Optimal Lysogenic Propensity as a function of Multiplicity of Infection in Stressed Environments

Devang Thakkar, Supreet Saini

Abstract

Bacteriophage-bacteria systems have complex growth dynamics that dependent on a multitude of factors. Despite their extremely high amplification factors compared to their hosts, phages manage to maintain a healthy number of bacterial cells in the system. One of the important factors on which their dynamics depends is the multiplicity of infection, or the relative abundance of the phages and the bacteria. In this work, we consider environments with varying levels of stress for the bacteria and estimate the optimal propensity of lysogeny P(lyso) for varying multiplicities of infection (MoI). We find that coexistence is best ensured by a sigmoid-like curve between P(lyso) and MoI that changes quantitatively with changing environments.

1 Introduction

Several efforts have been made in the past to understand the lysogeny-lysis decision in phage-bacteria populations. The primary aim of the phage is to avoid going extinct, and it does so by multiplying exponentially through lysis. However, in order to survive, it needs to find new bacterial hosts in order to gain nutrients for replication. Thus, a phage needs to find an optimal strategy that is powerful enough so as to protect the phage from extinction but not so powerful that it wipes off the all bacteria in the system. Such a phage that balances its lysogenic and lytic propensities is referred to as a *temperate phage*, an example of which is the lambda phage. [Gandon, 2016]

We are trying to understand the impact of environmental stresses on the coexistence of phage-bacteria systems. We are investigating in-silico, the dependence of the propensity of lysogeny as a function of the multiplicity of infection in the presence of various environmental stresses. Previous work on the coexistence of such systems covers the following topics:

- The impact of the infection rate and the phage degradation rate on coexistence [Heilmann et al., 2010]
- A bet-hedging approach to ensure survival in case of sporadic spikes of degradation rates [Maslov and Sneppen, 2015]
- The stochasticity in the lysogeny-lysis decision at a higher multplicities of infection [Avlund et al., 2009]
- A game theoretic approach to investigate the lysogenic propensity for different MoI [Sinha et al., 2017]

2 Method

A phage-bacteria system can be characterized with the following parameters:

- phage and bacterial populations (jointly expressed using multiplicity of infection)
- bacterial growth rate
- phage burst rate
- bacterial degradation rate
- phage degradation rate

We shall consider two additional parameters to descibe the environment, namely p_1 - the probability of an environment that is good for phages, and p_2 - the probability of an environment that is good for bacteria. An explicit assumption here is that a bacterial cell can only be infected by a single phage. Thus, total phage = free phage + lysed phage or, total phage = free phage + infected bacteria. Another point to be noted here is that the terms - multiplicity of infection and average phage input have been used interchangeably.

2.1 Equations governing the model

We discretize the differential equations governing the system for single time steps for ease of understanding and implementation. Thus, the equations shown below are of the form

$$x_{new} = x_{old} + rate * \Delta t \tag{1}$$

2.1.1 Notation

- $N_{b,h}$: Number of healthy bacteria (Initial Value: 10000)
- $N_{b,i}$: Number of infected bacteria (Initial Value: 0)
- $N_{p,free}$: Number of free phage (Initial Value: $N_{b,h} * MoI$)
- r: Normal growth rate of cell division (Initial Values: 1,2,5)
- a: Burst rate for phage during lysis (Initial values: 10, 20)
- MoI: Total phage/total bacteria (Initial values: [0.01, 0.02, ..., 2.00])
- p_1: Probability of good phage environment (Initial Value: [0.1, 0.2, ..., 1.0])
- p_2: Probability of good bacteria environment (Initial Value: [0.1, 0.2, ..., 1.0])
- λ_b: Decay rate for bacteria in bad periods (Initial Value: 0.1, 1)
- λ_p: Decay rate for phage in bad periods (Initial Value: 1,2,3)
- $P(lyso)$: Probability of choosing lysogeny (To be calculated)

2.1.2 Case 1 - Good p_1, Good p_2

$$N_{b,h,new} = N_{b,h,old} + r * \Delta t * N_{b,h,old} - N_{p,free} \tag{2}$$

New number of healthy bacteria = Old number of healthy bacteria + Increase due to cell division - Decrease due to infection by phages

$$N_{b,i,new} = N_{b,i,old} + r * \Delta t * N_{b,i,old} + P(lyso) * N_{p,free} \tag{3}$$

New number of infected bacteria = Old number of infected bacteria + Increase due to cell division + Increase due to phages opting for lysogeny

$$N_{p,free,new} = N_{p,free,old} + a * \Delta t * [1 - P(lyso)] * N_{p,free,old} - P(lyso) * N_{p,free} \tag{4}$$

New number of free phages = Old number of free phages + Increase due to amplification following lysis - Decrease due to phages opting for lysogeny

2.1.3 Case 2 - Good p_1, Bad p_2

$$N_{b,h,new} = N_{b,h,old} + r * \Delta t * N_{b,h,old} - N_{p,free} \tag{5}$$

New number of healthy bacteria = Old number of healthy bacteria + Increase due to cell division - Decrease due to infection by phages

$$N_{b,i,new} = (N_{b,i,old} + P(lyso) * N_{p,free}) * e^{-\lambda_b \Delta t} \tag{6}$$

New number of infected bacteria = Exponential decrease of (Old number of infected bacteria + Increase due to phages opting for lysogeny)

$$N_{p,free,new} = N_{p,free,old} + a * \Delta t * [1 - P(lyso)] * N_{p,free,old} - P(lyso) * N_{p,free} \tag{7}$$

New number of free phages = Old number of free phages + Increase due to amplification following lysis - Decrease due to phages opting for lysogeny

2.1.4 Case 3 - Bad p_1, Good p_2

$$N_{b,h,new} = N_{b,h,old} + r * \Delta t * N_{b,h,old} - N_{p,free} \tag{8}$$

New number of healthy bacteria = Old number of healthy bacteria + Increase due to cell division - Decrease due to infection by phages

$$N_{b,i,new} = N_{b,i,old} + r * \Delta t * N_{b,i,old} + P(lyso) * N_{p,free} \tag{9}$$

New number of infected bacteria = Old number of infected bacteria + Increase due to cell division + Increase due to phages opting for lysogeny

$$N_{p,free,new} = (N_{p,free,old} + a * \Delta t * [1 - P(lyso)] * N_{p,free,old} - P(lyso) * N_{p,free}) * e^{-\lambda_p \Delta t} \tag{10}$$

New number of free phages = Exponential decrease of (Old number of free phages + Increase due to amplification following lysis - Decrease due to phages opting for lysogeny)

2.1.5 Case 4 - Bad p_1, Bad p_2

$$N_{b,h,new} = N_{b,h,old} + r * \Delta t * N_{b,h,old} - N_{p,free} \tag{11}$$

New number of healthy bacteria = Old number of healthy bacteria + Increase due to cell division - Decrease due to infection by phages

$$N_{b,i,new} = (N_{b,i,old} + r * \Delta t * N_{b,i,old} + P(lyso) * N_{p,free}) * e^{-\lambda_b \Delta t} \tag{12}$$

New number of infected bacteria = Exponential decrease of (Old number of infected bacteria + Increase due to cell division + Increase due to phages opting for lysogeny)

$$N_{p,free,new} = (N_{p,free,old} + a * \Delta t * [1 - P(lyso)] * N_{p,free,old} - P(lyso) * N_{p,free}) * e^{-\lambda_p \Delta t} \tag{13}$$

New number of free phages = Exponential decrease of (Old number of free phages + Increase due to amplification following lysis - Decrease due to phages opting for lysogeny)

2.2 Implementation

Our first effort in this direction was to understand the effect of the lysogenic propensity on the coexistence of the phage-bacteria population. The first approach was to observe the result of running Gillespie simulations of the above equations for fixed curves of Probability of Lysogeny P(lyso) versus Multiplicity of Infection MoI and individual values of p1 and p2. The code for this iteration is available on Github in Run1. This approach validated our qualitative belief that for the chosen values, the time for which the phage and the bacteria coexist increases with higher lysogenic propensity but nothing more.

Our second approach to this problem was slightly off the trodden path. The task at hand is to find the optimal values of $P(lyso)$ for each value of MoI, p_1 and p_2. Computationally speaking, we need to find a curve in the 2-D space that would maximize coexistence. The problem with the Gillespie simulations of the previous approach is that it would be difficult to maximize the coexistence without involving infinite populations of both the species. Thus, instead of looking at results of entire simulations, we consider the outcomes of a single time step.

The reason for the extinction of phages is often one of the two - they do not multiply enough to keep up with the stresses in the environment, or they multiply too often, lysing up the bacterial hosts faster than the bacteria may be reproduced - leading to the extinction of the bacteria and thus the extinction of the phages. An optimal strategy in this case might be to try to keep up with the bacterial growth rate, in other words, the phage could choose between lysis and lysogeny in such a manner that the resulting MoI is closest to unity.

For each of the values of p_1, and p_2, we create a random environment conforming to these values. Next, for each of the values of MoI, we execute the above equations multiple times - 1000 or 2000 depending on the need - and find the average resultant MOI and select the $P(lyso)$ which leads to a resultant closest to one. Thus, we can construct a curve that would lead to a high probability of coexistence in the $P(lyso)$ - MoI space for each value of p_1 and p_2. The code for this iteration is available on Github in Run2.

3 Results

We perform these simulations for four sets of values of (λ_p, λ_b) - (1.0, 0.1), (2.0, 0.1), (2.0, 1.0), and (3.0, 1.0). Our findings have been enumerated below for greater clarity:

1. On increasing the value of λ_p, the value of $P(lyso)$ decreases for bad phage environments, while it remains constant for good phage environments - irrespective of the bacterial environment, as shown in Figure 1.

2. On increasing the value of λ_b, the value of $P(lyso)$ decreases *slightly* for bad bacterial environments, while it remains constant for good bacterial environments - irrespective of the phage environment, as shown in Figure 2.

3. For a given value of λ_p and λ_b, the value of $P(lyso)$ increases *significantly* for increasing values of p_1, but decreases *slightly* for increasing values of p_2, as shown in Figure 3. The first trend - concerning the phage environmental stress - is pretty obvious. The second trend merits a slightly detailed explanation - the phage appears to be more likely to commit itself to lysogeny in case of bad bacterial environments. This is primarily because of the way in which the equations have been framed - a bad environment would lead to a lower number of bacteria in the system; and in order to achieve an MoI of 1, the phages would go for a higher value of $P(lyso)$.

References

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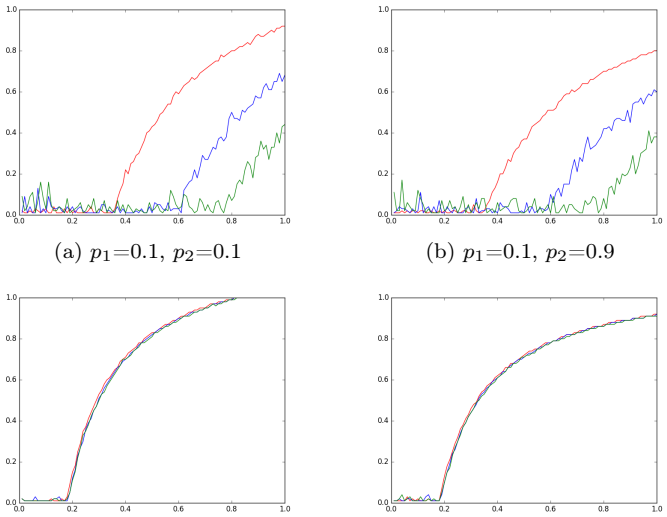
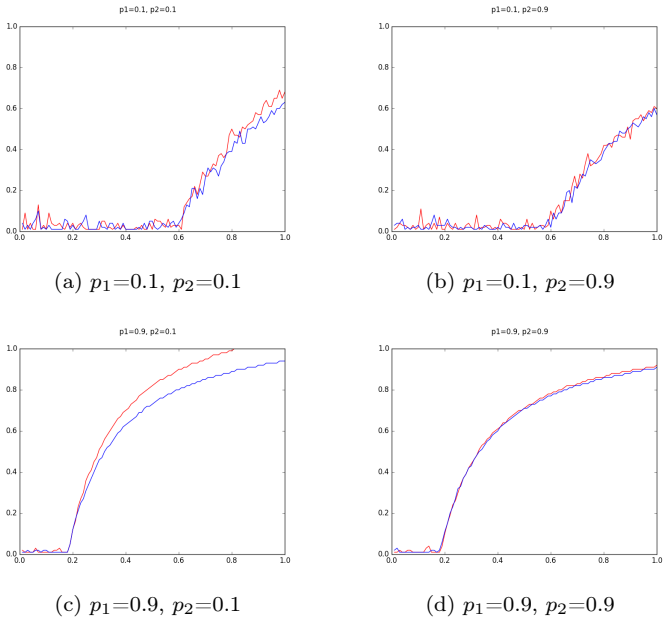


(a) p_1=0.1, p_2=0.1 (b) p_1=0.1, p_2=0.9

(c) p_1=0.9, p_2=0.1 (d) p_1=0.9, p_2=0.9

Figure 1: Tabulation of plots that compare the effect of changing the value of λ_p for different environments (Red - λ_p=1, Blue - λ_p=2, Green - λ_p=3; λ_b=0.1). The first row refers to a bad phage environment whereas the second row refers to a good phage environment. The left column refers to a bad bacterial environment whereas the right refers to a good bacterial environment. As can be expected, for good phage environments, changing the value of λ_p barely affects the graph.



(a) p_1=0.1, p_2=0.1 (b) p_1=0.1, p_2=0.9

(c) p_1=0.9, p_2=0.1 (d) p_1=0.9, p_2=0.9

Figure 2: Tabulation of plots that compare the effect of changing the value of λ_b for different environments (Red - λ_b=0.1, Blue - λ_b=1.0; λ_p=2). The first row refers to a bad phage environment whereas the second row refers to a good phage environment. The left column refers to a bad bacterial environment whereas the right refers to a good bacterial environment. As can be expected, for good bacterial environments, changing the value of λ_b barely affects the graph. However, the point to be noted here is that even for bad bacterial environments, the value of $P(lyso)$ does not change significantly.

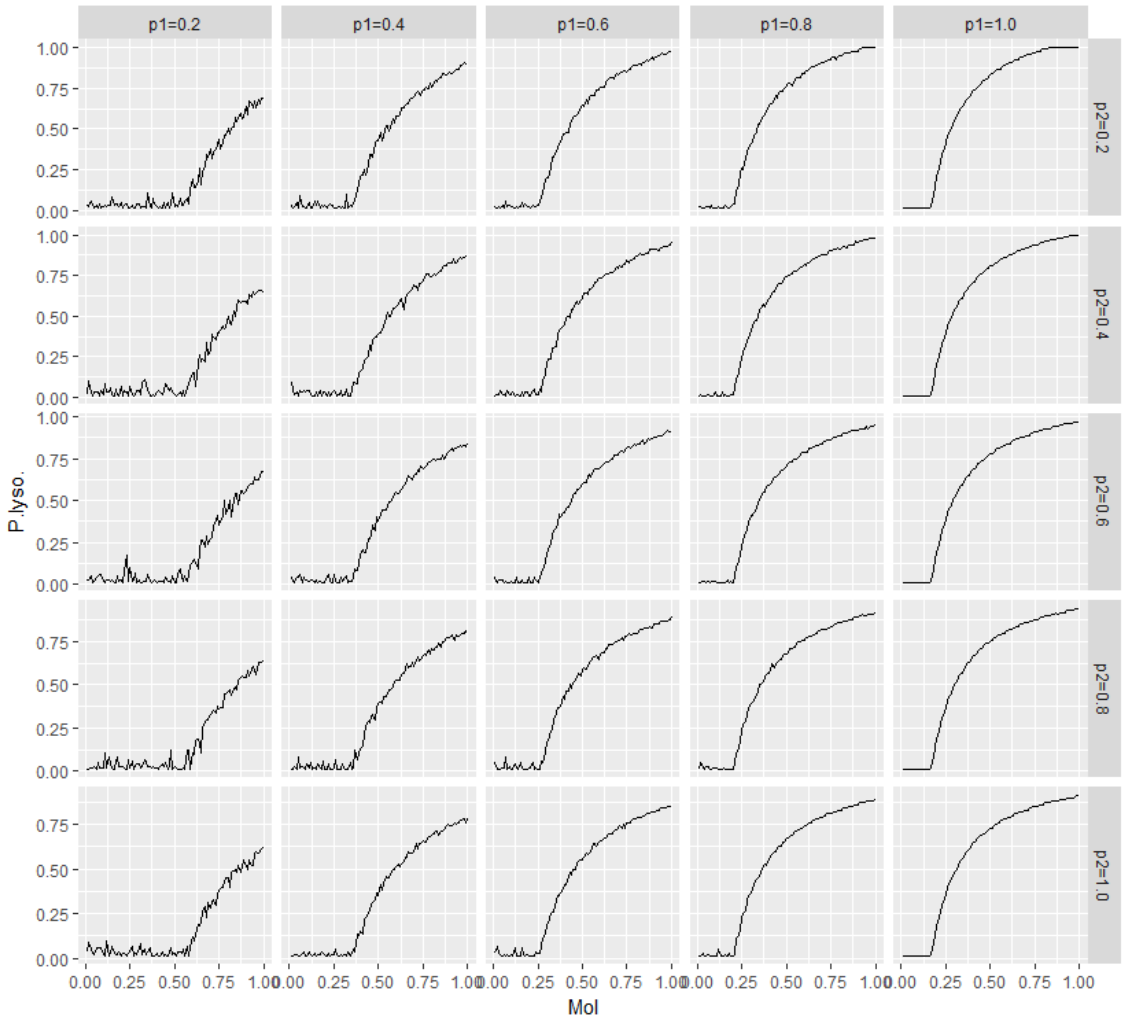


Figure 3: A lattice plot - used specifically for representing multivariate data - has been generated to investigate the relation between p_1, p_2, $P(lyso)$, and MoI for λ_p=3 and λ_b=0.1; The important trends here are as follows: the value of $P(lyso)$ increases *significantly* for increasing values of p_1 and decreases *slightly* for increasing values of p_2.