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

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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 spatial dimension within the intestine of chickens by considering only the convection term, i.e, just looking for stationary population distribution along the digest tract. This leads to the consideration of a system of ordinary differential equations. We discuss that the 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 of the o.d.e system allows an understanding of the shape of these stationary states. Solutions of the model for several different values of burst size b, adsorption coefficients κ and $\bar{\kappa}$, growth rate α, detachment rate μ and velocity v show that dynamics is sensitive to all of them.

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.

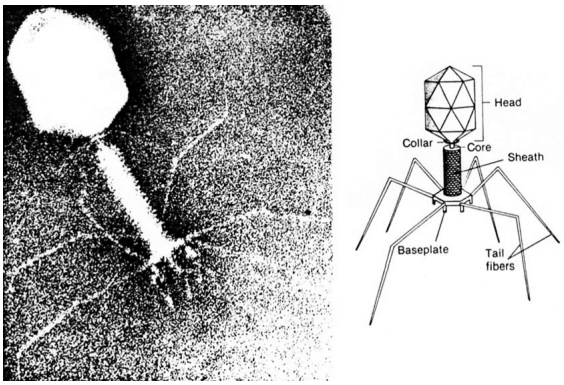

Figure 1.1: Left: Electron Micrograph of bacteriophage, Right: Model of phage . The phage possesses DNA contained within an icosahedral head. The tail consists of a hollow core through which the DNA is injected into the host cell. The tail fibers are involved with recognition of specific viral "receptors"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

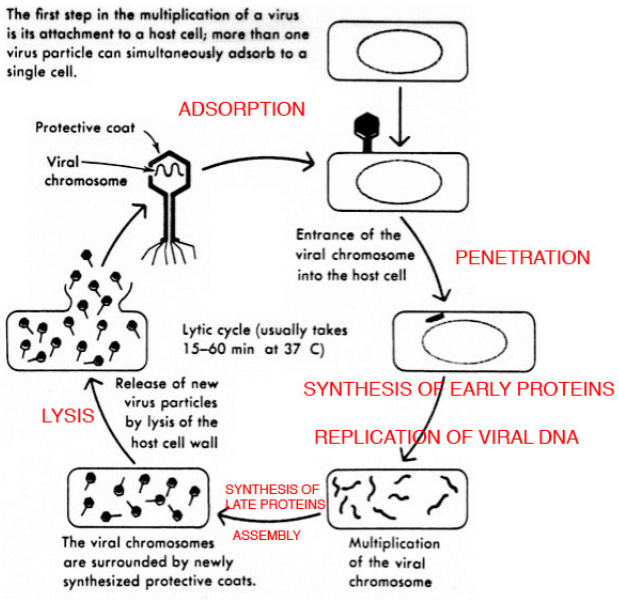

Figure 1.2: The lytic cycle of a bacterial virus, e.g. Bacteriophage, see [3].

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.