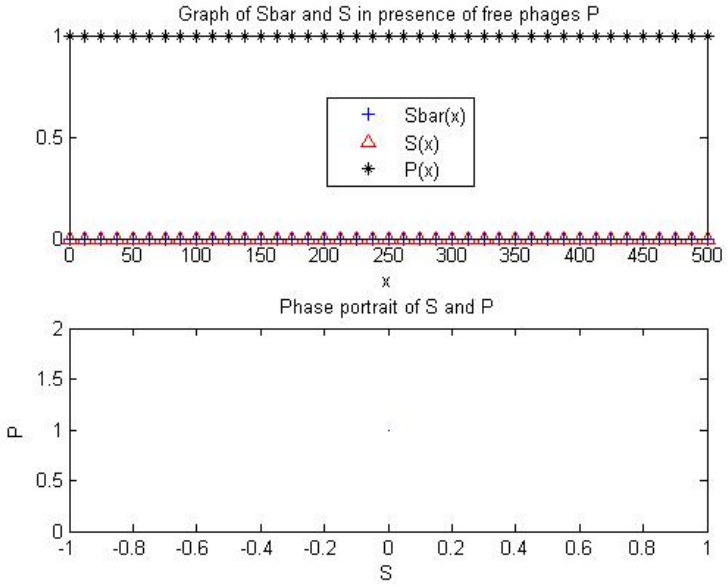

Figure 3.9: In this plot $P_0 \geq 1$ where $\bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$.

In this figure 3.9 we see a result of even more larger dose than all the above cases, i.e. $P_0 \geq 1$, this is very high such that it has treated or infected the bacteria very quickly so all the bacteria are finished or killed and we cannot see any bacteria in the intestine, also the phage population is constant, it's because there are no bacteria in the intestine so they cannot infect them and thus cannot replicate and grow.

From the above analysis we can conclude that a small dose of P can work the same as the large doses of phages P, however less efficiently, but it is enough to kill the bacteria.

Chapter 4

Constant Stationary Solutions of the Model

4.1 In the absence of free phages P

We now consider our system of ODE's (3.8) and (3.9), and study it analytically to look for the equilibrium points of it first in the case when **there are no phages i.e.** $P = 0$. This assumption satisfies equation (3.9) thus by putting $\frac{dS(x)}{dx} = 0$ in (3.8), we are left with the following algebraic expression:

$$F(S,0) =: \bar{F}(S) = \left(\alpha\left(1 - \frac{S}{U}\right)\right)S - \lambda S + \mu\bar{G}(S) = 0, \tag{4.1}$$

where

$$G(S,0) =: \bar{G}(S) = \frac{-(\mu-\alpha) + \sqrt{(\mu-\alpha)^2 + \frac{4\alpha\lambda S}{\bar{U}}}}{2\frac{\alpha}{\bar{U}}}.$$

We begin with our initial guess $S = 0$ and see if it is an equilibrium of (4.1), which could mean that all the bacteria finish or the organism is recovered at equilibrium from bacterial infection without the treatment of bacteriophages P . Thus by putting $S = 0$ in (4.1), we get the following:

$$\bar{F}(0) = \mu\frac{-(\mu-\alpha) + |\mu-\alpha|}{2\frac{\alpha}{\bar{U}}},$$

which implies that

$$\bar{F}(0) = \begin{cases} 0 & \text{if } \mu \geq \alpha \\ \frac{\mu(\alpha-\mu)}{\frac{\alpha}{\bar{U}}} & \text{if } \mu < \alpha \end{cases}. \tag{4.2}$$

The above function shows that $S = 0$ is an equilibrium point of our system (3.8) and (3.9) for $P = 0$ only when $\mu \geq \alpha$. This result shows that when there are no phages P the bacterial infection S can only finish by itself or the organism can become safe from it only when the detachment rate μ of $\bar{S}$ is greater or equal to its growth rate α, this allow the attach bacteria population $\bar{S}$ to detach quickly and add into free bacteria population S and leave the organism rather than to produce quickly and infect the organism. Whereas in the other case when $\mu < \alpha$, the attached bacteria population $\bar{S}$ grow more than to detached from the wall therefore the organism remains infected therefore $S = 0$ is not an equilibrium point of our system (3.8) and (3.9) in this case.

We now further investigate (4.1) and look for its nonzero equilibrium points first in the case when $\mu < \alpha$. For this purpose we use Maple to get our required result which can be seen as follows, where $S = x, \alpha = a, \lambda = L, \mu = m, \bar{U} = v, U = u$:

```
> a = 0.03;
> m = 0.02;
> L = 0.01;
> u = 4;
> v = 10;

> C := 2*(a*x^2/u-(a-L)*x)*a/v;
0.00004500000000 x  - 0.0001200000000 x

> Z := m*sqrt((m-a)^2+4*a*L*x/v);
0.02 (0.0001 + 0.0001200000000 x)

> Y := m*(m-a);
-0.0002

> Final := C+Y-Z;
0.00004500000000 x  - 0.0001200000000 x - 0.0002
- 0.02 (0.0001 + 0.0001200000000 x)

> solve(Final, x);
5.648090637
```

Which implies that (4.1) has a unique positive equilibrium point when $\mu < \alpha$ which is $(S, P) = (5.648090637, 0)$. We will now verify our result through Matlab by plotting the following graphs.

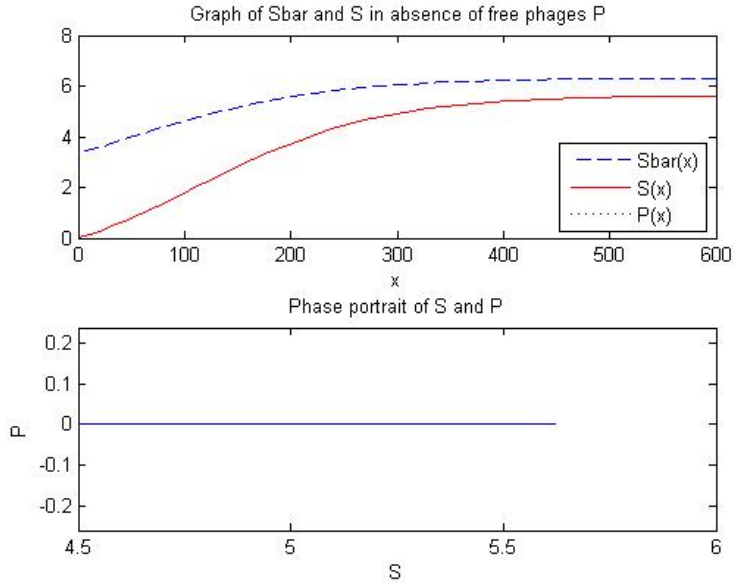

Figure 4.1: In this plot $\mu < \alpha$ where $P_0 = 0, \bar{U} = 10, U = 4, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, v = 5$. We can see the stationary solution $(S, P) = (5.648090637, 0)$ in the phase portrait.

Now considering the other case when $\mu > \alpha$, finding the solution through Maple as follows:

```
> a = 0.02;
> m = 0.03;
> L = 0.01;
> u = 4;
> v = 10;
```

```
> solve(Final, x);
0., 5.593076209
```

Thus in this case when $\mu > \alpha$ we have two equilibrium points i.e. $(S, P) = (0, 0)$, which verifies the previous results for this case, and $(S, P) = (5.593076209, 0)$, We can see only the zero solution through Matlab in this case in the following figure 4.2 as it can only show one solution at a time, which is the first one.

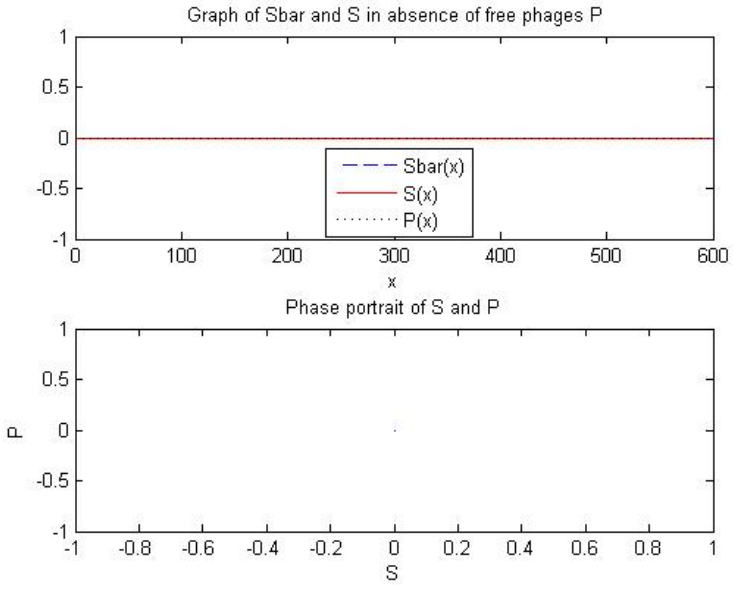

Figure 4.2: In this plot $\mu > \alpha$ where $P_0 = 0, \bar{U} = 4, U = 10, \alpha = 0.02, \mu = 0.03, \lambda = 0.01, v = 5$.

Now we consider the case when $\mu = \alpha$, and find the solutions through Matlab as follows:

```
> a = 0.02;
> m = 0.02;
> L = 0.01;
> u = 4;
> v = 10;

> solve(Final, x);
0., 5.734920049
```

In this case when $\mu = \alpha$ we also get two equilibrium points i.e. $(S, P) = (0, 0)$, which verifies the previous results for this case, and $(S, P) = (5.734920049, 0)$, we can only see the zero solution through Matlab as the above figure 4.2 in this case.

We can conclude from the above results that in the case when there are no phages $P = 0$, we have different equilibrium points for different cases which depend on the parameters of our system (3.8) and (3.9). They are , $(S_1, P) = (0, 0), (S_2, P) = (5.734920049, 0), (S_3, P) = (5.593076209, 0)$ and $(S_4, P) = (5.648090637, 0)$, where S_2, S_3, S_4 refer to a single equilibrium point of the system when there are no phages and they are different because we get them by considering three different possibilities of parameters. We have observed that these equilibrium points are constant stationary solutions of our model of equations (3.1) - (3.3).

4.2 In the presence of free phages P

Now we will look for the equilibrium points of our system of ODE's (3.8) and (3.9) in presence of free phages P i.e. $P > 0$. From the previous case we know $(S, P) = (0, 0)$ is an equilibrium of our system when $\mu \geq \alpha$. We will now first look for the equilibrium of the type $(S, P) = (0, P)$ for any constant $P > 0$, this type of equilibrium tells us that how much phage population P is enough or required to kill all the bacteria populations $\bar{S}$ and S within the organism. Hence for finding them we put $S = 0$ in (3.8) and (3.9) and get the following:

$$F(0, P) =: \bar{F}(P) = \mu \bar{G}(P), \tag{4.3}$$

$$H(0, P) =: \bar{H}(P) = (b-1)\bar{G}(P)\overline{\kappa}P, \tag{4.4}$$

where

$$G(0, P) =: \bar{G}(P) = \frac{-(\bar{\kappa}P + \mu - \alpha) + \sqrt{(\bar{\kappa}P + \mu - \alpha)^2}}{2\frac{\alpha}{\overline{\overline{U}}}},$$

that is

$$\bar{F}(P) = \mu \frac{(\alpha - \mu - \overline{\kappa}P) + |\overline{\kappa}P + \mu - \alpha|}{2\frac{\alpha}{\overline{\overline{U}}}},$$

and

$$\bar{H}(P) = (b-1)\left(\frac{(\alpha - \mu - \overline{\kappa}P) + |\overline{\kappa}P + \mu - \alpha|}{2\frac{\alpha}{\overline{\overline{U}}}}\right)\overline{\kappa}P,$$

which implies that

$$\bar{F}(P) = \begin{cases} 0 & if\ \mu \geq \alpha \\ 0 & if\ \mu < \alpha\ \wedge\ P \geq \dfrac{\alpha - \mu}{\bar{\kappa}} \\ \mu \dfrac{(\alpha - \mu - \bar{\kappa}P)}{\frac{\alpha}{\overline{\overline{U}}}} & if\ \mu < \alpha\ \wedge\ P < \dfrac{\alpha - \mu}{\bar{\kappa}} \end{cases}, \tag{4.5}$$

and

$$\bar{H}(P) = \begin{cases} 0 & if\ P = 0 \\ 0 & if\ \mu \geq \alpha \\ 0 & if\ \mu < \alpha\ \wedge\ P \geq \dfrac{\alpha - \mu}{\bar{\kappa}} \\ (b-1)\left(\dfrac{(\alpha - \mu - \bar{\kappa}P)}{\frac{\alpha}{\overline{\overline{U}}}}\right)\bar{\kappa}P & if\ \mu < \alpha\ \wedge\ P < \dfrac{\alpha - \mu}{\bar{\kappa}} \end{cases}, \tag{4.6}$$

therefore

$$\bar{F}(P) = \bar{H}(P) = \begin{cases} 0 & if\ \mu \geq \alpha \\ 0 & if\ \mu < \alpha\ \wedge\ P \geq \dfrac{\alpha - \mu}{\bar{\kappa}} \end{cases}. \tag{4.7}$$

The above function in (4.7) show us that equations (4.3) and (4.4) are both always satisfied for any point

$(S, P) = (0, P)$ when $\mu \geq \alpha$, this implies that if the growth rate α is less than the detachment rate μ then the production of attached bacteria $\bar{S}$ is less than their detachment rate from the wall, therefore their large population detach from the wall and add in to free bacteria population S and eventually move down the intestine or wash out. We can say that they all vanish from the intestine of the organism. We have observed the same behavior also when they are both equal i.e $\mu = \alpha$. We see that the phage population P is not increased and they show a constant behavior, it's because when $\mu \geq \alpha$ all the bacteria vanish and the phages don't get the chance to infect them or the infections are so small and they don't have any influence on their population growth, so they don't replicate and don't grow, this agrees with the previous result in this section. On the other hand when $\mu < \alpha$ the growth rate of $\bar{S}$ is larger than the detachment rate which implies that more attached bacteria $\bar{S}$ are produced than detached and less become free S and move down the intestine, also because of large number of infections in this case, as bacteria population do not vanish and phages P replicate very quickly, the phage population P increases very much. Therefore (4.7) tells us that in this case all the bacteria will finish eventually when the phage population will increase and reach $P \geq \frac{\alpha - \mu}{\bar{\kappa}}$. The equations (4.3) and (4.4) are both satisfied for these points $(S, P) = (0, P_s) = (0, \frac{\alpha - \mu}{\bar{\kappa}})$ and $(S, P) = (0, P_i)$ for any P_i such that $P_i \geq P_s$ always, therefore these points are the required equilibrium points of our system (3.8) and (3.9) in this case. We observe that they are the constant stationary solutions of our model of equations (3.1) - (3.3). Now we look at the following plots from Matlab to verify the above results.

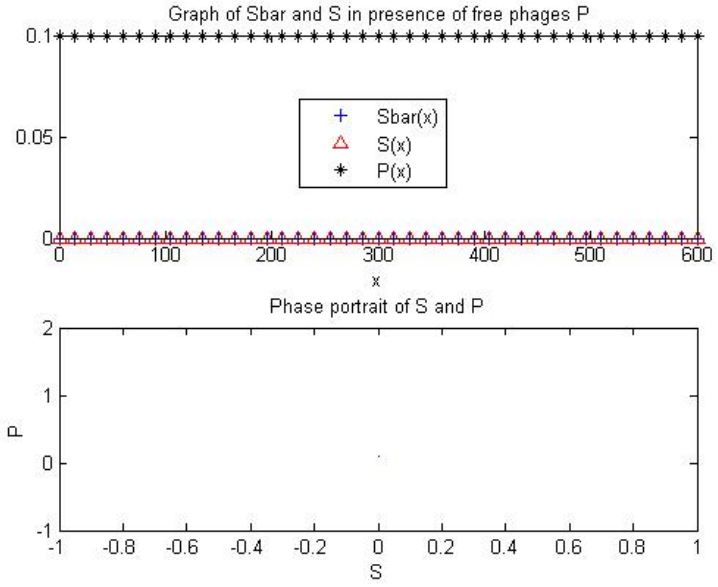

Figure 4.3: In this plot $\mu \geq \alpha$, where $P_0 = 0.1, \bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.02, \mu = 0.03, \lambda = 0.01, b = 10, v = 5$. This shows us that when $\mu \geq \alpha$ all the bacteria population vanish, as they leave the organism, therefore phage population P remain constant because they cannot infect the bacteria and cannot replicate and grow.

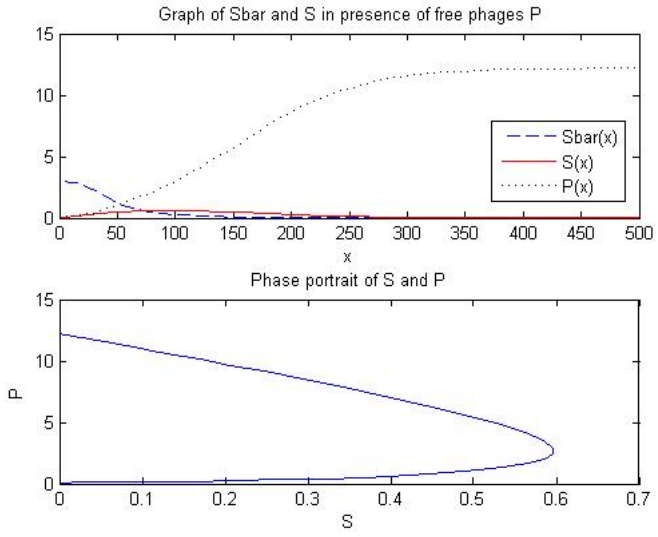

Figure 4.4: In this plot $\mu < \alpha$, where $P_0 = 0.1, \bar{U} = 4, U = 10, \kappa = \bar{\kappa} = 0.01, \alpha = 0.03, \mu = 0.02, \lambda = 0.01, b = 10, v = 5$. Here we can see that both bacteria populations $\bar{S}$ and S don't grow and start decreasing as phage population increases and it kills all the bacteria, this can be seen as attached bacteria population $\bar{S}$ and free bacteria population S are both zero in the end of the intestine. The phage population become constant when all the bacteria die as no infections can happen any more and the phages P cannot replicate and their population don't grow thus tend towards its constant stationary points $P > \frac{\alpha - \mu}{\bar{\kappa}}$, which is the constant stationary solution of model (3.1) - (3.3). It can be seen in the phase portrait above.

The equations (4.3) and (4.4) are further solved with Maple by using **fsolve** function which solves `non linear simultaneous equations`. We want to find out the equilibrium points when $S \neq 0$ i.e. the phages P reach their stationary state before killing all the bacteria. We find out that the above given are the only stationary solutions of our model when $P \neq 0$. Which is understood as the phages P cannot stop growing and become constant if the infections are happening and the replication process is continued. In figure 4.5 we can see the phase portrait showing different solutions tending towards the constant stationary states of our model for different values of P.

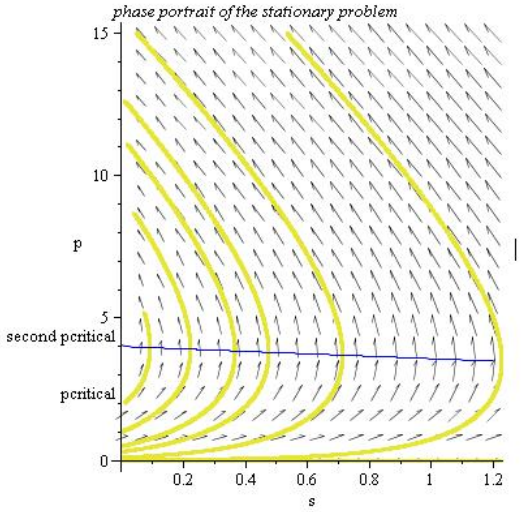

Figure 4.5: Phase portrait with different doses of P.

Chapter 5

Stability Analysis of the Constant Stationary Solutions

In this section we will discuss the stability of the equilibrium points of system (3.8) and (3.9) found in the previous section, they are observed to be the constant stationary solutions of our model of equations (3.1) - (3.3). We will analyze them to see their behavior with respect to the x variable. To claim our results we need to know some preliminary definitions and results from chapters 2 and 3 of [4].

5.1 Preliminary definitions

Definition 5.1 *A linear system $\dot{x} = Ax$ is said to be **simple** if the matrix A is non-singular, (i.e. det $A \neq 0$ and A has non-zero eigenvalues). The only solution to $Ax = 0$ is then $x = 0$ and the system has a single isolated fixed point at the origin of the phase portrait.*

Definition 5.2 *A linear system $\dot{x} = Ax$ is **non-simple** if A is singular (i.e. det $A = 0$ and at least one of the eigenvalues of A is zero). It follows that there are non-trivial solutions to $Ax = 0$ and the system has fixed points other than $x = 0$. For linear systems in the plane, there are only two possibilities: either the rank of A is one; or A is null. In the first case there is a line of fixed points passing through the origin; in the second, every point in the plane is a fixed point.*

Definition 5.3 *A fixed point at the origin of a non-linear system $\dot{y} = Y(y)$, $y \in S \subseteq R^2$, is said to be **simple** if its linearized system is simple. This definition can be used even when the fixed points of interest is not at the origin by introducing local coordinates discussed below.*

Definition 5.4 *A fixed point of a non-linear system is said to be **non-simple** if the corresponding linearized system is non-simple. Such linear systems contain a straight line, or possibly a whole plane of fixed points.*

5.2 Linearization at a fixed point

Suppose the system $\dot{y} = Y(y)$ can be written in the form

$$\dot{y_1} = a\,y_1 + b\,y_2 + g_1\,(y_1, y_2)\,, \quad \dot{y_2} = c\,y_1 + d\,y_2 + g_2\,(y_1, y_2)\,, \tag{5.1}$$

where $\left[\frac{g_1\,(y_1, y_2)}{r}\right] \to 0$ as $r = \left({y_1}^2 + {y_2}^2\right)^{\frac{1}{2}} \to 0$. The linear system

$$\dot{y_1} = a\,y_1 + b\,y_2, \quad \dot{y_2} = c\,y_1 + d\,y_2 \tag{5.2}$$

is said to be the **linearization**(or **linearized system**) of (5.1) at the origin. The components of the linear vector field in (5.2) are said to form the linear part of **Y**.

We can also obtain the **linearizations** by utilizing Taylor expansions. If the functions $X_i\,(x_1, x_2)\,(i = 1, 2)$ are continuously differentiable in some neighborhood of the point (ξ, η) then for each i

$$X_i\,(x_1, x_2) = X_i\,(\xi, \eta) + (x_1 - \xi)\,\frac{\partial\,X_i}{\partial\,x_1}\,(\xi, \eta) + (x_2 - \eta)\,\frac{\partial\,X_i}{\partial\,x_2}\,(\xi, \eta) + R_i\,(x_1, x_2)\,. \tag{5.3}$$

The remainder functions $R_i\,(x_1, x_2)$ satisfy

$$Lim_{r \to 0}\left[\frac{R_i\,(x_1, x_2)}{r}\right] = 0, \tag{5.4}$$

where $r = \left\{(x - \xi)^2 + (y - \eta)^2\right\}^{\frac{1}{2}}$. If (ξ, η) is a fixed point of $\dot{x} = X(x)$, then $X_i\,(\xi, \eta) = 0\,(i = 1, 2)$ and on introducing local coordinates y_1, y_2, where $y_1 = x_1 - \xi, \quad y_2 = x_2 - \eta$ are the Cartesian coordinates for the phase plane with their origin at $(x_1, x_2) = (\xi, \eta)$, we obtain

$$\dot{y_1} = y_1\,\frac{\partial\,X_1}{\partial\,x_1}\,(\xi, \eta) + y_2\,\frac{\partial\,X_1}{\partial\,x_2}\,(\xi, \eta) + R_1\,(y_1 + \xi, y_2 + \eta)\,, \tag{5.5}$$

$$\dot{y_2} = y_1\,\frac{\partial\,X_2}{\partial\,x_1}\,(\xi, \eta) + y_2\,\frac{\partial\,X_2}{\partial\,x_2}\,(\xi, \eta) + R_2\,(y_1 + \xi, y_2 + \eta)\,. \tag{5.6}$$

Equation (5.4) ensures that (5.5) and (5.6) are in the form (5.1) with $g_1\,(y_1, y_2) = R_1\,(y_1 + \xi, y_2 + \eta)\,(i = 1, 2)$ and the **linearization** at (ξ, η) is given by

$$a = \frac{\partial X_1}{\partial x_1}, \;\; b = \frac{\partial X_1}{\partial x_2}, \;\; c = \frac{\partial X_2}{\partial x_1}, \;\; d = \frac{\partial X_2}{\partial x_2}, \tag{5.7}$$

all evaluated at (ξ, η). Thus in matrix form the **linearization** is $\dot{y} = Ay$, where

$$A = \left[\begin{array}{cc} a & b \\ c & d \end{array}\right]_{(x_1, x_2) = (\xi, \eta)} \tag{5.8}$$

Theorem 5.1 *This theorem relates the phase portrait of a non-linear system in the neighborhood of a fixed point to that of its linearization.*

Let the non-linear system $\dot{y} = Y(y)$ have a simple fixed point at $y = 0$. Then in neighborhood of the origin the phase portraits of the system and its linearization are qualitatively equivalent provided the linearized system is not a center(i.e. when the phase portrait consists of continuum of concentric circles).

We will use this definition when the fixed point of interest is not at the origin. We can do this by introducing local coordinates as discussed earlier.

5.3 Eigenvalues and Stability

Consider a linear system $\dot{x} = Ax$, where A is the *coefficient matrix*. The eigenvalues of matrix A are the values of λ for which

$$p_A(\lambda) = \lambda^2 - tr(A)\lambda + det(A) = 0. \tag{5.9}$$

Here $tr(A)$ is the trace of A and $det(A)$ is its determinant. Thus the eigenvalues of A are

$$\lambda_1 = \frac{1}{2}\left(tr\,(A) + \sqrt{\Delta}\right) \;\; and \;\; \lambda_2 = \frac{1}{2}\left(tr\,(A) - \sqrt{\Delta}\right) \tag{5.10}$$

with

$$\Delta = (tr\,(A))^2 - 4\det\,(A)\,. \tag{5.11}$$

It determines the nature of the eigenvalues which are *real distinct* if $(\Delta > 0)$, *real equal* if $(\Delta = 0)$ and *complex* if $(\Delta < 0)$. We can also know about the *stability* at fixed point (ξ, η) as follows:

(1) : For $\Delta > 0$ we get real distinct eigenvalues and , if we have

a: $(tr(A) < 0, det(A) > 0)$ then both eigenvalues are negative $(\lambda_1 < 0, \lambda_2 < 0)$ and (ξ, η) is a *stable node*.

b: $(tr(A) > 0, det(A) > 0)$ then both eigenvalues are positive $(\lambda_1 > 0, \lambda_2 > 0)$ and (ξ, η) is an *unstable node*.

c: $(det(A) < 0)$ then both eigenvalues are equal with opposite signs $(\lambda > 0, \lambda < 0)$ and (ξ, η) is a *saddle point*.

(2) For $\Delta = 0$ we get repeated real eigenvalues $(\lambda_1 = \lambda_2 = \lambda_0 \neq 0)$. Thus we get degenerate or improper node (ξ, η) which is *stable* when $\lambda_0 < 0$ and it is *unstable* when $\lambda > 0$.

(3) For $\Delta < 0$ we get complex eigenvalues. Let $\lambda_1 = \alpha + i\beta$ and $\lambda_2 = \alpha - i\beta$ be these eigenvalues, then we have

a: $(tr(A) = 0, \alpha = 0)$ then we get pure imaginary roots and the fixed point is called a *centre* i.e. the phase portrait consists of continuum of concentric circles.

b: $(tr(A) = 0, \alpha \neq 0)$ then the fixed point is said to be a *focus* or we get *spiral point*, which is *stable* if $\alpha < 0$ and *unstable* if $alpha > 0$ i.e. the phase portrait consists of an *attracting*$(\alpha < 0)$ or *repelling*$(\alpha > 0)$*spiral*. The parameter $\beta > 0$ determines the angular speed of description of the spiral.

5.4 Stability analysis of the constant stationary solutions of the model

In order to find out the stability of equilibrium points found in previous section, we begin by linearizing our system, which is a non-linear system of equations (3.8) and (3.9), where

$$F(S,P) = \left(\alpha\left(1-\frac{S}{U}\right)-\kappa P\right)S - \lambda S + \mu G(S,P), \tag{5.12}$$

$$H(S,P) = (b-1)\left(\kappa S + \bar{\kappa} G(S,P)\right)P, \tag{5.13}$$

and

$$G(S,P) = \frac{\left[-\left(\overline{\kappa}P + (\mu-\alpha)\right) + \sqrt{\left(\overline{\kappa}P+(\mu-\alpha)\right)^2 + 4\frac{\alpha\lambda S}{\overline{U}}}\right]}{2\frac{\alpha}{\overline{U}}}. \tag{5.14}$$

We apply the results from (5.7) and (5.8) and find the matrix A by derivating the above functions $F(S,P)$, $H(S,P)$ and evaluating A at constant stationary solutions(fixed points) of our model (3.1) - (3.3), as follows:

$$a = \frac{\partial F}{\partial S} = (\alpha - \lambda - \kappa P) - \frac{2\alpha S}{U} + \frac{\mu\lambda}{\sqrt{(\bar{\kappa}P+\mu-\alpha)^2 + \frac{4\alpha\lambda S}{\bar{U}}}},$$

$$b = \frac{\partial F}{\partial P} = -\kappa S + \frac{\overline{\kappa}\mu\overline{U}}{2\alpha}\left(\frac{(\overline{\kappa}P+\mu-\alpha)}{\sqrt{(\bar{\kappa}P+\mu-\alpha)^2 + \frac{4\alpha\lambda S}{\bar{U}}}} - 1\right),$$

$$c = \frac{\partial H}{\partial S} = (b-1)\left(\left(\frac{\bar{\kappa}\lambda}{\sqrt{(\bar{\kappa}P+\mu-\alpha)^2 + \frac{4\alpha\lambda S}{\bar{U}}}} + \kappa\right)P\right),$$

$$d = \frac{\partial H}{\partial P} = (b-1)\left(\kappa S + \left((\bar{\kappa}P+\mu-\alpha)\left(\frac{\bar{\kappa}P}{\sqrt{(\bar{\kappa}P+\mu-\alpha)^2 + \frac{4\alpha\lambda S}{\bar{U}}}} - 1\right) + \sqrt{(\bar{\kappa}P+\mu-\alpha)^2 + \frac{4\alpha\lambda S}{\bar{U}}} - \bar{\kappa}P\right)\right),$$

where a, b, c, d are the entries of matrix A as in (5.8). Now we evaluate A at equilibrium points of the system (3.8) - (3.9) and find out the eigenvalues of A and check the stability of our constant stationary solutions of our model of equations (3.1) - (3.3) with respect to x variable. Below are the equilibrium points of the system (3.8) - (3.9) found in previous section.

$1 : (S,P) = (0,0)$ when $(\mu \geq \alpha)$.

$2 : (S,P) = (\hat{S}, 0)$, where $\hat{S} = 5.734920049$ when $(\mu = \alpha)$, 5.593076209 when $(\mu > \alpha)$, 5.648090637 when $(\mu < \alpha)$.

$3 : (S,P) = (0, P_s) = (0, \frac{\alpha-\mu}{\bar{\kappa}})$ when $\mu < \alpha$.

$4 : (S,P) = (0, P_i)$, where $P_i \geq P_s$, when $\mu < \alpha$.

We now find the linearization matrix A and its eigenvalues with the help of Matlab on above points and make a stability analysis on them to observe their behavior with respect to x variable as follows:

- A_1 at $(S, P) = (0, 0)$

$$A_1 = \begin{bmatrix} 0.0400 & -0.0667 \\ 0 & 0.0003 \end{bmatrix} \tag{5.15}$$

The eigenvalues of A_1 are $\lambda_1 = 0.0400$ and $\lambda_2 = 0.0003$, which are both real and positive which implies that $(S, P) = (0, 0)$ or the origin is an **unstable node** for $\mu < \alpha$. For $\mu > \alpha$ the eigenvalues are $\lambda_1 = 0.0400$ and $\lambda_2 = 0$, which also shows that the origin is an **unstable node**. However for $\mu = \alpha$ we cannot linearize the system because the matrix A is undefined for this case.

- A_2 at $(S, P) = (5.734920049, 0)$

$$A_2 = \begin{bmatrix} -0.0380 & -0.1073 \\ 0 & 0.5163 \end{bmatrix} \tag{5.16}$$

The eigenvalues of A_2 are $\lambda_1 = -0.0380$ and $\lambda_2 = 0.5163$, which are both real with opposite signs which implies that $(S, P) = (5.734920049, 0)$ is a **saddle point** for $\mu = \alpha$. However for the other two cases $\mu > \alpha$ and for $\mu < \alpha$, we get the same result i.e. a saddle point.

- A_3 at $(S, P) = (5.593076209, 0)$

$$A_3 = \begin{bmatrix} -0.0331 & -0.0591 \\ 0 & 0.5035 \end{bmatrix} \tag{5.17}$$

The eigenvalues of A_3 are $\lambda_1 = -0.0331$ and $\lambda_2 = 0.5035$, which are both real with opposite signs which implies that $(S, P) = (5.593076209, 0)$ is a **saddle point** for $\mu > \alpha$. However for the other two cases $\mu < \alpha$ and for $\mu = \alpha$, we get the same result i.e. a saddle point.

- A_4 at $(S, P) = (5.648090637, 0)$

$$A_4 = \begin{bmatrix} -0.0575 & -0.1210 \\ 0 & 0.5088 \end{bmatrix} \tag{5.18}$$

The eigenvalues of A_4 are $\lambda_1 = -0.0575$ and $\lambda_2 = 0.5088$, which are both real with opposite signs which implies that $(S, P) = (5.648090637, 0)$ is a **saddle point** for $\mu < \alpha$. However for the other two cases $\mu > \alpha$ and for $\mu = \alpha$, we get the same result i.e. a saddle point.

- A_5 at $(S, P) = (0, P_s) = (0, \frac{\alpha - \mu}{\bar{\kappa}})$

For this point matrix A become undefined as the derivatives do not exist at this point. Hence we cannot linearize the system at this point.

- A_6 at $(S, P) = (0, P_i)$, where $P_i \geq P_s$

For this we first consider $P_i = 2$, whereas $P_s = 1$ we get,

$$A_6 = \begin{bmatrix} 0.0200 & 0 \\ 0.3600 & 0 \end{bmatrix} \tag{5.19}$$

The eigenvalues of A_6 are $\lambda_1 = -0.0000$ and $\lambda_2 = 0.0200$, which shows that this equilibrium point is non simple as matrix A_6 is singular. Hence we cannot linearize the system at this point.

- Now we check for $P_i = 4$

thus we have;

$$A_7 = \begin{bmatrix} -0.0133 & 0 \\ 0.4800 & 0 \end{bmatrix} \tag{5.20}$$

The eigenvalues of A_7 are $\lambda_1 = 0$ and $\lambda_2 = -0.0133$, which again show that this equilibrium point is also non simple as matrix A_7 is singular hence linearization of the system is not possible.

- Now we check for some larger value i.e. $P_i = 10$

we get,

$$A_8 = \begin{bmatrix} -0.0778 & 0 \\ 1.0000 & -0.0000 \end{bmatrix} \tag{5.21}$$

The eigenvalues of A_8 are $\lambda_1 = -0.0000$ and $\lambda_2 = -0.0778$, thus this is also a non simple equilibrium point.

Thus we can say that the system posses a continuum of equilibrium since all the points including $(S, P) = (0, \frac{\alpha - \mu}{\kappa})$ and when P is greater than this are non simple. Thus our model (3.1) - (3.3) also contain a continuum of constant stationary points i.e. $(S, P_s) = (0, \frac{\alpha - \mu}{\kappa})$ and $(S, P) = (0, P_i)$, where $P_i \geq P_s$ which are all non simple.

Chapter 6

Model Parameter Analysis

In this chapter we will study the parameters used in our model and will analyze how they can affect the model i.e. how sensitive is the dynamics of infections to them.

6.1 Parameter description

The description of the parameters used in the model can be seen in the following table:

Notation	Meaning	Units
α	Bacterial growth rate	T^{-1}, min^{-1}
κ	Adsorption constant for S and P	$min^{-1}ml.indiv^{-1}$
$\bar{\kappa}$	Adsorption constant for $\bar{S}$ and P	$min^{-1}ml.indiv^{-1}$
λ	Wall detachment rate	min^{-1}
μ	Wall attachment rate	min^{-1}
U	Carrying Capacity for S	indiv
$\bar{U}$	Carrying capacity for $\bar{S}$	indiv
ν	Velocity of S and P in 1 spacial dimension x	cm.min^{-1}
b	Burst Size of viruses P	-

Table 6.1: Parameter and their description

6.2 Analysis w.r.t μ and α

Following is the table for different values of μ and α. One can find their analysis in chapter 4 for the following values.

Parameter	$\mu < \alpha$	$\mu = \alpha$	$\mu > \alpha$
α	0.03	0.01	0.02
κ	0.01	0.01	0.01
$\bar{\kappa}$	0.01	0.01	0.01
λ	0.01	0.01	0.01
μ	0.02	0.01	0.03
U	10	10	10
$\bar{U}$	10	10	10
ν	5	5	5
b	10	10	10

Table 6.2: Different values of μ and α.

6.3 Analysis w.r.t κ and $\bar{\kappa}$

We will now analyze our model for different values of κ and $\bar{\kappa}$ and will see how it behaves. Following

Parameter	$\kappa << \bar{\kappa}$	Large $\kappa = \bar{\kappa}$	Small $\kappa = \bar{\kappa}$	Very Small $\kappa = \bar{\kappa}$	$\kappa >> \bar{\kappa}$
α	0.03	0.03	0.03	0.03	0.03
λ	0.01	0.01	0.01	0.01	0.01
μ	0.02	0.02	0.02	0.02	0.02
κ	0.000000097	0.1	0.00097	0.000097	0.01
$\bar{\kappa}$	0.01	0.1	0.00097	0.000097	0.000000097
U	10	10	10	10	10
$\bar{U}$	10	10	10	10	10
ν	5	5	5	5	5
b	10	10	10	10	10

Table 6.3: Different values of κ and $\bar{\kappa}$.

graphs shows how the model behaves for different values of κ and $\bar{\kappa}$ given in above table 6.3 with $\mu < \alpha$ and $P_0 = 0.1$.

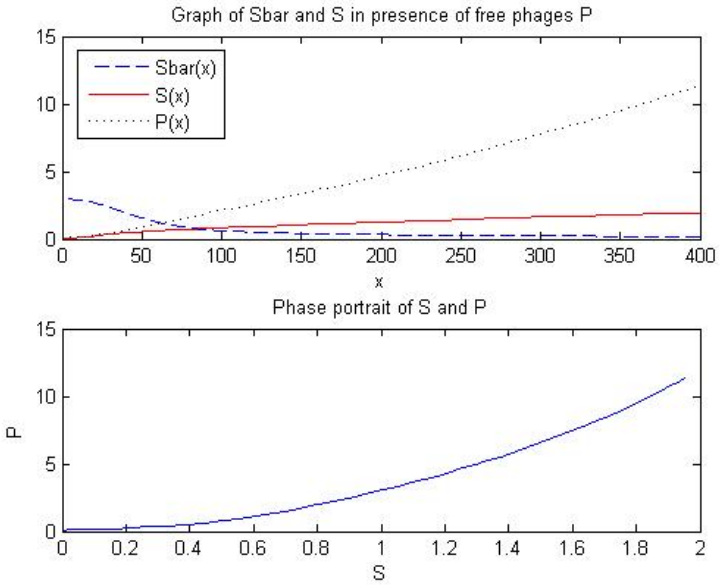

Figure 6.1: For $\kappa << \bar{\kappa}$ population of viruses P increasing, free bacteria S increasing and attached bacteria $\bar{S}$ dying.

As κ and $\bar{\kappa}$ are the transmission or absorption coefficients, in figure 6.1 we can see that for very small κ there are very less infections of viruses P and free bacteria S therefore they succeed to grow and increase and are not finished whereas the attached bacteria $\bar{S}$ are dying gradually because of large $\bar{\kappa}$ i.e. because of large number of infections of viruses P and attached bacteria $\bar{S}$, thus the population of viruses P also increases due to their large production during infections.

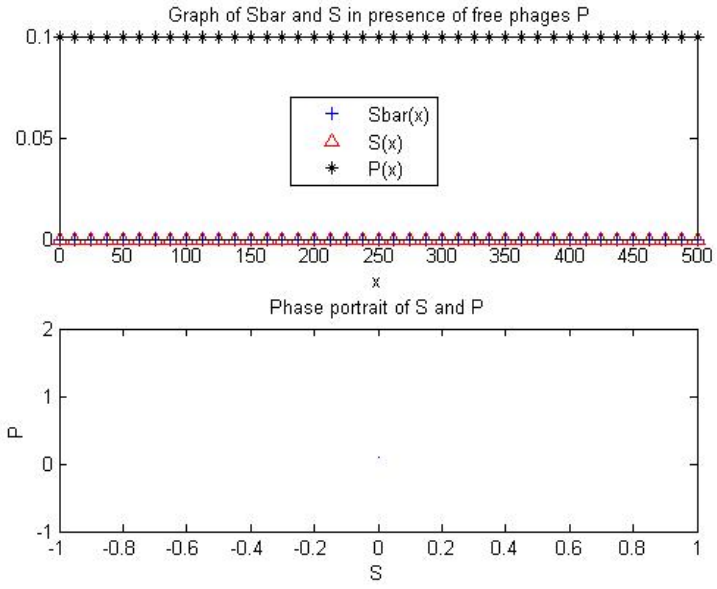

Figure 6.2: For large $\kappa = \bar{\kappa}$ bacteria S and $\bar{S}$ die and finished, and population of viruses P remain constant.

Figure 6.2 shows that due to large κ and $\bar{\kappa}$ the number of infections of viruses P with attached and free bacteria $(\bar{S}, S)$ is very large, therefore all the bacteria are dead and finished. As there are no more bacteria so no more infections can happen and the population of viruses (phages) P remains constant because of their constant influx.

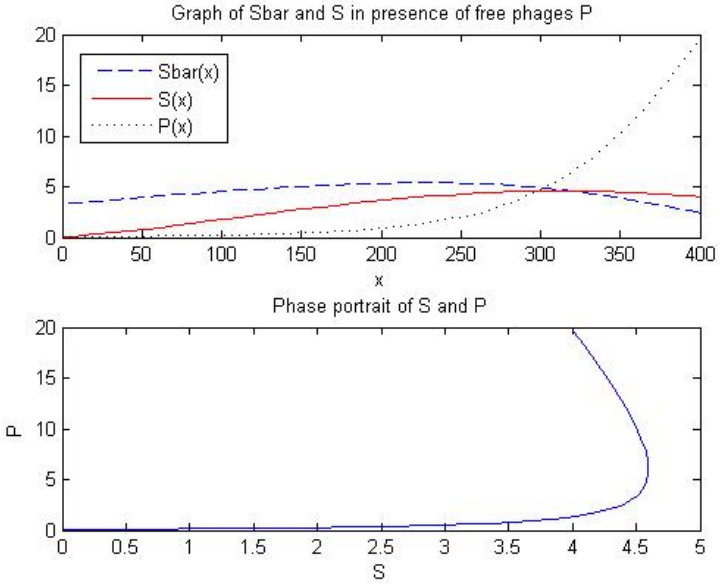

Figure 6.3: For small $\kappa = \bar{\kappa}$ population of viruses P increasing whereas bacteria S and $\bar{S}$ decreasing gradually .

This Figure 6.3 shows the case when both κ and $\bar{\kappa}$ are equal but are comparatively smaller than the above values of κ and $\bar{\kappa}$ i.e. number of infections is smaller than the above case. This can be clearly seen in this figure 6.3 as less infections allow the attached and free bacteria to grow to some extent but then because of replication process the population of viruses grow very well and both bacteria population begin to decline along the intestine.

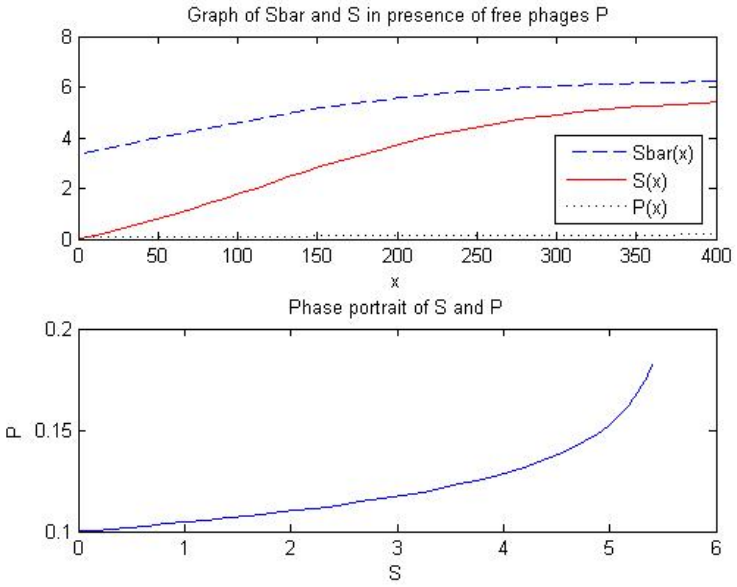

Figure 6.4: For smaller $\kappa = \bar{\kappa}$ population of bacteria S and $\bar{S}$ increasing whereas population of viruses P growing very slowly.

This figure 6.4 shows a very interesting case of very small κ and $\bar{\kappa}$ this means that the number of infections is very small. The above figure 6.4 clearly shows that in this situation both bacteria population $(\bar{S}, S)$ keep growing and then become stationary however due to very less infections the virus population P grow very slowly as the replication rate is very very small.

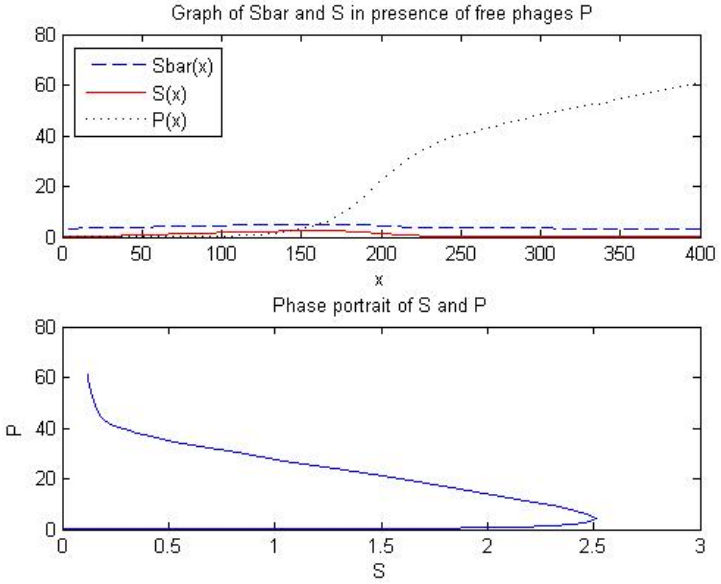

Figure 6.5: For $\kappa >> \bar{\kappa}$ population of viruses P increasing, bacteria S dying and $\bar{S}$ remaining.

The above figure 6.5 shows the case when $\kappa >> \bar{\kappa}$ i.e. The number of infections of viruses P and free bacteria S is very large however the number of infections of viruses P and attached bacteria $\bar{S}$ is very very small. This can be clearly seen in the figure 6.5 as attached bacteria population $\bar{S}$ increase in the beginning of intestine but due to small number of infections it do not die completely but decreases a little . We can also see that the population of S is first increased and then decreased to zero, this is because the attached bacteria $\bar{S}$ population is not dying completely and they keep on detaching from the

wall and keep on adding in free bacteria population hence increasing their number but as the number of infection of viruses P and free bacteria S is very large therefore S will die completely as they reach the end of intestine.

6.4 Analysis w.r.t burst size b

We will show here what happens when the burst size b is very small or very large; where $P_0 = 0.1$, the values of b can be seen in the following table and below are the figures accordingly:

Parameter	Very small b	Small b	Normal b	Large b	Very large b
α	0.03	0.03	0.03	0.03	0.03
λ	0.01	0.01	0.01	0.01	0.01
μ	0.02	0.02	0.02	0.02	0.02
κ	0.01	0.01	0.01	0.01	0.01
$\bar{\kappa}$	0.01	0.01	0.01	0.01	0.01
U	8	8	8	8	8
$\bar{U}$	10	10	10	10	10
ν	5	5	5	5	5
b	1	3	20	50	100

Table 6.4: Different values of b.

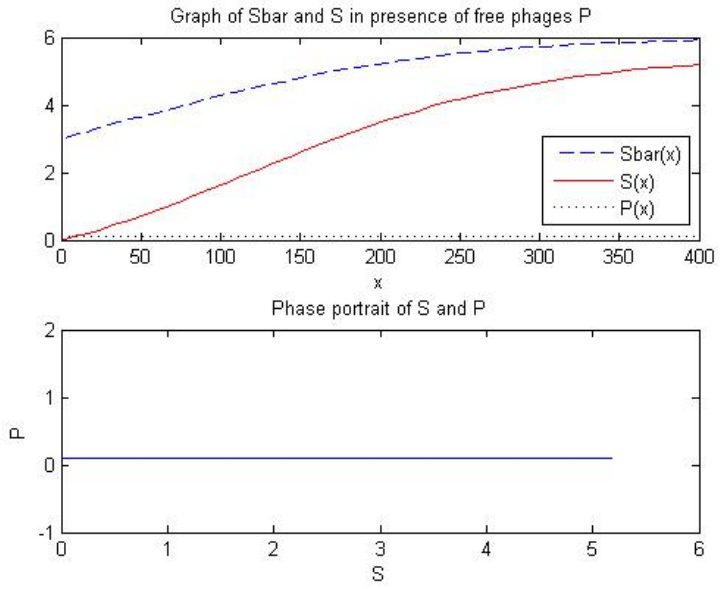

Figure 6.6: For $b = 1$ the population of phages P do not grow and remain constant which show that replication of P is very very small, so their population don't effect the bacteria populations $\bar{S}$ and S even if any infections happen, so both bacteria populations grow and tend towards their constant stationary states.

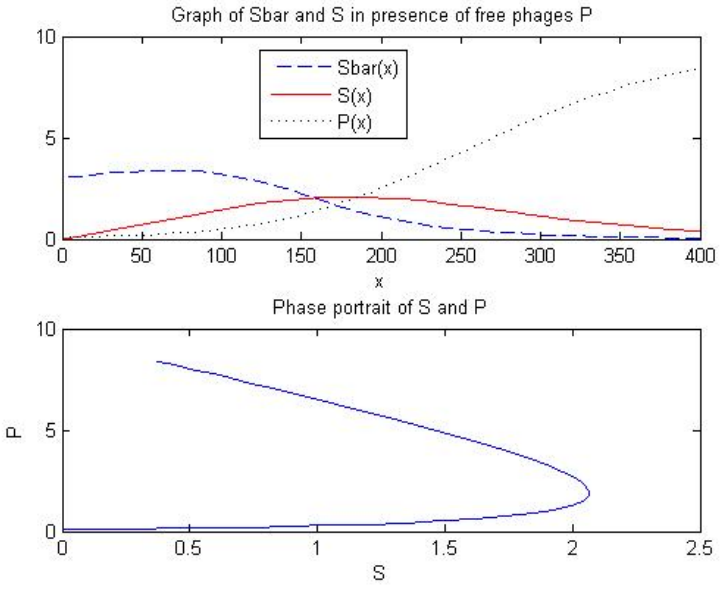

Figure 6.7: For $b = 3$ we see that the population of phages P start growing slowly and we can also see how it starts infecting the bacteria population $\bar{S}$ and S as both bacteria population begin to decline as they move along the intestine. But as the burst size is small phages P will not succeed to kill all the bacteria populations.

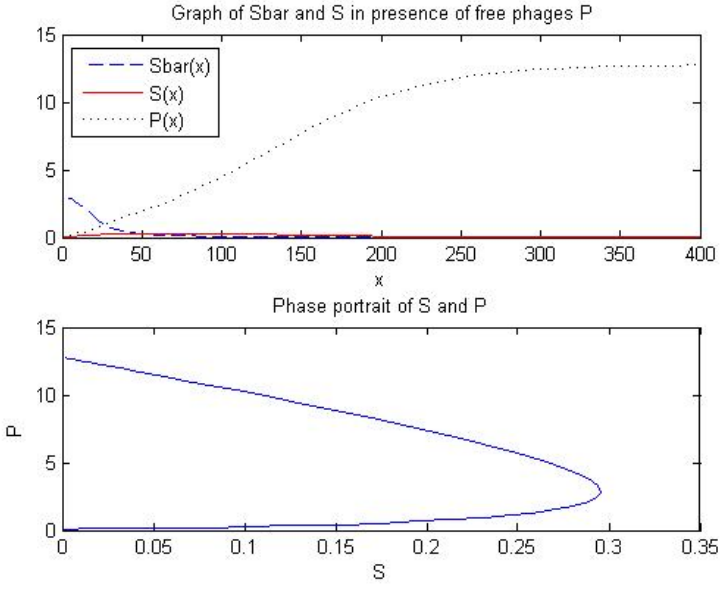

Figure 6.8: For $b = 20$ the population of phages P replicate and grow and infect both bacteria population $\bar{S}$ and S and kill all the bacteria successfully at $x = 200$ in the intestine.

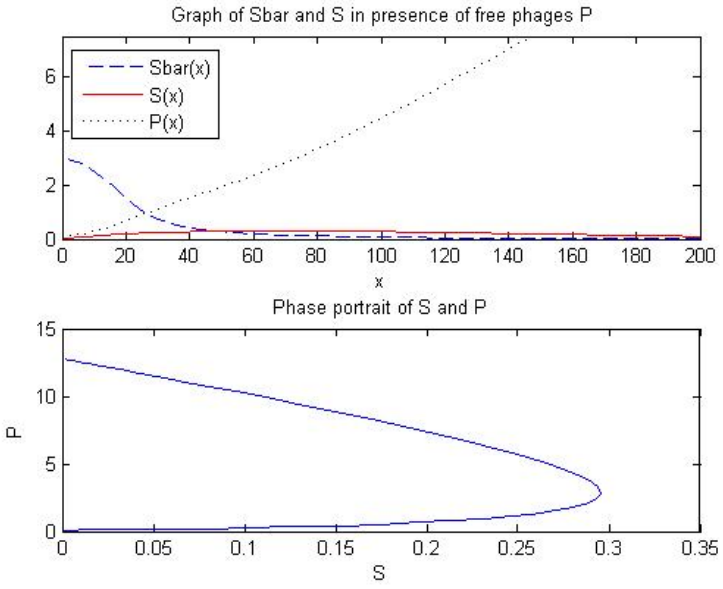

Figure 6.9: This figure is a maximize view of figure 6.8 for $b = 20$.

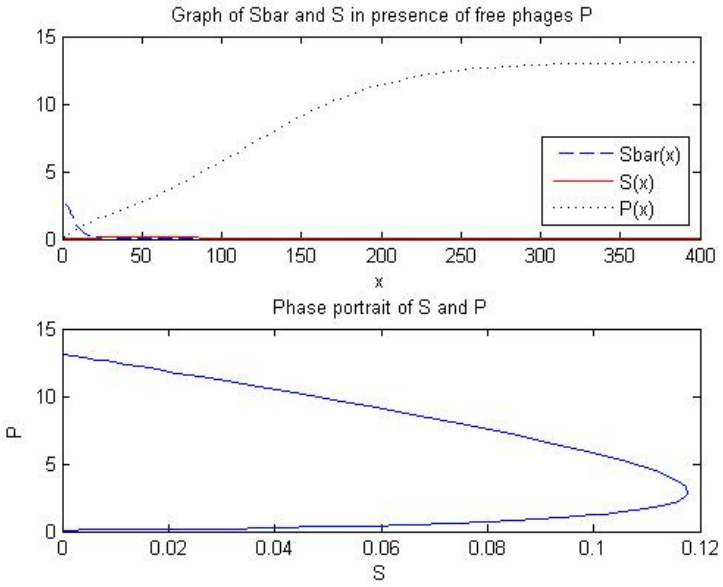

Figure 6.10: For $b = 50$ we see that because of large production of phages P through high replication rate b the infection rate is high too, therefore both bacteria populations $\bar{S}$ and S could not succeed to sustain their growth and die very soon in the intestine at $x = 100$.

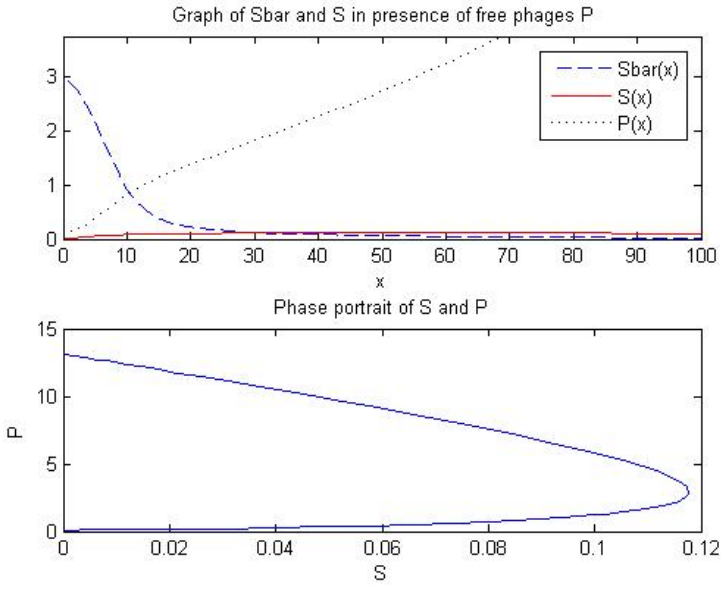

Figure 6.11: This figure is a maximize view of figure 6.10 for $b = 50$.

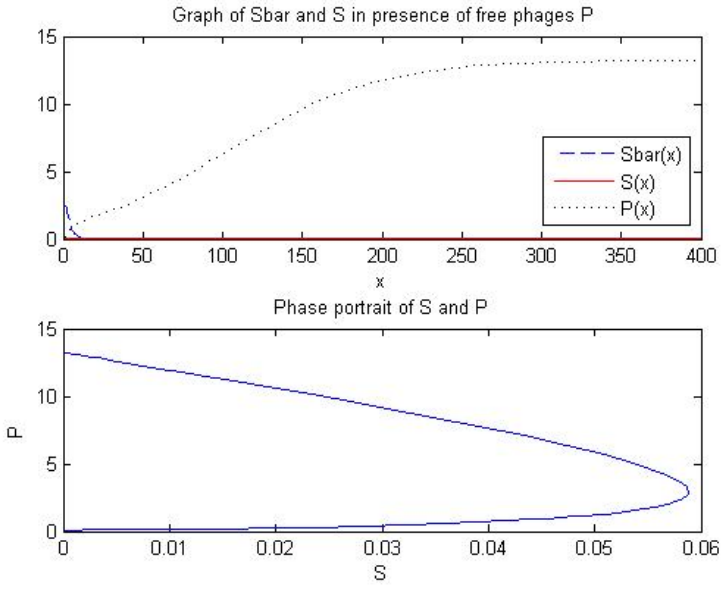

Figure 6.12: For $b = 100$ we can see that because of very large production of phages P as replication rate b is very high, the infection rate is very high too, therefore both bacteria populations $\bar{S}$ and S could not succeed to sustain their growth and die very soon in the intestine at $x = 35$.

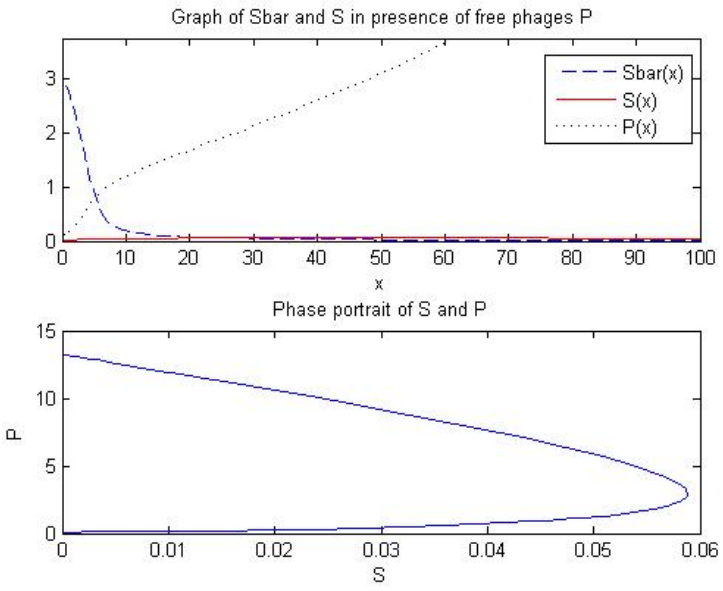

Figure 6.13: This figure is a maximize view of figure 6.12 for $b = 100$.

From the above we can conclude that the higher is the burst size the sooner bacteria die.

6.5 Analysis w.r.t velocity ν

We will now investigate our model by changing the velocity(with which the food is passing through the intestine of the organism), as free phages P and free bacteria S pass through the intestine with food so they are moving with same velocity, so we will see how the phages P infect and kill the bacteria by moving with different velocities in the intestine. Below can be seen the different values of ν in the table, and the figures for these values.

Parameter	Very small ν	Small ν	Normal ν	Large ν	Very large ν
α	0.03	0.03	0.03	0.03	0.03
λ	0.01	0.01	0.01	0.01	0.01
μ	0.01	0.01	0.01	0.01	0.01
κ	0.01	0.01	0.01	0.01	0.01
$\bar{\kappa}$	0.01	0.01	0.01	0.01	0.01
U	8	8	8	8	8
$\bar{U}$	10	10	10	10	10
ν	1	3	6	10	15
b	10	10	10	10	10

Table 6.5: Different values of ν.

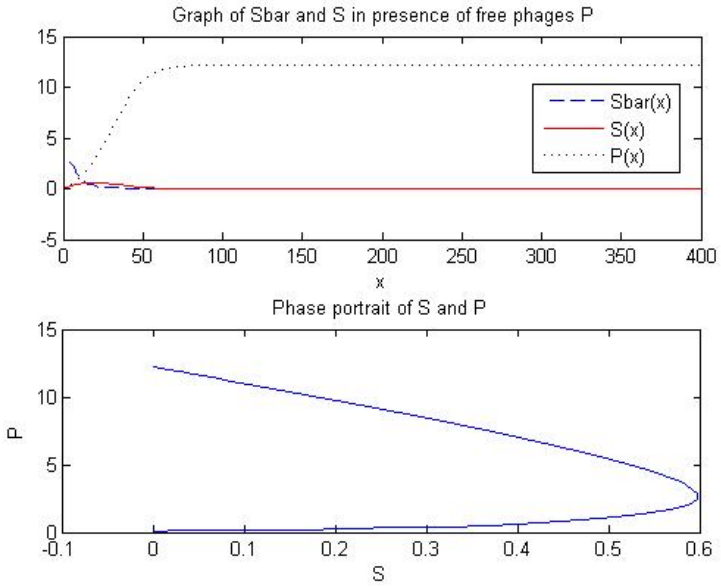

Figure 6.14: In this plot $\nu = 1$, it shows that when P and S are moving with very slow speed then the chances of infections of P with $\bar{S}$ and S are high, as can be seen in this figure, because of high infections all the bacteria are killed at $x = 60$.

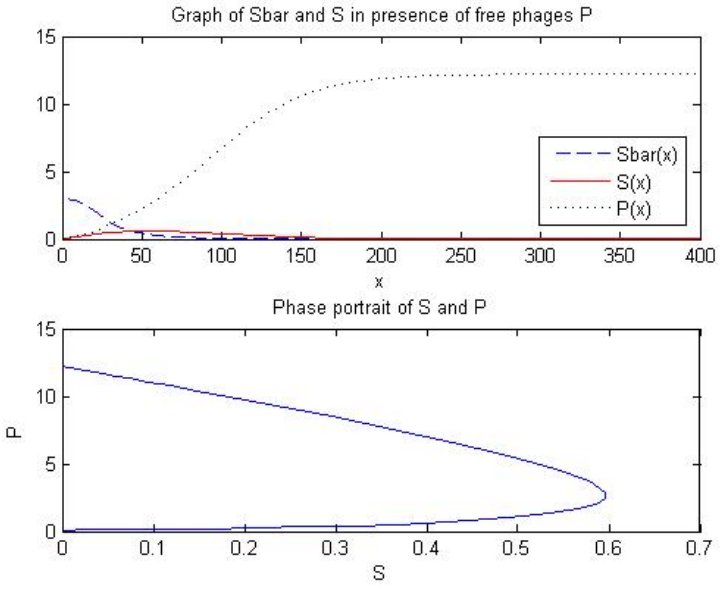

Figure 6.15: In this plot $\nu = 3$, it shows that when P and S are moving with slow speed then the chances of infections of P with $\bar{S}$ and S are high but less than before, as can be seen in this figure, because of high infections here all the bacteria are killed at $x = 160$. This is different from 6.14, because now P and S are moving a bit fast than before.

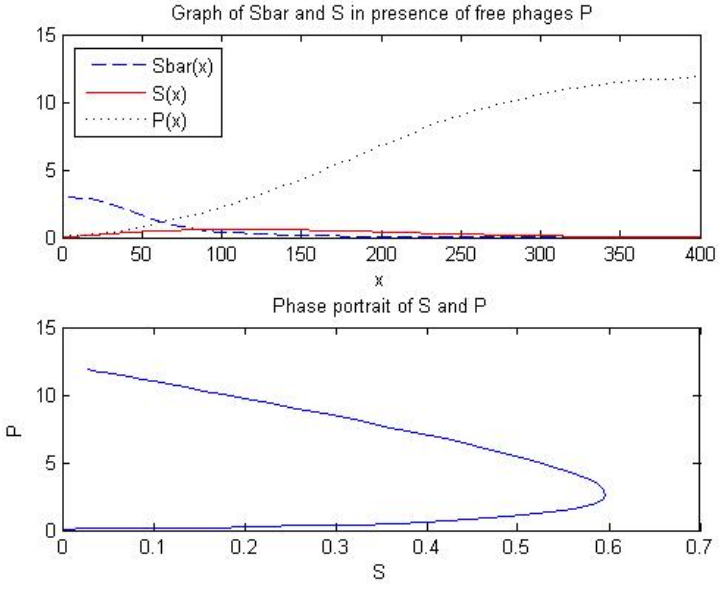

Figure 6.16: In this plot $\nu = 6$, it shows that now P and S are moving with high speed than before so the chances of infections of P with $\bar{S}$ and S are less than before, as can be seen in this figure, because of less infections the bacteria population succeed to grow but after phage population increased they all are killed at $x = 320$, which is almost the end of intestine.

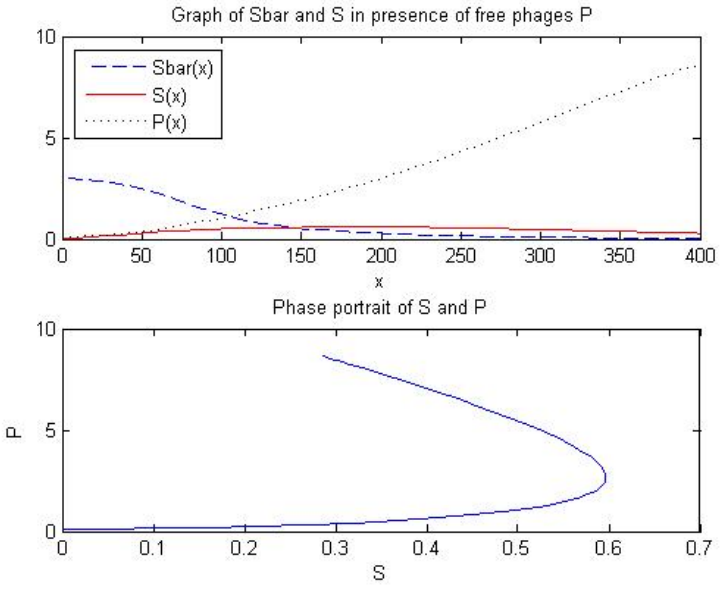

Figure 6.17: In this plot $\nu = 10$, it shows that now P and S are moving with higher speed than before so the chances of infections of P with $\bar{S}$ and S are now very less than before, as can be seen in this figure, because of less infections both bacteria population succeed to sustain but after phage population increased only $\bar{S}$ are all killed at the end of the intestine $x = 400$, and S bacteria population are not all killed so the left bacteria S move down the intestine with free phages P and leave the organism.

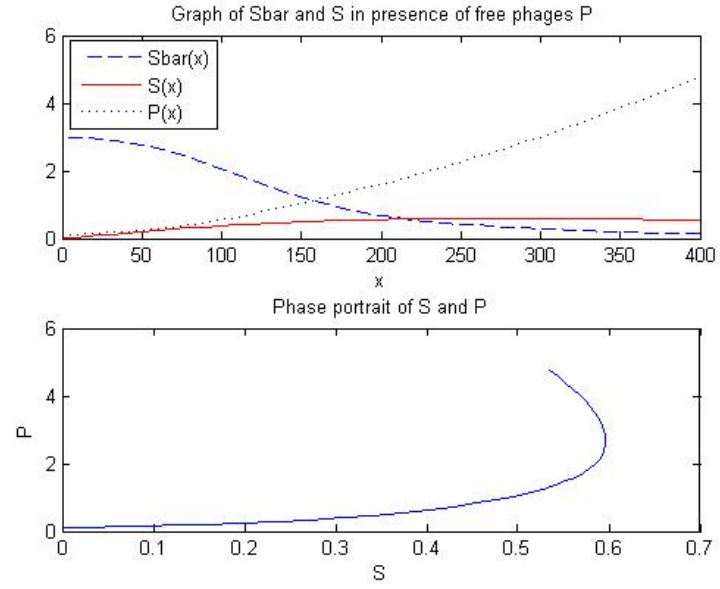

Figure 6.18: In this plot $\nu = 15$, it shows that now P and S are moving with very high speed through the intestine and now the chances of infections of P with $\bar{S}$ and S are very very very less, as can be seen in this figure, because of few infections both bacteria population succeed to sustain and none of them is killed completely so the organism will stay infected with $\bar{S}$ and S and they move down the intestine along with P and leave the organism.

From the above analysis we conclude that small ν can cause high infections of bacteria and phages whereas large ν can prevent them from infections with phages.

Chapter 7

Conclusions

Intestinal infections in chickens are not dangerous for chickens but they are a big threat to the well being of other animals as well as they have the potential to cause damage to human health through their food. Thus these infections and their treatment is very important to study and understand.

This work was aimed to study the dynamics of these infections and their treatment within a single host. We study that how these infections can be treated by bacteriophages. We present a mathematical model which describes the interaction of bacteria, infecting the organism within the intestine, and bacteriophages within the intestine of a single chicken. In our model we consider two types of bacteria infecting the the organism and two type of phages for the treatment of these infections. Ones attached to the wall of the intestine and the others are the free ones in the intestine which can move down the intestine in one spacial dimension x. We consider two different cases. Firstly when the organism is not treated with phages and secondly when the organism is given a dose of phages to see how the treatment works. We derive the conditions in which the organism can stay infected and in which the infections can finish them self and in the presence of phages. We also discuss the stability of the infections and the phages which remain inside the organism in different cases and conditions. We also observe the sensitivity of the dynamics on different parameters like adsorption constants κ and $\bar{\kappa}$, burst size b and the velocity v. We come up with the following conclusions:

- The detachment rate μ and the attachment rate λ have a strong influence on the dynamics of bacterial infection in intestine. We observed that if $\mu > \lambda$ it is more likely that the organism become infection free without any treatment of bacteriophages P.

- Similar is the case with the growth rate α. When the detachment rate μ is larger than the growth rate of attached bacteria $\bar{S}$ then the organism become infection free without any treatment of bacteriophages P.

- When the infection is treated with different amount of dose of bacteriophages it is observed that a small dose of bacteriophages is sufficient to kill all the bacteria in the intestine and to make the organism infection free.

- We observe that the bacterial infection show a constant stationary behavior in the intestine. We investigate that in the absence of phages P, the infection finish completely only when $\mu > \alpha$ otherwise they tend towards a constant stationary state which shows that the organism remain infected with attached bacteria population $\bar{S}$ as well as a constant amount of free bacteria population S leaves the organism which can later infect the other living beings and create an illness in them. The stability analysis with respect to x variable shows that none of these constant stationary states are stable.

- When we treat the organism with bacteriophages we observe that they also posses a constant stationary behavior in the intestine. They keep on increasing until they finish all the bacteria in the intestine and then they become constant and do not grow. This behavior validates the fact that the

phages cannot grow or replicate in the absence of their specific bacteria. It is also observed that if we provide the organism with the dose of bacteriophages which is comparable to their recorded constant stationary state then the bacteria finishes completely immediately. We study that our model posses a continuum of such constant stationary points.

- The adsorption constants κ and $\bar{\kappa}$ have a great influence on the dynamics of interaction of bacteriophages and bacteria infecting the intestine. We observe that when the adsorption rate is very high i.e. both of these constants are large then the bacteria finishes completely immediately. However when they are small the interaction of bacteria and phages is also less, so the organism remains infected.

- The burst size b which is also the reproduction rate of phages is also of vital importance. It is observed that when the burst size is small the phages fail to kill all the bacteria.

- The velocity v through which free phages P and free bacteria S move down in the intestine with food also needs attention. We observe that when the food pases through the intestine slowly then the interaction of bacteria and phages is higher so the infection reduction rate is higher. However if it passes quickly the chances of their interaction become very less.

Chapter 8

Matlab Codes

8.1 Eigenvalues

```
global alpha lamda mu kbar Ubar U k b v
alpha = 0.03;
lamda = 0.01;
Ubar=10;
mu = 0.02;
k = 0.01;
kbar = 0.01;
S=0;
P = 200;
U= 4;
v = 5;
b = 10;

A1=[((alpha-lamda-k*P)-(2*alpha*S/U)+(mu*lamda/sqrt((kbar*P+mu-alpha)^2
+(4*alpha*lamda*S/Ubar))))(-k*S+(kbar*mu*Ubar/(2*alpha))*
((kbar*P+mu-alpha)/(sqrt((kbar*P+mu-alpha)^2
+(4*alpha*lamda*S/Ubar))-1)));((b-1)*(k+kbar*lamda/sqrt((kbar*P+mu-alpha)^2
+(4*alpha*lamda*S/Ubar)))*P)((b-1)*(k*S+((kbar*Ubar/2*alpha)*(-kbar*P+(kbar*P+
*((kbar*P/sqrt((kbar*P+mu-alpha)^2
+(4*alpha*lamda*S/Ubar)))-1)+sqrt((kbar*P+mu-alpha)^2+(4*alpha*lamda*S/Ubar)))
A1
E1=eig(A1);
E1
```

8.2 Solutions of Model

data.file

```
global alpha lamda mu kbar Ubar U k b v X

X=500;
alpha = 0.03;
lamda = 0.01;
Ubar=10;
mu = 0.02;
k = 0.01;
```

```
kbar = 0.01;
%P0=(alpha-mu)/kbar;
P0 = 0.1;
S0=[0,P0];
U= 4;
v = 5;
b = 10
```

prog.file

```
function [y]=prog(x,S)
global alpha mu Sbar Ubar kbar k b v lamda U

Sbar = (-(kbar*S(2)+ mu-alpha)+ sqrt((kbar*S(2)+ mu-alpha).^2
+ 4*(alpha/Ubar)*lamda.*S(1)))/(2*(alpha/Ubar));
y = zeros(2,1);

y(1) = (1/v)*(alpha*(1-S(1)/U).*S(1)-k*S(2).*S(1)-lamda*S(1)+ mu*Sbar);
y(2) = (1/v)*(b-1)*(k*S(1)+kbar*Sbar).*S(2);
```

solve.file

```
[x,S] = ode45('prog',[0,X],S0);
Sbar = (-(kbar*S(:,2)+ mu-alpha)+ sqrt((kbar*S(:,2)+ mu-alpha).^2
+ 4*(alpha/Ubar)*lamda*S(:,1)))/(2*(alpha/Ubar));
subplot(2,1,1) % breaks the figure into a 2-by-1 matrix;
plot(x,Sbar,'b--');
hold on
% selects top half
plot(x, S(:,1),'r'); % S
hold on
plot(x, S(:,2), 'k:'); % P
%hold on
%plot(x,S(:,3),'b') % P
hold off
legend('Sbar(x)','S(x)','P(x)');
%title('Graph of Sbar, S and P for different velocities v'), xlabel('x');
title(' Graph of Sbar and S in presence of free phages P'), xlabel('x')
%title('Graph of Sbar')
subplot(2,1,2) % selects bottom half
plot(S(:,1), S(:,2))
% plots second versus first component of u
title('Phase portrait of S and P'), xlabel('S'), ylabel('P');
```

8.3 Numerical solutions of model

prog.file

```
function [y] = prog1(S)
global alpha mu Ubar kbar k b lamda U
%Sbar = (-(kbar*S(2)+ mu-alpha)+ sqrt((kbar*S(2)+ mu-alpha).^2
+ 4*(alpha/Ubar)*lamda.*S(1)))/(2*(alpha/Ubar));
```

```
y = [(alpha*(1-S(1)/U).*S(1)-k*S(2).*S(1)-lamda*S(1)+ mu*((-(kbar*S(2)+ mu-alp
+ sqrt((kbar*S(2)+ mu-alpha).^2 + 4*(alpha/Ubar)*lamda.*S(1)))/(2*(alpha/Ubar)
(b-1)*(k*S(1)+kbar*((-(kbar*S(2)+ mu-alpha)+ sqrt((kbar*S(2)+ mu-alpha).^2
+ 4*(alpha/Ubar)*lamda.*S(1)))/(2*(alpha/Ubar)))).*S(2)];
```

solve.file

```
S0 = [0,1]; % Initial guess
Options = optimset('Display','iter');
[S,fval] = fsolve(@prog1, S0, Options);
```

Bibliography

[1] http://en.wikipedia.org/wiki/bacteriophage.

[2] http://pathmicro.med.sc.edu/mayer/phage.htm.

[3] http://textbookofbacteriology.net/phage.html.

[4] D.K. Arrowsmith and C.M. Place. *Ordinary differential equations, A qualitative approach with applications*. Chapman and Hall Mathematics series.

[5] Barbara Boldin. Persistence and spread of gastro-intestinal infections: the case of enterotoxigenic escherichia coli in piglets. *Bulletin of Mathematical Biology*, 70:pp. 2077–2101, 2008.

[6] Juan Jose Rivaud Gallardo. Master thesis on 'sistema de simulacion numerica para un modelo de terapia con virus bacteriofagos'. Julio de 2008.

[7] Stefhen A. Gourley and Yang Kuang. A delay reaction-diffusion model of the spread of bacteriophage infection. *SIAM J. APPL. MATH, Society for Industrial and Applied Mathematics*, 65:pp. 550–566, 2005.

[8] A. Hurley, J. J. Maurer, and M. D. Lee. Using bacteriophages to modulate salmonella colonization of the chickens gastrointestinal tract lessons learned from *In Silico* and *In Vivo* modeling. *Avian Diseases*, 52:pp. 599–607, 2008.

[9] Robert J. H. Payne and Vincent A. A. Jansen. Understanding bacteriophage therapy as a density-dependent kinetic process. *J. theor. Biol.*, 48:pp. 208–237,, 2001.

[10] David Bascompte Viladrich. Research work on 'dinamica d'un model de terapia amb bacteriofags. equilibris i estabilitat'. Setembre de 2007.

Campus de Bellaterra, Edifici C
08193 Bellaterra, Spain
Tel.: +34 93 581 10 81
Fax: +34 93 581 22 02
crm@crm.cat
www.crm.cat