



Sara Zarei, Forest Rohwer, and Peter Salamon

AP0913





Mathematical Modeling of Cystic Fibrosis Ecology

Sara Zarei, Forest Rohwer, Peter Salamon

Computational Science Research Center, San Diego State University, San Diego, CA, USA

Abstract - Cystic fibrosis is an inherited chronic disease that affects the lungs, digestive system and even circulatory system of CF patients. Understanding the CF patient's lung and airway as an ecosystem is a novel and powerful point of view. There are many different microbes in CF lungs that no one has ever cultured and the chronically colonized CF airways represent a complex and diverse ecosystem. Once we understand the CF lung in terms of its community and evolutionary ecology, we can then better understand the disease progression and the influence of different treatments on CF patients. A complete mathematical model of CF would need equations that follow the concentrations of all different kinds of bacterial and phage species in each compartment. This type of encyclopedic model is impossible to build in one go, therefore we can start with simple models that only look at one phage-host interaction. As part of our modeling efforts, we expect to figure out which variables are the most important using the metagenomic data currently being prepared by San Diego State University's Phage group.

1 Introduction

Cystic fibrosis is an inherited chronic disease that affects the lungs, digestive system and even circulatory system of CF patients. Children with Cystic Fibrosis are all born with this disease; they carry a defective gene that causes the body to produce unusually thick, sticky mucus that leads to clogging their lungs and thereby making it susceptible to lung infections. It also obstructs the pancreas and stops natural enzymes from helping the body break down and absorb food. These exacerbations are characterized by dyspnea (difficulty in breathing), cough, sputum production and occasionally hemoptysis. The treatment of cystic fibrosis focuses on eradicating the early infections of Pseudomonas spp. or controlling established airway infections with the goals of relieving the symptoms of airflow obstruction.

Understanding the CF patient's lung and airway as an ecosystem is a novel and powerful point of view. There are many different microbes in CF lungs that no one has ever cultured and the chronically colonized CF airways represent a complex and diverse ecosystem [4]. Once we understand the CF lung in terms of its community and evolutionary ecology we can then better understand the disease progression and the influence of different treatments on CF patients. Approaching the CF chronic airway infection as a community that follows specific ecological principles will allow us to find out whether there are better times to introduce specific antibiotics or whether this therapy should be cycled and if so at what periods should such cycling occur?

Currently, therapy includes the use of bronchodilators and anti-inflammatory agents. Antibiotic therapy is critical for eradicating early airway microbial colonization and controlling established airway infections. Patients with exacerbations of airway infections are typically treated with systemic antibiotic therapy. Despite very aggressive treatment, the median age of survival is approximately 38 years [4].

One of the most effective CF treatments is to control the food web components so that we disrupt the unhealthy balance of this ecosystem with minimal damage to the lungs. In any ecological system there are two main controls, top down and bottom up. The top down control refers to when a top predator controls the structure/population dynamics of the ecosystem. The bottom up control in ecosystems refers to ecosystems in which the nutrient supply and productivity control the ecosystem structure. In Cystic fibrosis the two controls play an important role in improving treatments. Microbial growth in CF lungs depends on both the nutrients and the predators. Active bacteria thrive on all the possible substrates in CF lungs. These substrates could consist of dead bacteria and all sorts of debris. On the other hand the immune system and phage will exert top down control.

2 Phage-bacteria interaction models

In this paper a few mathematical models of phagebacteria coexistence are reviewed and their suitability for modeling CF biomes is assessed. In some of these models we refer to two groups or compartments of bacteria : inactive and active. Inactive bacteria do not multiply due to lack of nutrients and are not subject to infection by phage. Active bacteria thrive on organic matter, multiply and are infected by phage.

They go through lysis and migrate between compartments. In addition to following active and inactive bacterial populations, the models also describe the phage population. Once phages are assembled inside their hosts, cell lysis occurs causing a release of new phages. The number of released phages of one infected cell is the burst size and the time spent between adsorption and release of phages is called the latent period. Viral lysis is a major cause of bacterial mortality. On average 10 to 20 percent of the bacterial production is lysed daily by viruses [3]. This contributes greatly to the buildup of debris in the CF lungs and is the main reason phage have great impact on both mortality and production of bacteria.

A complete mathematical model of CF would need equations that follow the concentrations of all different kinds of bacterial and phage species in each compartment. That means we should have different equations that can represent all different microorganisms that can be found in CF patients' lungs, airways, intestine as well as circulatory system and pancreas. This type of encyclopedic model is impossible to build in one go, therefore we can start with simple models that only look at one phage-host interaction. The choice of good model requires finding the important controlling variables in the set of equations. As part of our modeling efforts, we expect to figure out which variables are the most important using the metagenomic data currently being prepared by San Diego State University's Phage group. Metagenomic methods collect and analyze genetic material recovered directly from environmental samples.

By surveying literature about predator-prey models of Phage-host interactions we found a number of papers that present mathematical models of phage-bacterial interaction. In the absence of abundant data from CF patients, these models are the only possible models that we can implement and analyze. In addition we need to consider the fact that none of these already formulated models were formulated specifically for the Cystic fibrosis ecosystem but instead were all intended to model different microbiomes.

2.1 Lotka-Voltera model

Lotka-Voltera Model is a simplified model of a phage-host ecosystem that represents the relationship between bacterial population size (S) and the phage population (P). The equations below are for a generalized Lotka-Volterra model.



In Lotka-Voltera modeling of phage-host communities, the bacterial dynamics undergo intrinsic growth and decay cycles

due to the interaction with the phage. As a result, both populations oscillate in time. The bacterial population size S depends on both microbial reproduction and phage predation. The phage population grows as it interacts with the bacteria and has an algebraic decay when no bacteria are present. In above equations r, κ , γ , β represent constants for bacterial growth, phage infection rate, phage decay, and phage production through lysed bacteria, respectively [5]. This model has interesting implications that can be helpful in certain medical research such as predicting the cycling of the microbial and phage populations. Consider using phage (or similar therapy) to reduce the total number of bacteria. In this case timing would be an important factor to consider. For the Lotka-Volterra model, once we inject phage it will have a large effect on the system. The largest effect on the dynamics is achieved by suddenly infusing the phage at once.



Figure (1a) and (2a) represent the concentration of bacteria and phage as a function of time in two stages, before and after the injection of phage that is represented here by a vertical line. In addition figures (1b) and (2b) represent the phage counts versus bacteria counts before (blue color) and after (black color) the injections respectively. The difference between these two pairs is the time at which the phage was injected into the system. As we see in figure (1a) the phage predator was injected to the system at the peak bacterial community size versus in figure (2a) where the injection took place when bacterial population size was at its lowest point. As a result, the injection at peak time caused the microbial cycling to grow while injecting phage at lowest bacterial population size decreased the overall bacterial cycling. This illustrates how timing can have an effect on certain therapies. In Cyctic Fibrosis our goal is to conduct the therapy in a way that lead to a decrease in the overall bacterial population as well as the resulting phage response. Basic Lotka-Volterra models are likely to be too simple to be considered for the behavior of the predator-prey interactions in a CF lung. Therefore we would need more complex models that can describe the complex, chronically infected airways of cystic fibrosis patients more precisely.

2.2 Two compartment model of phagebacteria interaction

The next model presents the phage-bacteria coexistence in marine environment where the bacteria population is divided into two compartments, inactive and active [5]. The model consists of three ordinary non-linear delay differential equations that describe the growth rate of susceptible (active) bacteria, phage and inactive bacteria respectively. First equation represents the growth rate of susceptible bacteria and there is a logistic factor to account for a limited supply of substances. In the same equation the phage predation has been directly subtracted from the bacteria growth. In addition to that there are the two migration terms between N (inactive) and B (active) population that are present in the growth equation. The V equation includes a phage decay term. phage-bacteria adsorption factor and a production term of lysing after a time delay. Last equation represent the growth rate for inactive bacteria which do not have any interaction with phage so their growth equation only consist of grazing factor and bacterial migration terms.



Growth rate of inactive Grazing term Bacterial migration bacteria $\frac{dN}{dt} = -g_N N(t) - m_N N(t) + m_B B(t) (2.5)$



Figure (3) Phage-bacteria interaction

Figure (3) represents the simulation of above model as it depicts, an increase in active bacteria population is followed by an increase of its phage. The number of phage increases when there are high amount of bacteria, this leads to a decrease of bacteria population that eventually leads to a drop in phage population due to lack of prey.

2.3 Modeling bacteriophage infection with latency period

The next model [1] uses three time-delay differential equations that represent the interaction between susceptible and infected bacteria, S and I, with phage viruses, P. Using the law of mass action the rate of infection is K P (t) S(t), where K is the effective per bacteria phage absorption constant rate and P(t) and S(t) represent the number of viruses and susceptible bacteria per liter respectively. Using a logistic growth model we can represent the rate of change in number of susceptible bacteria using the first equation listed below. The second equation represents the change in concentration for infected bacteria. Since infected bacteria may have different causes of mortality than just viral lysis, e.g. protozoan and immune cell grazing, there is a constant death rate of μ_i in the equation. The third term of the infected bacteria equation represents the number of deaths of infected bacteria at time t, that were infected by phage at time t-T. where T represents the latency time. The last equation provides the rate of change of phage concentration in this simple ecosystem. Beta represents the constant input of free phage from the surrounding environment. The rate of lysis of infected bacteria at time t was represented as $e^{-\mu_i T} KS(t-T)P(t-T)$. Since each infected bacteria delivers "b" phage after lysis, that leaves the input rate of phage at time t to be $e^{-\mu_i T} KS(t-T)P(t-T)$.

$$\frac{dS(t)}{dt} = \alpha S(t)(1 - \frac{S(t) + I(t)}{C}) - KS(t)P(t) \quad (2.6)$$

$$\frac{dI(t)}{dt} = -\mu_i I(t) + KS(t)P(t) - e^{-\mu_i T} KS(t-T)P(t-T) \quad (2.7)$$

$$\frac{dP(t)}{dt} = \beta - \mu_p P(t) - KS(t)P(t) + be^{-\mu_i T} KS(t-T)P(t-T) \quad (2.8)$$

In the above model, one of the most important variables in the sense that its value has a dramatic effect on the system's behavior is the "effective per bacteria phage absorption constant rate K. In this sense, K is a controlling variable in our set of differential equations. This is illustrated in the following four figures showing simulations from this mode using different values of K.



By comparing these figures we can observe the fact that, the higher the interaction rate between phage and bacteria, the higher the rate of phage production is going to be. In Figure (4) where the rate of interaction is half as large as in Figure (5), the phage production curve gets into a stable stage after about 50 seconds.

In several different mathematical models, the graph of phage concentration in the system has the form of sharp spikes for rather broad ranges of parameter values. This corresponds to the fact that free phage do not live long, but due to their burst factor can build to high concentrations very rapidly. This is one reason some more simpler models fail. For instance, the following mathematical model [2] was tried unsuccessfully in the cheese industry.

$$\frac{dx}{dt} = ax - bvx \quad (2.9)$$
$$\frac{dy}{dt} = ay + bvx - ky \quad (2.10)$$
$$\frac{dv}{dt} = KLy - bvx - mv \quad (2.11)$$

- x(t) is the concentration of uninfected bacteria.
- y(t) is the concentration of lytic bacteria.
- v(t) is the concentration of free phage.
- a is the replication coefficient of the bacteria
- b is the transmission coefficient
- k is the lysis rate coefficient
- L is the burst size

• M is the decay rate of free phage



Figure (7) Bacteria-Phage In Cheese Industry

As shown in this figure, the phage concentration goes toward negative values. This shows the failure of the above model. Perhaps the model had incorrect assumptions concerning the interaction between bacteria and bacteriophage as well as possible errors in estimating the model parameters.

3 Conclusion

In conclusion, we argued that mathematical models of Cystic fibrosis viewed as a microbial ecosystem offer possible routes to the identification of controlling variables and eventually a tool for studying the effect of treatment regimens. Metagenomic data from the sputum of CF patients will enable informed selection of terms to use in the equations employed by these models and allow us to formulate and validate better models.

4 References

[1] Bereta, E. Kuang, Y. Modeling and Analysis of a Marine Bacteriophage Infection with Latency Period. Nonlinear Analysis: Real World Applications. Vol.2. 35-74. (2001)

[2] Celine, C. Bacteria-Phage Mathematical Model Applied to the Cheese Industry. MS thesis, Massey University, 18-19. (2003)

[3] Weinbauer. M.G. Hofle, M.G. Significance of Viral Lysis and Flagellate Grazing as Factors Controlling Bacterioplankton Production in a Eutrophic Lake. Applied and Environmental Microbiology. Vol.64. 431-438. (1998)

[4] Conrad, D. Furlan, M. Haynes, M. Salamon, P. Quinton, P. Rainey, P. B. Rohwer, F. Ecology and Cystic Fibrosis Therapy. To appear in Nature. (2009)

[5] Rabinovitch, A. A Two Compartment model of phagebacteria interaction. To appear in Nature. (2009)