Phage-Antibiotic Therapy with Bacterial Swimmers in a Biofilm

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ABSTRACT

We improved and analyzed a nonlinear population dynamics model of phage-antibiotic combination therapy that accounts for the synergistic elimination of bacteria using phages and the immune system. We simulate the combination therapy model for four strains of the same bacteria that have flagella, two that are phage sensitive (and antibiotic resistant) and two that are antibiotic sensitive (and phage resistant). Within these two types, one is a planktonic bacterium, and the other is within a biofilm. We chose to use phage-antibiotic combination therapy because research shows that they exceed in elimination better than phages and antibiotic by themselves. This model also takes in account the interaction that free swimming bacteria have on the biofilm.

INTRODUCTION

Collaborative groups of bacteria known as biofilms cling to surfaces and are shielded by an extracellular matrix. Biofilms are frequently resistant to standard antibiotics, posing a significant problem for chronic illness treatments. Phage-antibiotic therapy is a promising method that combines bacteriophages, which infect and destroy bacteria, with antibiotics to improve the efficacy of both drugs. Phages can disrupt biofilms by dissolving the extracellular matrix, exposing bacteria to antibiotics, and inhibiting the production of new biofilms by interfering with quorum sensing, a bacterial communication system. Phages can also work in tandem with antibiotics to increase their permeability into biofilms, stimulate bacterial metabolism and sensitivity, and reduce the establishment of resistance. Phage-antibiotic therapy has been demonstrated in several studies to be an efficient means of reducing biofilms of several bacterial species, including Pseudomonas aeruginosa and Escherichia coli, both in vitro and in vivo. The selectivity of phages, the fluctuation of biofilm form and composition, the emergence of phage-resistant bacteria, and the control of phage-antibiotic interactions are some of the obstacles and restrictions associated with this strategy. As a result, more study is required to enhance the selection, mix, and delivery of phages and antibiotics for biofilm elimination.

Several bacilli and other flagellated bacteria in both premature and mature biofilms have highly motile populations within the biofilm matrix. These movements create temporary openings that irrigate the biofilm and allow macromolecules to enter, including antibiotics. Notably, we developed a mathematical model to explore how motile bacteria can influence the dynamics of antibiotic-phage therapy combination.

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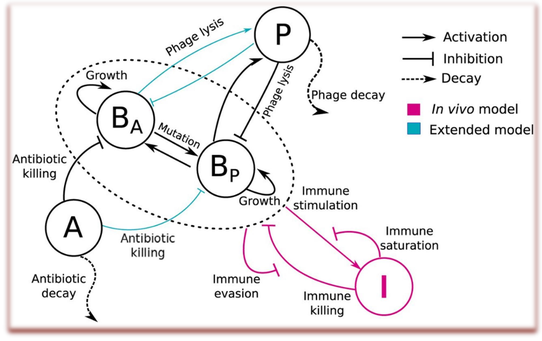
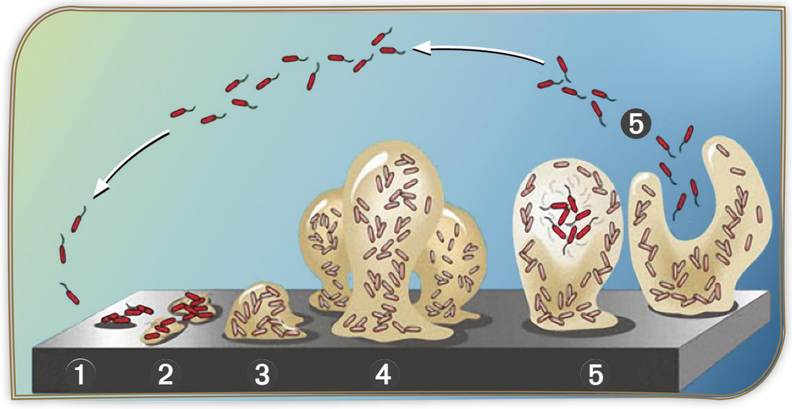
What The Symbols Represent
B_p) Biofilm bacteria susceptible to phages
B_a) Biofilm bacteria susceptible to antibiotics
K) The carrying capacity of bacteria K_a) The carrying capacity of antibiotics K_I)The carrying capacity of the immune system
N) The sum of all bacterial species
μ) The mutation rate
α, γ, r) The growth rate
ρ, η) Activation parameters
β, θ, δ) Death rates
$u(t)$ – control parameter from either phages or antibiotics
σ) the rate at which the immune cells are produced

Parameters and default values	Definitions
$\mu = 2.85 \times 10^{-8}$	Probability of the emergence of either page –sensitive or anti-biotic sensitive bacteria due to mutation
$K = 1 \times 10^{10}$	The carrying capacity of bacteria
$K_I = 2.4 \times 10^{7}$	Maximum capacity for an immune response
P = 7.4×10^{8}	Initial dose of phage
$r_a = 0.675\ h^{-1}$	Maximum growth rate of antibiotic – sensitive bacteria
$r_p = 0.75\ h^{-1}$	Maximum growth rate of phage – sensitive bacteria
$\beta = 100$	Burst size of the bacteria due to phage infection
I = 2.7×10^{6}	Initial immune response
$\delta = 0.07\ h^{-1}$	Phage rate of decay
$\theta = 18.5\ h^{-1}$	Maximum kill rate of antibiotics



This model (comes from Rodriguez-Gonzalez, Rogelio A., et al) was extended to incorporate two types of free-swimming bacteria. The mathematical model we made include the extended model and applies it to all bacteria types



(M, Luisetto, et al.)

FUTURE DIRECTION

We will examine the implications of combination therapy on heterogeneous microbial species containing all four bacteria categories. To do this, we conducted a comprehensive examination of four (in vivo) therapeutic models: antibiotic-only, antibiotic-innate immunity, phage-only, and phage-antibiotic combination in the presence of innate immunity. We changed the antibiotic's concentration and the bacterial composition of the bacteria in each model (Rodriguez-Gonzalez, Rogelio A., et al). The data for the model will tell us what combination will have a synergetic, antagonist, or additive effect. In this model, we assume phage are only produced by bacteria after the initial injection.

Our current model does not have an equation that explains how tunneling from motile bacteria can undermine the biofilm. An extension could incorporate that equation.

METHODS

We have extended the mathematical model from other papers. The equations were made using the same parameter that are in the Weitz paper.

We modified the equation for the immune system and antibiotics. We rewrote the immune equation so that it represent the instability of the immune system. The previous equation assumed that in the absence of bacteria the immune system would stay at the same amount it was previously. They did not have a kill rate to accurately describe the dynamics of the immune system.

THE SPECIES	THE MATHMATICAL MODEL
Bacteria within the biofilm that is susceptible to phages	$\dot{B_p} = rB_p\left(1-\frac{N}{K}\right)(1-\mu) + \frac{r(N-B_p)}{3}\left(1-\frac{N}{K}\right)\mu - \beta B_p P$
Bacteria in the biofilm that is susceptible to antibiotics	$\dot{B_a} = rB_a\left(1-\frac{N}{K}\right)(1-\mu) + \frac{\dot{r}(N-B_a)}{3}\left(1-\frac{N}{K}\right)\mu - \frac{\theta A B_a}{A+K_a}$
Free swimming bacteria that is susceptible to phages	$\dot{F_p} = rF_p\left(1-\frac{N}{K}\right)(1-\mu) + \frac{\dot{r}(N-F_p)}{3}\left(1-\frac{N}{K}\right)\mu - \beta F_p P$
Free swimming bacteria that are susceptible to antibiotics	$\dot{F_a} = rF_a\left(1-\frac{N}{K}\right)(1-\mu) + \frac{r(N-F_a)}{3}\left(1-\frac{N}{K}\right)\mu - \theta A F_a$
Antibiotics	Their model: $\dot{A} = A_I - \theta A$ Our model: $\dot{A} = -\frac{\eta A N_A}{A+K_a} - \eta A + u_a(t)$
Phages	$\dot{P} = \gamma(B_a + F_a)\frac{P}{1+P} - \delta P + u_p(t)$
The Immune system	Their model: $\dot{I} = \alpha I(1-\frac{I}{K_I})(\frac{N}{N+K})$ Our model: $\dot{I} = I\left(\frac{\rho N}{\eta+N} - \mu N - \delta\right) + \sigma$