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Modelling the interaction between bacteriophages and their bacterial hosts

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ABSTRACT

A mathematical model simulating the interaction between bacteriophages and their bacterial hosts has been developed. It is based on other known models describing this type of interaction, enhanced with an ability to model the system influenced by other environmental factor such as pH and temperature. This could be used for numerous estimations of growth rate, when the pH and/or the temperature of the environment are not constant. The change of pH or the temperature greatly affects the specific growth rate which has an effect on the final results of the simulation. Since the model aims on practical application and easy accessibility, an interactive website has been developed where users can run simulations with their own parameters and easily calculate and visualise the result of simulation. The web simulation is accessible at the URL http://www.phisite.org/model.

1. Introduction

The raising problem of bacterial resistance against antibiotics pointed out the need of novel alternative solutions to eliminate pathogenic bacteria. As a result, the last years of phage research was predominantly devoted to the search of new phages and their potential application as therapeutic agents, generally known as 'phage therapy'. Bacteriophages, also called phages, are viruses infecting prokaryotic organisms. Phages are ubiquitous and are the most abundant organisms on the planet [1,2] and represent important components of ecological systems. They can modify microbial culture by lysis, transmission of genetic material and by lysogenic conversion. Phages are very important for basic research, but their practical application is still low. Phages can be used in identification of bacterial pathogens [3] or in detection of bacterial contaminations [4]. They are natural enemies of bacteria and are mostly harmless to the human organism. This makes them a promising agent for elimination of undesired bacteria in food industry, medicine or in agro-biotechnology. Phages can be applied individually as solo species; however phages represents one of the major selecting forces in the evolution of bacteria and can develop resistance against phages in couple of days or hours. To slow down this rapid adaptation process, phages can be applied in combinations as 'phage cocktails', they can be cyclised (changed over the time) or they can be applied in combination with antimicrobial drugs, like antibiotics [5]. Another possibility is the application of genetic modification of phages or the development of synthetic bacteriophages. There are still several problems in practical application of phages as therapeutic agents, e.g. difficulties during the transport of phages to the place of infection or the fact that phages can cause release of endotoxins and pyrogens, which are the side products of the bacterial lysis and can harm humans or other treated subjects.

For the successful practical application of phages it is necessary to understand the interaction between the phages and their hosts in details [6]. Interaction between phages and bacteria were studied in marine environment [7–9], in rhizosphere [10–13] or in fermentation processes, e.g. in the production of biofuels [14,15]. Mathematical modelling of biological systems is a vital tool in this area and has an important application in ecology or in evolutionary and systems biology [16]. One of the most common mathematical techniques used in mathematical modelling to describe a dynamic behaviour of biological system are differential equations [17]. Several mathematical models were developed to describe the qualitative and quantitative aspects of the interaction between phages and bacteria [18,19]. There are mathematical models that include the influence of antibiotics together with the effect of the host's immune system and might be applied in phage therapy [20,21]. Other models describe the phage-host interaction from ecological point of view, for example the phage-host interaction in marine environment [7,22]. The interaction between the phage and bacteria depends on several factors, both biological (CRISPRs, bacterial resistance, bacterial fitness) and physical (temperature and

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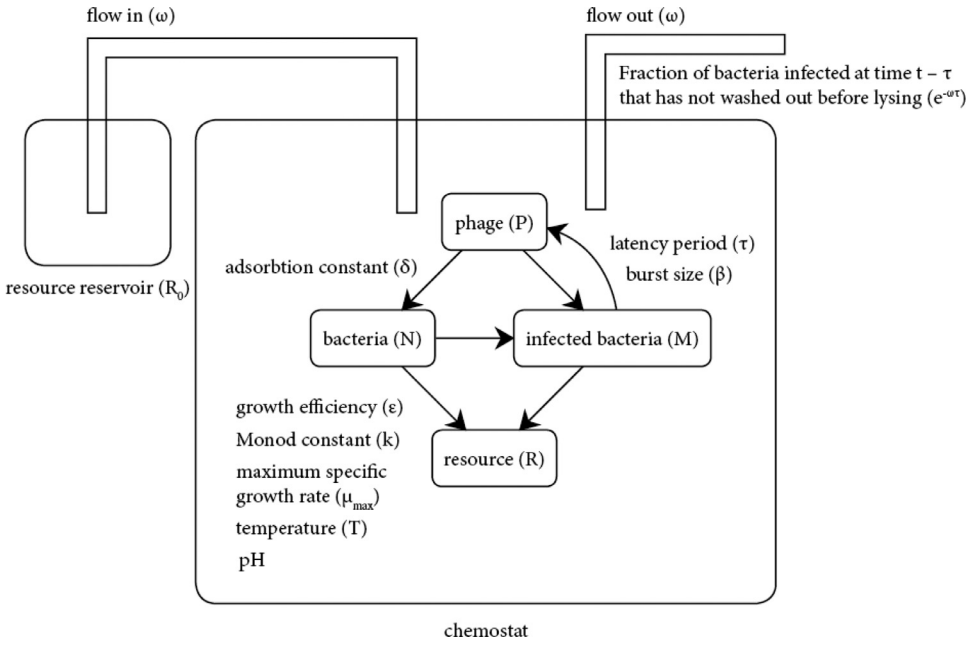

Fig. 1. Interaction of bacteria and bacteriophages in a simple bioreactor (chemostat).
Source of energy is flowing from the resource reservoir (R_0) in to the system, where the population of bacteria (N) consumes the resource of energy for their growth. The bacterial growth is a function of maximum specific growth rate (μ_{max}), growth efficiency (ε) and of Monod constant (k) – the concentration of resources in medium at which the growth is the half. The maximal specific growth rate is defined as a function of optimal growth rate, temperature and pH [25]. At the same time, bacteriophages (P) are attacking bacteria and adsorbing on their surface with constant adsorption rate δ. Hence, infected bacteria are formed. Bacteria and infected bacteria compete for the resource of energy. Bacteriophages attach also to the surface of infected bacteria, but they don't infect them resulting in decrease of free phages in the system. After latent period infected bacteria are lysed and new phages are added to the system and their number is defined by the 'burst size'.

pH affecting adsorption of phages and bacterial growth, concentration of organic acids affects the growth of bacteria).

Aim of the work described in this paper was to develop an improved mathematical model based on combinations of existing models describing the phage-host interaction under different conditions and affected by several factors as pH and temperature. It was aimed also at developing an interactive utility simulating the dynamics between the phages and their hosts, which would be easily available for users via a web application.

2. Methods

Using the criterion of relative size and mode of action, the interactions between the virulent phages and their bacteria are usually defined as parasitism [23]. Because replication by most virulent phages necessarily results in bacterial death, some authors describe these interactions as predation and certain interactions could even be termed mutualistic, as some temperate phage encode phenotypic characteristics that are of direct benefit to their hosts [24]. The interactions of the phage-host system in a simple controlled environment (chemostat) are described in Fig. 1.

2.1. Mathematical models describing the phage-bacteria interaction

The two, most commonly used mathematical models describing the phage-bacteria interaction are the mathematical model by Schrag and Mittler [25] and their modifications, which describe the phage-host interaction in a chemostat:

$$\frac{dR}{dt} = \omega.(R_0 - R) - \frac{\varepsilon.\mu_{max}.R.(N+M)}{k+R} \quad (1)$$

$$\frac{dN}{dt} = \frac{\mu_{max}.R.N}{k+R} - \delta.N.P - \omega.N \quad (2)$$

$$\frac{dM}{dt} = \delta.N.P - \delta.N(t-\tau).P(t-\tau).e^{-\omega.\tau} - \omega.M \quad (3)$$

$$\frac{dP}{dt} = \beta.\ \delta.N(t-\tau).P(t-\tau).e^{-\omega.\tau} - \delta.N.P - \delta.M.P - \omega.P \quad (4)$$

and the mathematical model by Beretta and Kuang [22]:

$$\frac{dN}{dt} = \mu_{max}N\left[1 - \frac{N+M}{C}\right] - \delta NP \quad (5)$$

$$\frac{dM}{dt} = -\mu_i M + \delta NP - e^{-\mu_i\tau}\delta N(t-\tau)P(t-\tau) \quad (6)$$

$$\frac{dP}{dt} = b - \mu_p P - \delta NP + \beta e^{-\mu_i\tau}\delta N(t-\tau)P(t-\tau) \quad (7)$$

which describes the phage-host interaction in marine environment. These two models differ in a way how they define the increase of bacterial population. The other parts (attack of phages on bacteria and generation of new phages) are almost the same in both models.

Several models describing the growth of bacterial population alone were developed. Some of them describe the bacterial growth affected by pH and/or temperature, e.g. the model of Rosso et al. [26]:

$$\mu_{max} = \mu_{opt}.\tau(T).\rho(pH) \quad (8)$$