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Mathematical model of the interaction of pathogenic bacteria and bacteriophages

Miller Cerón Gómez[1]
Universidad de Nariño, Pasto,Nariño, Colombia

Resumo. We present a mathematical model employing ordinary differential equations to model the interaction dynamics between bacterial pathogens and Bacteriophages. Our model incorporates a non-linear function with inhibitory effects to describe the infection dynamics within these populations. By utilizing the Lyapunov theory and the second additive compound matrix, we analyze the stability of the model. Additionally, a global sensitivity analysis is conducted to identify the most influential parameters. Parameter estimation is performed using growth data of Escherichia coli (E. coli) bacteria in the presence of Coliphages, which are bacteriophages targeting E. coli, at various levels of multiplicity of infection. Our findings reveal a critical threshold that determines whether bacteriophage concentration will lead to coexistence with the bacterium or extinction of the phages. The coexistence equilibrium is found to be locally asymptotically stable, while the phages extinction equilibrium is globally asymptotically stable, contingent upon the magnitude of this threshold. Furthermore, our analysis indicates that the infection rate of bacteria and the half-saturation phage density significantly influence the dynamics of the model. Importantly, our parameter estimation demonstrates the effectiveness of all multiplicities of infection in eliminating infected bacteria, albeit with smaller multiplicities resulting in a higher residual population of bacteriophages post-elimination.

Palavras-chave. Coliphages, E.coli, phage-bacteria, Lyapunov method, population dynamics.

1 Introduction

Bacteriophages, also known as phages, are abundant viruses that target bacteria, with estimates suggesting a total count of approximately 10^{31} viral particles, encompassing bacteriophages [5]. These phages exhibit two primary life cycles: lytic and lysogenic. In the lytic cycle, phages infiltrate host cells, replicate internally, and subsequently rupture the host cell to release progeny virions. Conversely, in the lysogenic cycle, phages infect the host without immediate replication, integrating into the host genome or existing as plasmids within the host cell. The genetic material is then passed on to subsequent generations of bacteria [4, 8]. Phages have garnered significant attention in medicine and industry for their applications in combating antibiotic resistance (phage therapy), serving as delivery vehicles for vaccines, or facilitating the display of proteins and antibodies [3, 7]. While phage therapy offers numerous benefits in addressing the global challenge of multidrug-resistant bacteria, it presents only a few drawbacks, most of which can be mitigated through careful phage selection, efficient formulation, and enhanced clinician knowledge and application techniques [11]. Understanding the dynamics of phages and bacterial hosts from various perspectives is essential to gain insight into the synergy within this interaction. Consequently, numerous mathematical models employing ordinary differential equations have been proposed to elucidate these dynamics. For example, Jain et al. investigated the dynamics of the lytic RNA

[1]millercg@udenar.edu.co

phage MS2 and its *E. coli* host [9], while Beke et al. developed a mathematical model considering pH and temperature in the interaction between bacteriophages and their bacterial hosts [1]. Cairns et al. explored the non-linear kinetics between the pathogen bacteria Campylobacter jejuni and a lytic phage, considering susceptible and resistant bacteria, infected cells, and free phage particles [2]. Additionally, Ndongmo et al. presented a model considering the lytic and lysogenic life cycles of phages and prophage induction in the interaction between phages and bacteria [13]. However, many of these studies either focus solely on mathematical developments without empirical validation or solely on empirical data without extensive mathematical analysis. In this study, we propose a mathematical model considering a free lytic phage, sensitive bacteria, and infected bacteria, where the incidence rate incorporates a saturation process due to free phages. We explore the stability analysis of equilibrium points using the Lyapunov indirect method. Furthermore, we conduct global sensitivity analysis to identify crucial model parameters and utilize data on the growth of *E. coli* bacteria in the presence of coliphages to fit the model parameters using a genetic algorithm, aiming to enhance understanding of the interaction between bacteria and phages.

2 Model formulation

Let $E(t)$ and $I(t)$ denote the populations sizes of sensitive bacteria and infected bacteria at time t, respectively and $C(t)$ the concentration of free phages at time t. Bacteria reproduce at a constant per capita rate, which depends on the species of bacteria, in this study we consider the *E.coli* bacteria type for make the simulations. We consider that there exists an intraspecific and interspecific competition between sensitive and infected bacteria as population size increases and resources become more limited, which is modeled by logistical growth with carrying capacity N and reproduction rate k. For the interaction between bacteria and phages we consider the Holling II functional response because we believe that there is saturation in the infection process, i.e., the more free phages there are, the less sensitive bacteria there will be. In this sense the sensitive bacteria acquire infection at rate $\beta E\dfrac{C}{a+C}$, where β is the infection rate of bacteria and a the half-saturation phages density, the mortality rate of this infected bacteria is υ. The free phages growth proportionally to the concentration of infected bacteria I at rate αI, where α is the release rate of viral particles and decay at rate λ. From the above suppositions we derive the following system of non-linear differential equations

$$\begin{aligned}
\frac{dE}{dt} &= kE\left(1-\frac{E+I}{N}\right)-\beta E\frac{C}{a+C}\\
\frac{dI}{dt} &= \beta E\frac{C}{a+C}-\upsilon I\\
\frac{dC}{dt} &= \alpha I-\lambda C.
\end{aligned} \tag{1}$$

The summary of the parameters present in the model is shown in Table 1

3 Results

Define by $R_0=\frac{\beta N\alpha}{\lambda\upsilon a}$ basic reproductive number, which interpretation is: One phage during its average lifetime, $\frac{1}{\lambda}$, infects one sensitive bacteria, with rate βN, this infected bacteria releases $\frac{\alpha}{\upsilon a}$ number of phage particles. In this way, R_0 is the net number of phages produced by a phage in a lytic cycle, in a concentration of sensitive bacteria.

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Tabela 1: Model parameters.

Parameter	Definition	Range	Value	Reference
k	bacterial growth rate	[0.4, 1.8]	1.11	This study
N	carrying capacity	[2.5, 4]	3.2	This study
β	The infection rate of bacteria	[1, 20]	Estimated for different MOI	-
a	Half-saturation phages density	[0.07, 20]	Estimated for different MOI	-
υ	Lysis rate of infected bacteria	[0.05, 4]	1.002	[9]
α	The release rate of viral particles	[1.4, 1.8]	1.63	[1]
λ	decay rate of viral particles	[0.0003, 2]	1.032×10^{-2}	[2]

3.1 Equilibrium points and stability

In this section, we determine the asymptotic stability of the equilibrium solutions of the system (1).

Proposition 3.1. *System* (1) *always has a trivial equilibrium* $P_0 = (0, 0, 0)$ *and the equilibrium point* $P_1 = (N, 0, 0)$. *If* $R_0 > 1$, *there exists an equilibrium* $P_2 = (E^*, I^*, C^*)$, *in which E.coli sensitive, E.coli infected and bacteriophages co-exist.*

Proposition 3.2. *The trivial equilibrium* P_0 *is always unstable and the equilibrium* P_1 *is locally asymptotically stable if* $R_0 \leq 1$, *and unstable otherwise.*

Proposition 3.3. *If* $R_0 \leq 1$, *the equilibrium point* P_1 *is globally asymptotically stable in* Ω.

Proposition 3.4. *If* $R_0 > 1$ *and* $R_0 < \frac{k}{\lambda}$ $(k > \lambda)$, *the point* P_2 *is locally asymptotically stable.*

3.2 Sensitivity analysis

In order to determine which are the parameters that most affect the competition dynamics between sensitive and infected bacteria with bacteriophages, we use the methodology proposed in [12]. We concluded that the more influential parameter in the model are the infection rate of bacteria (β) and Half-saturation phages density (a). The parameter β helps to increase the density of infected bacteria and the density of phages and decrease the density of sensitive bacteria. while the parameter a plays an inhibitory role, the larger it is, the less number of free viral particles will infect sensitive bacteria, which implies a smaller number of infected bacteria.

3.3 Parameter estimation

We select the parameters β and a to be estimated using experimental data published in [10], in particular those for *E.coli* ATCC® 11775™ (gram-negative) and T4-like A coliphages, where they elaborate curves for bacterial growth curves in the presence of bacteriophages using the MOI 0.01, 0.1 and 1 to compare and analyze the activity of bacteriophages. Since the data in [10] only show the total remaining bacteria, i.e., the data used do not distinguish between infected and susceptible bacteria, nor does it show coliphages growth data, we find the least square between the data and the sum of sensitive and infected bacteria $E(t)+I(t)$. To do this, we use a evolutionary algorithm called genetic algorithms (ga) where the function to minimize was $fmin(\beta, a) = \sum_i \{data_i - [E(i)+I(i)]\}^2$, where $E(t)$ and $I(t)$ are the outputs of the model (1), for an explanation of how the ga works see [6].

The estimates of these parameters are shown in the Table 2 and the curve fits is shown in the Figure (1a).

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Tabela 2: Parameter estimation for different MOI.

MOI	β	a	Initial condition [S(0) I(0) C(0)]
0.01	2.6	0.22	[0.24 0 0.0024]
0.1	3.81	0.4428	[0.19 0 0.019]
1	18.92	6.68	[0.18 0 0.18]

(a) (b)

Figura 1: The Figure (1a) shows the estimated growth curve of susceptible *E.coli* bacteria and infected *E.coli* bacteria in the presence of coliphages when the MOI is 0.1 and (1b) shows the growth curves of each population.

4 Discussion

The intricate relationship between bacteriophages and bacteria holds significant relevance in the context of antibiotic resistance, yet its complexity is described by various dynamics at different levels. We formulated a mathematical model considering populations of sensitive bacteria, infected bacteria, and bacteriophages, employing a nonlinear function with an inhibitory effect for the incidence rate. Three possible outcomes for the bacteria-phages relationship were identified: simultaneous extinction of uninfected bacteria, infected bacteria, and phages (trivial equilibrium); extinction of infected bacteria and phages (bacteriophages extinction equilibrium); and coexistence of sensitive bacteria, infected bacteria, and phages (coexistence equilibrium). Local stability analysis using Lyapunov's indirect method and the second additive compound matrix revealed that the trivial equilibrium is always unstable, while the phages extinction equilibrium is locally asymptotically stable when the reproduction number R_0 is less than or equal to 1, and unstable otherwise. The coexistence equilibrium is locally asymptotically stable when R_0 is greater than 1 and less than k/λ. However, based on our calculations, this inequality is a sufficient but not necessary condition for stability, as our simulations suggest stability may occur when $R_0 > k/\lambda$. Interestingly, despite good curve fits, parameter estimation revealed instability due to $k > \lambda$ and $R_0 > k/\lambda$, with the eigenvalues of the Jacobian matrix having complex conjugates with a positive real part, resulting in oscillations persisting over time. Sensitivity analysis highlighted the infection rate of bacteria (β) and half-saturation phage density (a) as the most influential parameters, with β increasing the density of infected bacteria and phages while decreasing the density of sensitive bacteria, and a playing an inhibitory role by reducing the number of free viral particles infecting sensitive bacteria, leading to fewer infected bacteria. Moreover, model and parameter estimation indicated higher growth of E. coli bacteria at a lower multiplicity of infection (MOI), with implications including slower coliphage growth and prolonged bacteria extinction time.

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