Applied Mathematics and Computation 316 (2018) 215–228

Contents lists available at ScienceDirect

Applied Mathematics and Computation

journal homepage: www.elsevier.com/locate/amc

Analysis of deterministic and stochastic mathematical models with resistant bacteria and bacteria debris for bacteriophage dynamics

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ARTICLE INFO

Keywords:
Phage
Resistant bacteria
Bacteria debris
Branching process
Stochastic differential equation

ABSTRACT

Bacteriophages, more colloquially known as phages, are viruses that kill bacteria. Phages are used to treat bacterial infections. In this paper, an underlying deterministic bacteriophage model is extended with the objective of investigating bacteria-phage dynamics taking into account resistant bacteria and bacteria debris, and is analyzed. In addition, this extended model accounts for multiple phage attachment and phage loss due to attachment to latently and actively infected bacteria. Based on this extended deterministic model, two new stochastic models, a continuous-time Markov chain (CTMC) model and an Itô stochastic differential equation (SDE) model were derived and analyzed. Numerical examples illustrate some of the dynamics of the bacteriophage interaction when resistant bacteria are present.

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1. Introduction

1.1. Bacteria complexes, resistant bacteria, and bacteria debris

In a previous paper Vidurupola and Allen [1] proposed a simple bacteriophage model given in (1) that accounts for states for susceptible bacteria, latently infected bacteria, actively infected bacteria, and free phage.

$$\begin{aligned}\dot{B} &= r(B+L+I)B - kBP - \mu B\\ \dot{L} &= kBP - \alpha L - \mu L\\ \dot{I} &= \alpha L - aI - \mu I\\ \dot{P} &= NaI - kBP - k_1(P)[L+I] - \gamma P.\end{aligned} \tag{1}$$

In this model (1), B, L, I, and P stand for susceptible bacteria, latently infected bacteria, actively infected bacteria and free phage particles. The growth rate of susceptible bacteria is denoted by the function $r(B+L+I)$ which depends on the total bacteria population $B+L+I$. It is a decreasing function of $B+L+I$. Term kBP in the model equations denotes the phage binding to susceptible bacteria and becoming latently infected bacteria. Latently infected bacteria become actively infected bacteria at a rate α. Actively infected bacteria die (burst) at a rate a producing N (burst size) copies of new phage.

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http://dx.doi.org/10.1016/j.amc.2017.08.022
0096-3003/Published by Elsevier Inc.

$k_1(P)[L+I]$ term denotes phage loss due to multiple phage attachment to L and I cells. k is an increasing function of p. μ is the natural death rate of bacteria and γ is the phage death rate.

In this paper, the author extends this model (1) by introducing three new state variables that account for resistant bacteria, bacteria complexes, and bacteria debris. Phage attached bacteria cells which are not yet latently or actively infected, referred to as the bacteriophage complexes, Q. All phage attached bacteria need not continue to be latent or actively infected bacteria; phage detachment and natural death of attached phage or bacteria can also be possible [2,3]. Therefore, to apply more realistic modeling procedure, to denote this between state of bacteria that are neither latent nor infected, a new state variable to denote bacteriophage complexes has been included. Moldovan et al. [4] are amongst the first to use an additional state variable to denote complexes in their bacteriophage ODE model to investigate adsorption kinetics. Smith and Trevino in their modeling approach in [3] consider various bacteriophage complexes depending on how many phages are attached to a bacterium. In the case of a multiple phage attachment is possible, a complex can have more than one phage attached to it. Thus, a phage detachment from a complex results a free phage, but no reduction in number of complexes. In the case of only a single phage attachment is possible, a phage detachment from a complex results a free phage and a susceptible bacteria cell, reducing complexes by one. In this extended deterministic model (2), the author assumes multiple phage attachment is possible with reversible bindings.

Bacterial resistance is due to loss or modification of the receptors so that the existing phages in the system are unable to bind [4–6]. Several experimental studies of bacteriophage interactions in the long run have shown the appearance of bacteria mutants that are resistant to the phage infection [6,7]. Luria and Delbruck [7] were amongst the first to show bacteria developing resistance using experiments. Experiments carried out by Bohannan and Lenski [5] on the evolution of bacteriophage resistance show bacteria rapidly evolve resistance to phage infection. They have studied the evolution of resistant mutants of *E. coli* against phage T4, and several other T-phages [5]. Experimental studies carried out by Cairns et al. [8] using *C. jejuni* and suitable virulent phage in an *in vitro* system have shown evidence of arise of phage-resistant population of *C. jejuni*. Studies of Scotts et al. [9] show *C. jejuni* has also given rise to resistant mutants *in vivo* in poultry. In addition, experiments with CP8 and CP34 phages administered orally to 25-day old chickens infected with *Campylobacter jejuni* have shown resistance to bacteriophage infection [10]. All these experimental evidence suggest considering resistant bacteria is significant to applications in phage therapy and calls for the inclusion of a state variable for resistant bacteria that can provide more accurate assessment of the bacteriophage interaction and the qualitative role that the resistant bacteria play in phage therapy [8].

Dead bacteria as a result of natural death and lysis explosions of bacteria are known as bacterial debris [2,11]. Bacterial debris too play a vital role in bacteriophage interaction as phage can attach to bacterial debris. Rabinovitch et al. [2,11], using a bacteriophage model based on the idea of shielding by bacterial debris have shown that the presence of bacterial debris in the bacteriophage system alters its asymptotic solution. In his bacteriophage model, Gallardo [2] also considers phage adsorption to bacterial debris. When a phage adsorbs into debris, its DNA is injected into it in a suicidal manner without the ability to replicate inside it. Hence, the phage is eliminated from the system. In the case of amount of debris is large enough, they can act as an effective shield to the remaining bacteria depending on phage adsorption rate to debris and degradation rate of debris [11].

Inclusion of states to represent resistant bacteria, R, bacteria complexes, Q, and bacterial debris, D give more realism in modeling bacteriophage interaction [2,5,8,9,11]. In this paper, in addition to the states in the model (1) used by Vidurupola and Allen in their previous paper [1], the author includes these three new states.

1.2. Mathematical models

Over the years, several mathematical models have been developed to analyze bacteriophage viral dynamics. But only a few models have been developed that account for resistant bacteria, bacteria complexes, and bacteria debris.

In 1996, Bull and Levin and colleagues [8,12–14] proposed a bacteriophage model applicable to phage therapy that contained phage-resistant bacteria. Their ordinary differential equations (ODEs) model included states for susceptible bacteria, phage, phage-resistant bacteria, the immune response, and antibiotics. During 2000–2003 period, Payne and Jansen [15–17] introduced several phage therapy models with antibiotics and phage resistant bacteria. In 2008, Smith [18] extended some of these models by including a general delay term, density dependent phage adsorption and multiple phage attachment along with phage-resistant bacteria. In 2009, Cairns et al. [8] introduced a model that considers phage insensitive or resistant bacteria. In 2011, Gallardo [2] incorporated a state variable to denote phage loss due to the adsorption of phages to dead and lysed bacteria. In 2012, Han and Simith [6] included a bacteriophage model with bacteriophage-sensitive and bacteriophage-resistant bacteria strains in a chemostat. They investigated persistence and extinction of bacterial strains and bacteriophage. Their analytical results provided sufficient conditions for the persistence of the phage-resistant bacteria.

Few stochastic models have also been applied to host-phage interactions. In 2002 and 2007 Carletti [19,20], in 2013 Bardina et al. [21], and in 2014 Vidurupola and Allen [1] have developed stochastic bacteriophage models, but non of these accounted for bacteriophage complexes, phage-resistant bacteria or bacteria debris.