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Cholera dynamics with Bacteriophage infection: A mathematical study

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ABSTRACT

Mathematical modeling of waterborne diseases, such as cholera, including a biological control using Bacteriophage viruses in the aquatic reservoirs is of great relevance in epidemiology. In this paper, our aim is twofold: at first, to understand the cholera dynamics in the region around a water body; secondly, to understand how the spread of Bacteriophage infection in the cholera bacterium *V. cholerae* controls the disease in the human population. For this purpose, we modify the model proposed by Codeço, for the spread of cholera infection in human population and the one proposed by Beretta and Kuang, for the spread of Bacteriophage infection in the bacteria population [1, 2]. We first discuss the feasibility and local asymptotic stability of all the possible equilibria of the proposed model. Further, in the numerical investigation, we have found that the parameter ϕ, called the phage adsorption rate, plays an important role. There is a critical value, ϕ_c, at which the model possess Hopf-bifurcation. For lower values than ϕ_c, the equilibrium E^* is unstable and periodic solutions are observed, while above ϕ_c, the equilibrium E^* is locally asymptotically stable, and further shown to be also globally asymptotically stable. We investigate the effect of the various parameters on the dynamics of the infected humans by means of numerical simulations.

1. Introduction

Apart from the natural disasters, like earthquake and tsunami, one of the most challenging problems for the survival of human population is the spread of the infectious diseases around the world. The outbreak of these diseases causes millions of people to become sick and the investment of enormous amount of money in the health care system [3]. Therefore it is necessary to find means of controlling these diseases. In general, water-borne diseases like cholera are a direct consequence of either poor hygienic conditions or a direct contact between healthy and an infected human.

Cholera is an acute gastro-intestinal infection caused by the gram-negative bacterium *V. cholerae*, which is found in the environmental aquatic reservoirs. A healthy human becomes infected with cholera through ingestion of water or food contaminated by certain strains of *V. cholerae*. It causes watery diarrhea leading to rapid dehydration and electrolyte imbalance. In the absence of adequate treatment, the disease can kill an infected human within few hours from the onset of diarrhea.

In endemic areas, such as South Asia, the disease occurs twice a year. Also, pandemic waves travel across the world making humans suffer with the disease. Humanity has suffered seven cholera pandemics since 1817, and almost all of them originated from Asia. In 1961, the seventh cholera pandemic began in Indonesia and continued to affect humans' life for about 4 decades, which is the longest pandemic on record [4]. In more than 52 nations around the world, cholera is still an endemic disease. The bacterium *V. cholerae* infects 1.4 to 4.3 million people with 28000 to 142000 deaths each year [5].

In 2010 the cholera outbreak in Haiti showed that the current control efforts in endemic areas fail due to lack of availability of safe water and basic sanitation facilities [6]. In Haiti, the 2010 earthquake completely destroyed the basic sanitary infrastructure [7]. In 2010, W. H. O. reported that in the endemic countries like Haiti, only 69% of the population had access to clean water and 17% had access to mandatory sanitation facilities [6]. This clearly indicates that without improving the sanitation and safe hygiene practices, the possibility of future cholera outbreaks is likely.

The Britisth physician John Snow first established the link between the cholera cases in London with the exposure of healthy humans to Thames River water [8]. After that the Italian Scientist Filippo Pacini discovered that the disease cholera spreads due to

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the presence of the bacterium *V. cholerae* in the aquatic reservoirs [9]. Since then, several studies have found that the major habitats of the bacterium *V. choleare* are the aquatic ecosystems [10–12]. The long known two important components for the success of any cholera control program are access to clean water and sanitation. Prevalence of the disease can be lowered using these tools. In the regions where cholera still continues to maintain its threat, the interventions, like chemical treatment to bacteria and vaccinating of healthy people are used for the first treatment of cholera. In this respect, Misra and Singh have proposed an SIRS epidemic model for the control of waterborne diseases like cholera by incorporating a delay in the use of disinfectants [9]. In the study, they have suggested that the use of disinfectants may control the disease prevalence in a region but a longer delay can destabilize the system. They have also suggested that the excess amount of disinfectants may have adverse effects on human health. Also, high abundance of the bacterial density in the aquatic reservoirs indicates that these strategies are insufficient to minimize the death toll associated with cholera [10]. Since water is the main vehicle of transmission of the bacterium *V. cholerae* to humans around the world, this is almost impossible to eradicate the bacteria from the aquatic reservoirs. Nevertheless, the major cholera outbreaks can be avoided under systematic control interventions.

The presence of natural organisms, such as Bacteriophage viruses, in the aquatic reservoirs plays an important role in the evolution of bacterial species, and particularly *V. cholerae* [2,13–21]. Bacteriophages are an essential part of the aquatic biology because of their omnipresence in the aquatic ecosystem; they are closely linked to the bacteria population. A Bacteriophage infects the bacterium through injecting its genetic material inside the cell [2,16]. Once the virus is inside the cell, it prevents other phages to attack it, while it starts reproducing within the host until the new viral particles reach a threshold beyond which the bacterium *V. cholerae* starts lysis and releases the new viruses in the aquatic medium, [2]. Faruque et. al. have conducted an empirical study to observe the relationship among the incidence of cholera, the prevalence of the *V. cholerae* in the aquatic reservoirs and the Bacteriophage viruses that attack virulent O1 and O139 serogroups in Dhaka, Bangladesh, India [22]. In this study, they have found that the absence of Bacteriophage viruses in the aquatic reservoirs may promote the cholera epidemics. Furthermore, Jensen et. al. analyzed a mathematical model combining the cholera epidemiology with bacteria population dynamics and phage interaction [23]. In this study they suggested that the introduction of the phages in the reservoirs promotes the depletion of the bacterial density.

In this paper, we simplify the biological cycle of bacteria-phage interaction by combing two phenomena; the spread of the cholera disease in the human population and the Bacteriophage infection in the bacteria population. When the single virus attacks and penetrates the healthy bacterium, it prevents for some time other phages to attack, while it reproduces. During this phase, we subdivide the class of the bacteria into two epidemiological categories; the class of healthy i.e., susceptible bacteria and the infected bacteria, as considered in [2].

The paper is organized as follows. The next section describes the model, the following one contains analysis of the system steady states, Section 4 shows simulations and the possible onset of bifurcations. A final discussion concludes the paper.

2. Model formulation

In this section, we formulate a mathematical model for the biological control of cholera. In the model formulation, we assume that the Bacteriophage viruses are used as a bio-control agent for the inhibition of the bacteria population *V. cholerae* in the aquatic reservoir. For this purpose, we combine two mathematical models; one is for the spread of cholera disease in human population, proposed by Codeço, [1], and the other one is for the spread of a Bacteriophage infection in the bacteria population in the aquatic reservoir, proposed by Beretta and Kuang [2]. We have modified the model [1] by including a constant immigration rate, the disease induced mortality in the infected class compartment and a natural death rate in human population. Further, we have modified the model [2]; in this model, logistic growth of the total bacteria population is assumed, but we assume that once a bacterium becomes infected, it cannot reproduce, due to transfer of genetic material from the virus to the host cell. We have also assumed that due to saturation effect [15], the interaction between *V. cholerae* and phage virus is modeled by a Holling type-II functional response.

Consider a region in which a human population live and consumes water from a nearby aquatic reservoir. Let us assume that there is enough bacteria density $B(t)$ in the aquatic reservoir so that the bacteria can transmit the disease to humans. Let us divide the human population into two mutually exclusive classes, the susceptible $S(t)$ and the infected $I(t)$. Susceptibles can contract the infection through consumption of water contaminated by the bacterium *V. cholerae* from the aquatic reservoir; in so doing they contract the cholera infection and become infected. For the disease control, we observe that the growth of the bacteria can be affected by the Bacteriophage viruses in the reservoir, $V(t)$. The phage infects the healthy bacterium by injecting in it its genetic material through the wall of the cell. Let us denote this class of the bacteria by, $J(t)$.

To formulate a mathematical model for this situation, we make the following assumptions:

A.1 All the humans who enter in the region under consideration at constant rate A either through birth or immigration are assumed to be susceptible. Susceptible humans get the infection through ingestion of water contaminated by *V. cholerae* [8].

A.2 Once the humans become infected, they experience fluid loss through vomiting and feces in the environment which then are washed out directly into the reservoir, from where humans consume water [24]. Thus, the density of *V. cholerae* is directly proportional to the number of infected humans in the region [1,25]. We, also assume that in the absence of shedding of the bacteria by infected humans and the viruses, the susceptible bacteria grow logistically as considered in [15].

A.3 The growth of the bacteria can be controlled by bacteriophage viruses in the aquatic reservoir [16,23]. In the presence of the virus population the class of bacteria splits into two classes; class of susceptible bacteria and the infected bacteria [2]. Susceptible bacteria B are those which are healthy and yet not have been attacked by the viruses [2]. A susceptible bacterium is attacked by a phage virus by injecting its genetic material inside the bacterium. The virus then starts to replicate in it, [16]. Also, the predation of susceptible bacteria due to viruses has been considered to follow Holling type-II functional response as in [15].

A.4 An infected bacterium has a latent period which is the time period between the enteric bacteriophage infection and the process of lysis. Moreover, the phages which are released in the lysis will search a new host cell in the reservoir for their growth, [2].

A.5 We consider also virus intrinsic mortality. However, the death rate of the viruses also includes the death caused by other factors, such as enzymatic attack, **pH** dependence, temperature variations, UV radiation, photooxidation, etc [2].

In the light of the above assumptions, the cholera dynamics with biological control is governed by the following system of non-