University of Copenhagen

Bachelor of Science Physics

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Stochastic modeling of lysis inhibition in T-even phage environments

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Abstract

We provide necessary theoretical preliminaries for the stochastic modeling of T-even phage environments and present a model with dynamic phage and bacteria count, using parameters obtained from Cortada and Mitarai [3]. Only the lytic cycle of phages is considered, but we allow for two different lysis outcomes to occur: Lysis from within (LI) and lysis from without (LO). Lysis inhibition is a central focus of this project and we study its impact on lysis outcomes and progression of the system as a whole.

First passage time distributions are depicted for a single-cell-system and it is shown that our model accurately predicts an Erlang distribution for LO-times in high phage concentration environments ($10^9 \frac{1}{\text{ml}}$). We further determine the phage concentrations that are necessary for lysis from without to occur with our choice of model parameters. For the single-cell-system we provide a quasi-analytical method for figuring this out which gives us $P_c \approx 1.3 \cdot 10^8 \frac{1}{\text{ml}}$. For the multi-cell-system this value is determined numerically and is estimated to be around $P_c \approx 1.5 \cdot 10^8 \frac{1}{\text{ml}}$. Furthermore we vary the rate of the lytic cycle r_{LI}, and find that our model's lysis outcomes are pretty robust to variations in this value, unless r_{LI} is really small ($r_{LI} \sim 10^{-1} \frac{1}{\text{min}}$). Lastly, we identify that it is possible for the system to enter a self-organizing steady state and derive the relation $P \geq \frac{1}{\eta \tau_d}$, which unexpectedly did not hold up in our simulations.

Contents

1 Introduction

Perhaps the longest ongoing rivalry between any two organisms on earth is that of the bacteria and the phages. With both sides having incredibly large numbers and rapidly evolving weapons, their mutual interactions become far too complex to handle deterministically. Therefore it is common to use tools from probability and stochastic theory, when creating models of bacteria-phage environments. We will in this project study if there are any insights to gain from applying a stochastic approach to model the lysis-inhibitory effects caused by T-even-phages on bacteria.

2 Preliminary Theory

2.1 Bacteriophages and Lysis mechanisms

Bacteriophages are viruses that infect and reproduce inside Bacteria. They are among the most common organisms on earth and can be found in nearly every environment where bacteria exist [2]. Phages are as diverse as they are abundant, but in this paper we narrow our focus to T-even phages.

The biological structure of a T-even phage can generally be describes as a long rod with fiber-legs at the bottom, that are used to latch onto bacteria, and a polygonal head at the top, where its genetic information is stored [2]. Phages mostly (but not exclusively) reproduce either through lytic or lysogenic replication [1]. We shall in this paper only focus on the former. The lytic replication cycle is initiated when a phage inserts its genetic material into a bacterium. In doing so, it hijacks the bacterium's regular protein production and forces it to produce and assemble its phage offspring. Then, through an active production of membrane-degrading proteins, the bacterium lyses and releases the newly produced phage progeny into the environment, as the cycle continues [4]. When a bacterium dies in this way, it is known as lysis from within (LI).

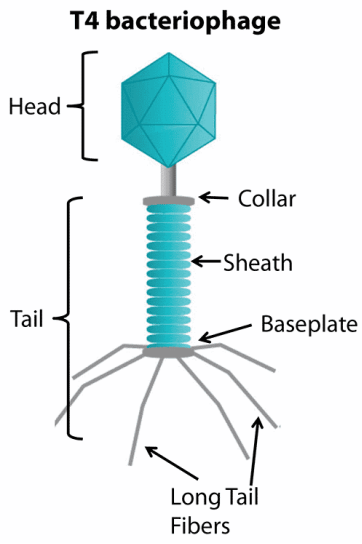

Figure 1: Structure of the T4 bacteriophage: The most well-known of the T-even phages. Source: [2]

T-even phages have been known to actively delay the lysis of bacteria by several minutes, when other phages attempt to infect its already hijacked host. A phage infection after the initial infection is called a superinfection and the lysis delay phenomenon it causes is known as lysis inhibition. One of the interesting consequences of lysis inhibition is the fact that it allows for several superinfections to occur, before the host lyses. It is known that when bacteria are exposed to environments with high phage concentrations, they lyse in a fashion that is distinct from the previous way of lysing. This is known as lysis from without (LO) and is a consequence of the bacteria's membrane not being able to withstand a large amount of infections in a short amount of time. Therefore lysis inhibition may act as a catalyst for lysis from without, allowing it to occur even when phage concentrations are moderate. We explore this phenomenon in further detail in our results.

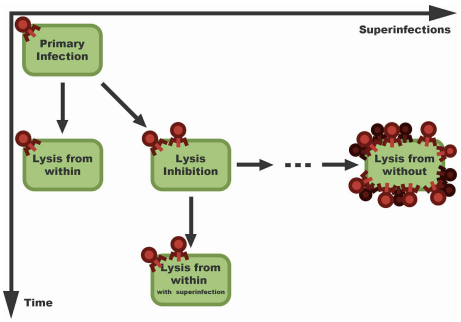

Figure 2: The two lysing outcomes depicted. The primary axis counts the number of superinfections while time passes on the secondary axis. Created by Y. Schürmann in Adobe Photoshop. Inspired by graphic from [3].

2.2 A brief introduction to Markov processes and the master equation

The analysis presented in this paper relies heavily on fundamentals of stochastic processes and thus a brief introduction into the subject is in order. We present a semi-formal definition of Stochastic processes and derive the master equation, as it pertains to our applications. The derivation showcased here is obtained from [5].

A stochastic process is a collection of stochastic variables $\mathbf{X}(\mathbf{t}) = \{x_{t_1}, x_{t_2}, x_{t_3}, ...\}$ given at the times $\mathbf{t} = \{t_1, t_2, t_3, ...\}$. The distribution of a stochastic variable at a certain time is given by a joint probability distribution $p(x,t)$. A common type of stochastic process is the Markov process, where the distribution of the current variable depends only on the previous variable.

$$p(x_n, t_n | x_{n-1}, t_{n-1}; x_{n-2}, t_{n-2}; ...; x_1, t_1) = p(x_n, t_n | x_{n-1}, t_{n-1}) \tag{1}$$

The most well-known property of Markov processes, is that they obey the Chapman-Kolmogorov-equation, which we shall now derive. Consider three points in a Markov chain, then we may connect the distribution of its paths in the following way:

$$p(x_3, t_3; x_2, t_2; x_1, t_1) = p(x_3, t_3 | x_2, t_2; x_1, t_1) p(x_2, t_2; x_1, t_1)$$

$$p(x_3, t_3; x_2, t_2; x_1, t_1) = p(x_3, t_3 | x_2, t_2; x_1, t_1) p(x_2, t_2 | x_1, t_1) p(x_1, t_1)$$

Invoking the defining characteristic of Markov processes (eq. (1)) yields:

$$p(x_3, t_3; x_2, t_2; x_1, t_1) = p(x_3, t_3 | x_2, t_2) p(x_2, t_2 | x_1, t_1) p(x_1, t_1)$$

Dividing through by $p(x_1, t_1)$ and applying Bayes' law gives us the Chapman-Kolmogorov-equation, which will be useful for deriving the master equation:

$$p(x_3, t_3; x_2, t_2|x_1, t_1) = p(x_3, t_3|x_2, t_2)p(x_2, t_2|x_1, t_1)$$

$$p(x_3, t_3|x_1, t_1) = \int p(x_3, t_3|x_2, t_2)p(x_2, t_2|x_1, t_1, t_1)dx_2 \tag{2}$$

A common property of stochastic processes is that the trajectories they produce are generally non-differentiable and can be both continuous or discontinuous. While this may seem like a roadblock for further analytical endeavors, we simply utilize the fact that their probability distributions are often both continuous and differentiable. A question that is of particular interest to us is how these distributions evolve with time, and that is what the master equation aims to address. Consider the expression:

$$\frac{\partial p(x, t|x_0, t_0)}{\partial t} = \lim_{\Delta t \to 0} \left[\frac{p(x, t + \Delta t|x_0, t_0) - p(x, t|x_0, t_0)}{\Delta t} \right]$$

We now apply the CK-equation to the first term on the RHS, i.e we substitute:

$$p(x, t + \Delta t|x_0, t_0) = \int p(x, t + \Delta t|x', t)p(x', t|x_0, t_0)dx'$$

which yields:

$$\int \frac{p(x, t + \Delta t|x', t)}{\Delta t} p(x', t|x_0, t_0)dx' - \frac{p(x, t|x_0, t_0)}{\Delta t}$$

Multiplying the last term by $1 = \int p(x', t + \Delta t|x_0, t_0)dx'$ gives us:

$$\int \left[\frac{p(x, t + \Delta t|x', t)}{\Delta t} p(x', t|x_0, t_0) - \frac{p(x', t + \Delta t|x_0, t_0)}{\Delta t} p(x, t|x_0, t_0) \right] dx'$$

Now we define the transition rates as $\omega(x|x', t) \equiv \frac{p(x, t+\Delta t|x', t)}{\Delta t}$, so that we can write:

$$\frac{\partial p(x, t|x_0, t_0)}{\partial t} = \int [\omega(x|x', t)p(x', t|x_0, t_0) - \omega(x'|x, t)p(x, t|x_0, t_0)]dx'$$

Marginalizing out the initial conditions gives us the master equation:

$$\frac{\partial p(x, t)}{\partial t} = \int [\omega(x|x', t)p(x', t) - \omega(x'|x, t)p(x, t)]dx' \tag{3}$$

The interpretation of the master equation is pretty straightforward and intuitive: The probability of being at x at time t changes by the rate of jumping from x' to x multiplied by the probability of being at x' minus the rate of jumping from x to x' multiplied by the probability of being at x. Essentially it represents the probability of entering the state minus the probability of leaving it. The expression is further integrated along dx' to account for all possible states. In the discrete limit, the master equation can be written as:

$$\frac{\partial}{\partial t} p_i(t) = \sum_{\substack{j \neq i \\ j=1}}^{N} [\omega_{ij}(t)p_j(t) - \omega_{ji}(t)p_i(t)] \tag{4}$$

Where the transition $i \to j$ occurs with rate $\omega_{ji}(t)$.

2.3 The Gillespie algorithm

Due to the probabilistic nature of stochastic processes, we often have to simulate many trajectories if we want to make any useful observations on the underlying process. To do this efficiently, we want to minimize the amount of computational power needed for our simulations. In this section we introduce the Gillespie algorithm, which achieves this goal and forms the basis of our model algorithm. Once again, the derivation is obtained from [5]. We begin by considering the discrete master equation:

$$\frac{\partial}{\partial t}p_i(t) = \sum_{j\neq i}\left[\omega_{ij}p_j(t) - \omega_{ji}p_i(t)\right]$$

Let T be the time of the next transition and assume that at time $\tau = 0$ we know that the system is in state i. We are interested in determining the probability of the system staying in state i as time increases. This motivates us to define the survival probability of state i:

$$S_i(\tau) = P(\tau < T)$$

The survival probability is essentially the probability that no transition out of i has occurred until τ. Now let $p_i(t) = S_i(\tau)$, and the master equation becomes:

$$\frac{\partial}{\partial \tau}S_i(\tau) = \sum_{j\neq i}\left[\omega_{ij}S_j(\tau) - \omega_{ji}S_i(\tau)\right]$$

But obviously no transition out of state i occurs as long as $\tau < T$, which means we can set $\omega_{ij} = 0$ for all states j. This yields a simple PDE, that can be solved easily:

$$\frac{\partial}{\partial \tau}S_i(\tau) = -\sum_{j\neq i}\omega_{ji}S_i(\tau) = -\Omega_i S_i(\tau)$$

$$S_i(\tau) = e^{-\Omega_i \tau} \tag{5}$$

Note that the probability of a transition occuring in the interval $[\tau, \tau + d\tau]$ is the negative derivative of the survival probability.

$$-\frac{d}{d\tau}S_i(\tau)d\tau = \Omega_i e^{-\Omega_i\tau}d\tau \tag{6}$$

We are interested in determining a distribution for the different transition times, which are all stochastically determined. To achieve this, we make use of a uniformly distributed random variable $\xi_1 \in [0, 1]$. Using this we can formulate an expression for $\tau(\xi_1)$:

$$1 = \int_0^\infty \Omega_i e^{-\Omega_i\tau}d\tau = \int_0^1 \Omega_i e^{-\Omega_i\tau}\left|\frac{d\tau}{d\xi_1}\right|d\xi_1$$

The integrand in the last equality corresponds to the uniform distribution of ξ_1 (Since it is normalized to 1 on the interval of ξ_1). From this we can conclude:

$$\Omega_i e^{-\Omega_i\tau}\frac{d\tau}{d\xi_1} = 1$$

$$\frac{d\xi_1}{d\tau} = \Omega_i e^{-\Omega_i\tau}$$

$$\xi_1(\tau) = \int_0^\tau \Omega_i e^{\Omega_i\tau'}d\tau' = 1 - e^{-\Omega_i\tau}$$

$$\tau(\xi_1) = -\frac{1}{\Omega_i}\ln(1-\xi_1)$$

$$\tau(\xi_1) = -\frac{1}{\Omega_i}\ln(\xi_1) \tag{7}$$

The last equality follows from the fact that ξ_1 ranges from 0 to 1, and therefore the two expressions are equivalent. We are now ready to piece together the Gillespie Algorithm:

Gillespie Algorithm

- Draw two Random numbers $\xi_1, \xi_2 \in [0, 1]$
- Calculate the time till next transition $\tau(\xi_1) = -\frac{1}{\Omega_i}\ln(\xi_1)$
- Determine the minimal j'th index that satisfies

$$\sum_{k=1}^{j} \omega_{ki} \geq \xi_2 \Omega_i$$

- Update $i \to j$; Propagate time forward $t \to t + \tau(\xi_1)$.
- Repeat

Not only is the Gillespie much faster than regular time discretization techniques, due to the fact that it skips timesteps where no events occur, but it also produces exact trajectories, rather than approximations.

3 Model

3.1 System description

We consider a uniformly distributed bacteria-phage culture enclosed in a volume V. The number of bacteria is given by an integer N, while the concentration of free phages is denoted by P. These are dynamical parameters that change as the system progresses, either through free phages infecting hosts or through the lysis of bacteria.

There are two ways in which a bacterium may lyse: From within or from without. Therefore each bacterium i is assigned two different parameters k_i and m_i. The first parameter tracks the number of phages on the bacterium's membrane. If k_i reaches a threshold value of T_{LO}, then the bacterium will lyse from without and release β new phages into the system. On the other hand m_i tracks the bacterium's internal molecular progress towards lysis from within, and will only increase in value if the bacterium has been infected by at least one phage (i.e. $k_i \geq 1$). If m_i reaches the thresshold T_{LI} the bacterium shall lyse from within and also release β phages into the environment. Note that the two outcomes are mutually exclusive and when either threshold is reached, both processes are terminated.

Lastly we consider the addition of lysis inhibition to our model. We simply add the condition that for every superinfection we decrease the bacteriums progress towards lysis from within by Δ. In other words, for a given i, if k_i increases by 1, then m_i is decreased by Δ.

3.2 The master equation

Through the description of the system in the previous section, we arrive at the following master equation:

$$\begin{aligned}\frac{d}{dt}p(k_i,m_i,t) =& r_{LO}p(k_i-1,m_i,t) - r_{LO}p(k_i+1,m_i,t) + r_{LI}p(k_i,m_i-1,t) - r_{LI}p(k_i,m_i+1,t)\\ &- r_{LO}p(k_i,m_i,t) + r_{LO}p(k_i,m_i+\Delta,t)\end{aligned} \tag{8}$$

Note that both lysis processes have absorbing upper boundaries and that lysis from within also has a reflecting lower boundary, due to inhibition (And the fact that we do not allow for negative molecules in the bacteria). This allows us to impose the following boundary conditions on the equation:

$$\frac{d}{dt}p(0,m_i,t) = -r_{LO}p(0,m_i,t)$$

$$\frac{d}{dt}p(k_i \geq 1,0,t) = -r_{LI}p(k_i,0,t) + r_{LO}p(k_i,m_i \leq \Delta,t) + r_{LO}p(k_i-1,0,t) - r_{LO}p(k_i,0,t)$$

$$\frac{d}{dt}p(T_{LO},m_i,t) = r_{LO}p(T_{LO}-1,m_i,t)$$

$$\frac{d}{dt}p(k_i,T_{LI},t) = r_{LI}p(k_i,T_{LI}-1,t)$$

3.3 Parameters

Parameters for the model, with the exception of r_{LI} and r_{LO}, are obtained from [3] and listed in the table below. An analysis on the derivation and validity of these parameters are beyond the scope of this paper, and we defer to the source for this discussion.

Parameter	**Value**	**Description**
V	0.01ml	Volume of culture
T_{LO}	100 phage	Threshold for LO
T_{LI}	250	Threshold for LI
β	100 phage	Phage burst size
η	$2 \cdot 10^{-9} \frac{\text{ml}}{\text{min}}$	Phage adsorption rate
τ_{LI}	27 min	Average time for LI when no superinfections occur
τ_d	5 min	Average time delay per superinfection
r_{LI}	$\frac{250}{27}\frac{1}{\text{min}}$	Rate of phage lytic cycle
Δ	$\frac{1250}{27}\frac{1}{\text{phage}}$	Molecular setback per superinfection

Figure 3: Table of model parameters

We determined r_{LI} by dividing the threshhold value T_{LI} by the average lysis time τ_{LI}. For the LO-process, the average lysis time will depend on the number of phages in the environment, since $r_{LO} = \eta P$. The setback value Δ is obtained through the calculation:

$$\tau_d = \Delta \frac{\tau_{LI}}{T_{LI}} = \frac{\Delta}{r_{LI}} \rightarrow \Delta = \frac{1250}{27} \tag{9}$$

3.4 Simulation algorithm

We simulate our system using the Gillespie as presented in the earlier chapter. The transition rates are $\omega_{LO} = N \cdot r_{LO}$ and $\omega_{LI} = A \cdot r_{LI}$ for LO and LI respectively. N is the number of live bacteria while A is the number of infected or 'activated' bacteria in the culture.

Model Algorithm

- If there are any live bacteria, then:
- Draw two random numbers $\xi_1, \xi_2 \in [0, 1]$.
- Calculate the time till next transition $\tau(\xi_1) = -\frac{1}{\omega_{LO}+\omega_{LI}} \ln(\xi_1)$
- If $\omega_{LO} \geq \xi_2(\omega_{LO} + \omega_{LI})$ is true, then a random bacterium i in the culture is infected by a phage. We thus increase k_i by 1 and decrease the phage concentration P by $\frac{1}{V}$. If this was the first time the Bacteria was infected, we increase A by 1. If this was not the first time that the Bacteria was infected, then m_i is decreased by Δ (down to a minimum value of 0).
    - If $k_i = T_{LO}$, then the bacterium lyses from without. P increases by $\frac{\beta}{V}$ and we reduce the number of active and alive bacteria in the culture, A and N, by 1.
- Otherwise, if $\omega_{LO} \geq \xi_2(\omega_{LO} + \omega_{LI})$ is not true, then a random infected bacterium i will produce a lysing molecule, resulting in m_i increasing by 1.
    - If $m_i \geq T_{LI}$, then the bacterium lyses from within. P increases by $\frac{\beta}{V}$ and we reduce the number of active and alive bacteria in the culture, A and N, by 1.
- Update the rates ω_{LO} and ω_{LI}.
- Propagate time forward $t \rightarrow t + \tau(\xi_1)$.
- Repeat.

3.5 Code Availability

Simulations were programmed in Python and all code used to derive the results in the next chapter is available through Github: https://github.com/Ideadben/Bachelors-Project

4 Results

4.1 Single-cell-system

We first consider a single bacterium exposed to a phage environment. In restricting ourselves to this elementary system, we both test the validity of our algorithm, through some simple predictions and provide insight into the processes that lead to a lysix event.

4.1.1 First passage times

Denote the singular bacterium as b and assign it the variables k_b and m_b. This bacterium will inevitably be infected by a phage and m_b will start to tick up. As every superinfection increases k_b and reduces m_b, the two processes compete with eachother to reach their respective thresholds first. By plotting k_b and m_b against time, we can observe their trajectories. While lysis times are stochastically determined, some times are more likely than others, resulting in a distribution known as a first passage time distribution (Fig. 5).

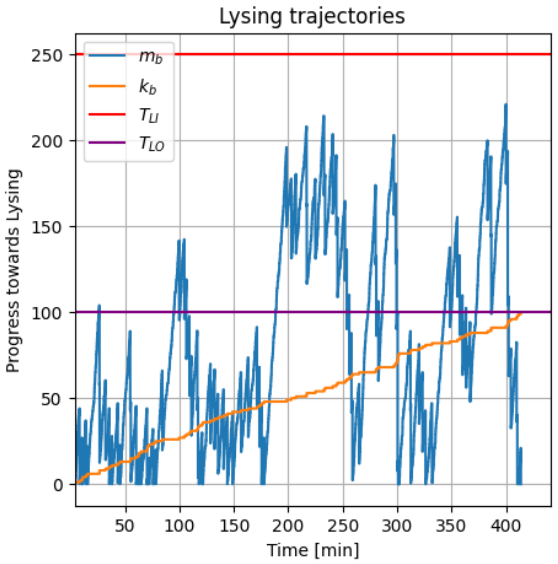

Figure 4: Example trajectories of the two competing lysis processes. In this case the bacterium would lyse from without, since $k_b = T_{LO}$ before $m_b \geq T_{LI}$.

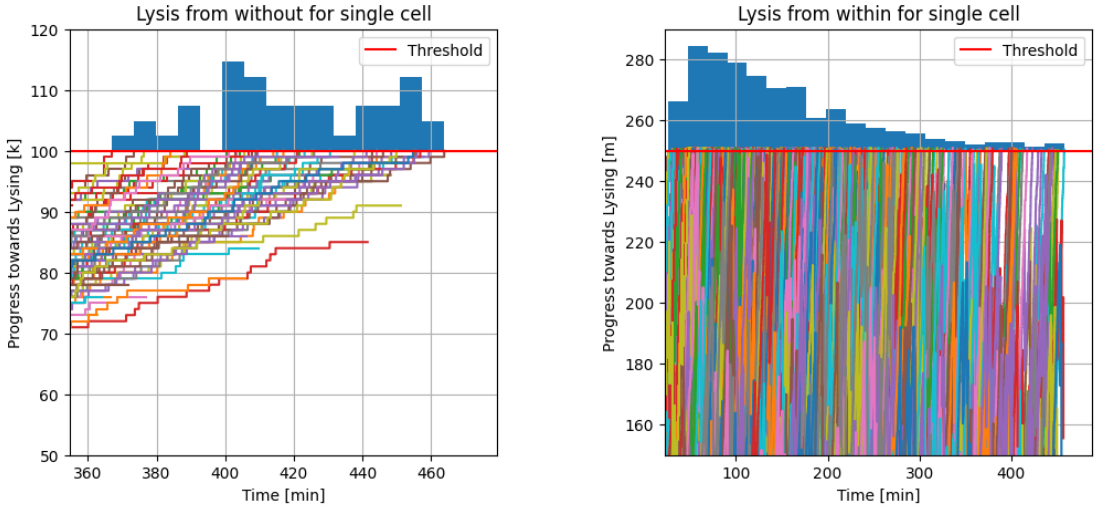

Figure 5: A single bacterium in our system is simulated 10^3 times. On the left hand side the number of phages on the bacterium's membrane (k_b) is depicted against time, while the right hand side plot shows the change in the bacterium's internal molecular progress in producing phage progeny and lysing (m_b). The initial phage concentration was set to $10^8 \frac{1}{\text{ml}}$. Histograms represent the first passage distributions of the lysis times and are normalized for readability. Trajectories that are terminated prematurely do not contribute to the distributions. This particular simulation resulted in 41 LO- and 959 LI-outcomes.

Due to the fact, that we are modelling lysis from without as a simple poisson-process, one should expect an Erlang distribution of the first passage times (See appendix). This is however hampered by the fact that the process terminates, if the bacterium lyses from within first. We can negate this by simply making the phage concentration much higher, so almost no lysis from within occurs (Fig. 6).

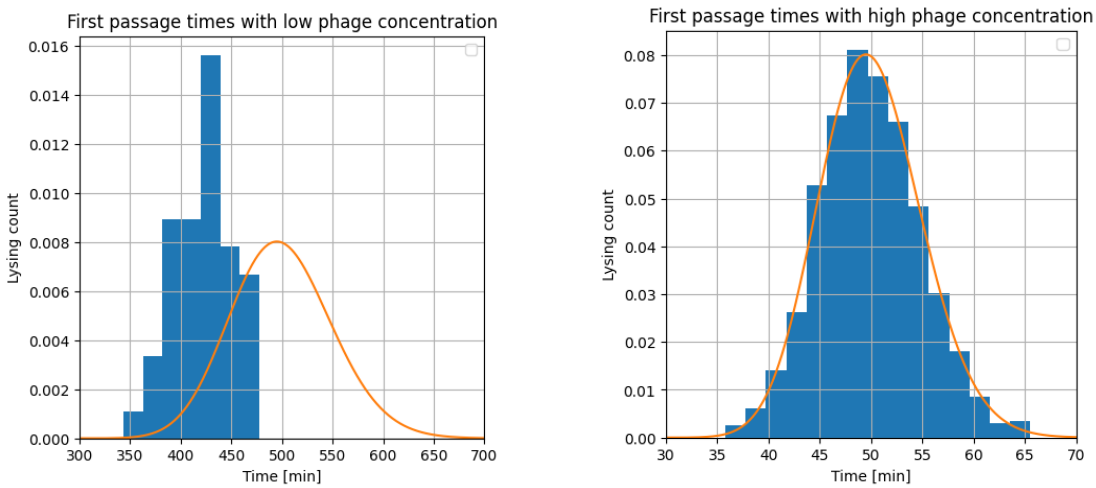

Figure 6: First passage time distributions are compared when the phage concentration is low ($10^8 \frac{1}{\text{ml}}$) and when it is high ($10^9 \frac{1}{\text{ml}}$). Both distributions are overlayed by an erlang distribution plot, which is the solution to first passage time problems involving poisson processes.

4.1.2 Critical phage concentration

We attempt to identify the critical phage concentration P_c, which we define as the concentration at which both lysis outcomes are equally likely. A crucial assumption in the following derivation is that the phage concentration is approximately constant, which is easily feasible in a single-cell-environment, where the concentration of phages is moderately high. Consider the fact, that the average amount the LI-process is inhibited by is:

$$n_{LI-inhibited} = n_{LO} \cdot \Delta$$

Where n_{LO} would be equal to the average amount of superinfections, had it not been for the reflecting lower boundary on the LI-process. Instead it will be smaller than the amount of average superinfections. For now we will ignore n_{LO} and estimate the best value for it later. Continuing with the above relation, we can define the average number of total transitions for the LI-process as n_{LI*}:

$$n_{LI*} = T_{LI} + n_{LI-inhibited}$$

$$n_{LI*} = T_{LI} + n_{LO} \cdot \Delta$$

The average LO time will be:

$$\tau_{LO} = \frac{T_{LO}}{\eta P_c}$$

In contrast, the average LI time, when accounting for inhibition, will be:

$$\tau_{LI*} = \frac{n_{LI*}}{r_{LI*}} \tag{10}$$

In writing down eq. (10), we implicitly make the assumption that LI$*$ is a poisson process with average lysing time of τ_{LI*}, transition rate r_{LI*} and threshhold n_{LI*}. Since we want the average lysing times to be the same for both processes we arrive at the equality:

$$\tau_{LO} = \tau_{LI*} \rightarrow \frac{T_{LO}}{\eta P_c} = \frac{n_{LI*}}{r_{LI*}}$$

$$P_c = \frac{T_{LO}}{\eta}\frac{r_{LI*}}{n_{LI*}} = \frac{1}{\eta}\frac{T_{LO}\cdot r_{LI*}}{T_{LI}+n_{LO}\cdot\Delta} \tag{11}$$

We then varied n_{LO} and provided different values for r_{LI*} across the interval $[0.1\frac{1}{\text{min}}, 20\frac{1}{\text{min}}]$, so that we could calculate the corresponding phage concentration using eq. (11). This phage concentration was then used in 10^3 single-cell-simulations and the resulting lysis outcomes are depicted in fig. 7. The graph suggests that the best value for n_{LO} in this interval for r_{LI} is $n_{LO} = 72$, which is consistent with our expectation that $n_{LO} < T_{LO}$. This value for n_{LO} yielded 0.4920 ± 0.0005 as the ratio of LO outcomes against total lyses.

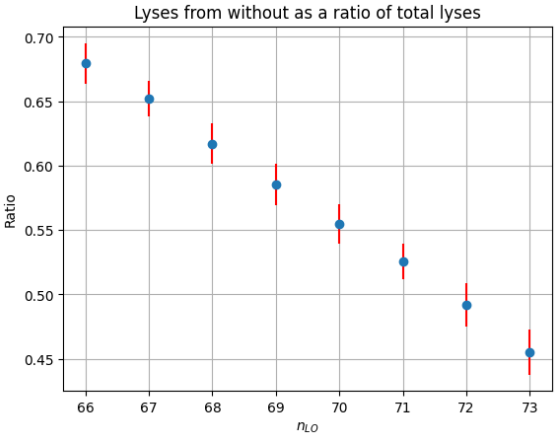

Figure 7: Ratio of lyses from without outcomes as a function of n_{LO}. Each point represents the average ratio calculated for 20 different values of $r_{LI*} \in [0.1, 20]$, with each value used in 10^3 single-cell-simulations. Errorbars show the standard deviation of each average.

We can now simply substitute $r_{LI*} = r_{LI}$ in eq. (11) and determine the critical phage concentration that results in approximately half of the bacteria lysing from without. It is found to be $P_c \approx 1.3 \cdot 10^8 \frac{1}{\text{ml}}$. We ran the model 50×1000 times with this phage concentration and obtained the histogram in fig. 8, which

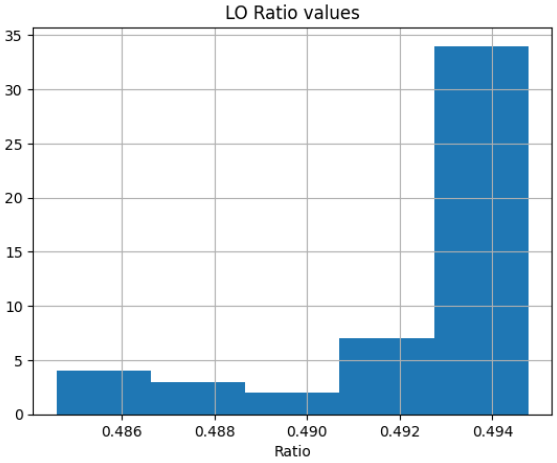

Figure 8: Histogram of ratio of LO outcomes when using the critical phage concentration P_c. 1000 single-cell-simulations are run 50 times and their LO-ratio is depicted on the x-axis.

Eq. (11) can be used to determine the critical phage concentration for a single-cell-system, but one should note the limitations of its use. The value $n_{LO} = 72$ is only approximately true when

$r_{LI} \in [0.1, 20]$. Widening this interval will likely increase the variance of each point in fig. 7. Furthermore choosing a different value for r_{LI}, than the one given in our parameter table 3, will change T_{LI} and Δ, which in turn may change n_{LO}.

This is not the fastest nor most efficient way of determing P_c, but it does give some insight into how the reflecting lower boundary affects the value of n_{LO} and provides further verification of our model. It is also a possiblity to determine n_{LO}, and thereby how much the LI-process is inhibited by on average, for different values of r_{LI} and P if that is of interest.

4.2 Parameter sensitivity

From here on out we take a look at the system as a whole, which means there are now multiple bacteria present and as a result, the phage concentration changes much more drastically as the system progresses. In this section we analyze our model's sensitivity to different parameters.

4.2.1 Critical phage concentration in a multi-cell-system

Just as in the previous section, we want to know what initial phage concentrations are required for lysis from without to occur in the system. To achieve this we vary the concentration and calculate the ratio of lyses from without as a ratio of total lyses.

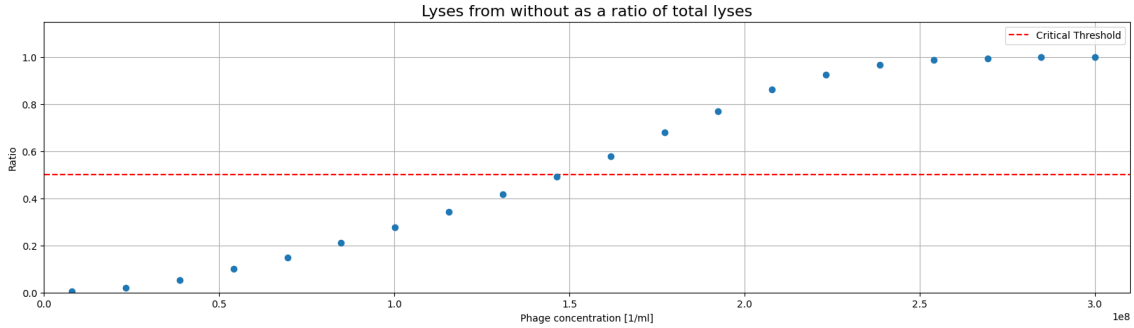

Figure 9: Ratio of lyses from without outcomes as a function of phage concentration in the environment. Each point represents a full simulation run with 10^4 bacteria. The red line marks where the majority of lyses shift from one type to another.

Our results indicate, that for our choice of parameters, the ratio of lyses from without outcomes is particularly sensitive in the range $[0.2 \cdot 10^8 \frac{1}{\text{ml}}, 2.5 \cdot 10^8 \frac{1}{\text{ml}}]$, with the critical concentration P_c located at around $1.5 \cdot 10^8 \frac{1}{\text{ml}}$.

4.2.2 Varying r_{LI}

Different species of phage may have different rates at which they complete their lytic cycle. We therefore find it relevant to vary r_{LI} and observe how sensitive our model is to the value of this parameter. To achieve this, a simple grid search algorithm is employed, where we varied r_{LI}, along with T_{LI} and Δ, such that τ_{LI} and τ_d are preserved.

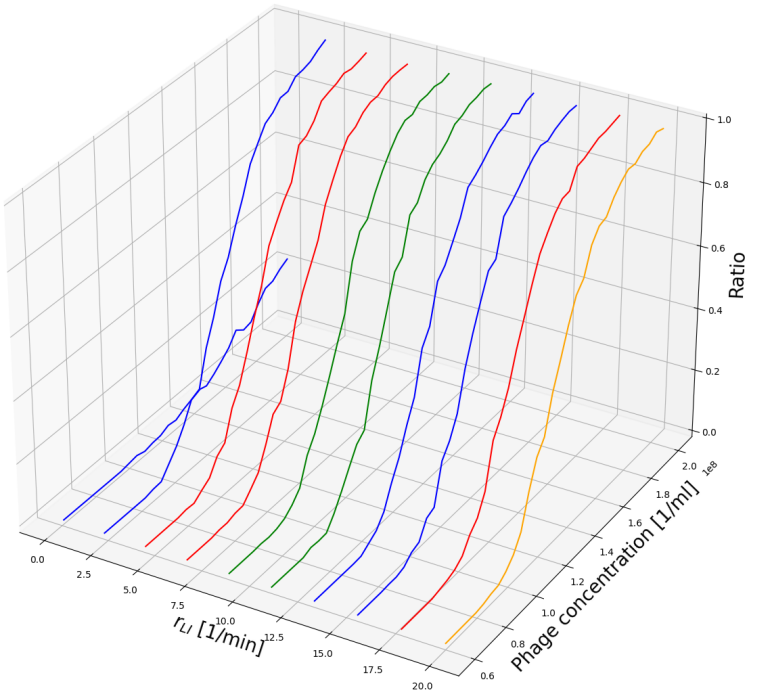

Figure 10: 3D-plot of simultaneously varying r_{LI} with the phage concentration. The ratio of LO outcomes is depicted on the z-axis. The curves are almost identical to the one shown in fig. 9, simply with a different choice of r_{LI} and number of bacteria. Each curve contains 30 points, with every point corresponding to a full simulation ran with 500 bacteria. Note that r_{LI} was varied between 10 evenly space points in the interval $[0.1, 20]$.

With the exception of $r_{LI} \sim 10^{-1}$, our choice of r_{LI} does not seem to impact lysing outcomes significantly. It is interesting however, that a really small value for r_{LI}, impacts LO-outcomes negatively. It would suggest that there is a tipping point somewhere in the lower end of r_{LI}, where the effects of lysis inhibition rapidly decline. This motivates us to explore this area closer.

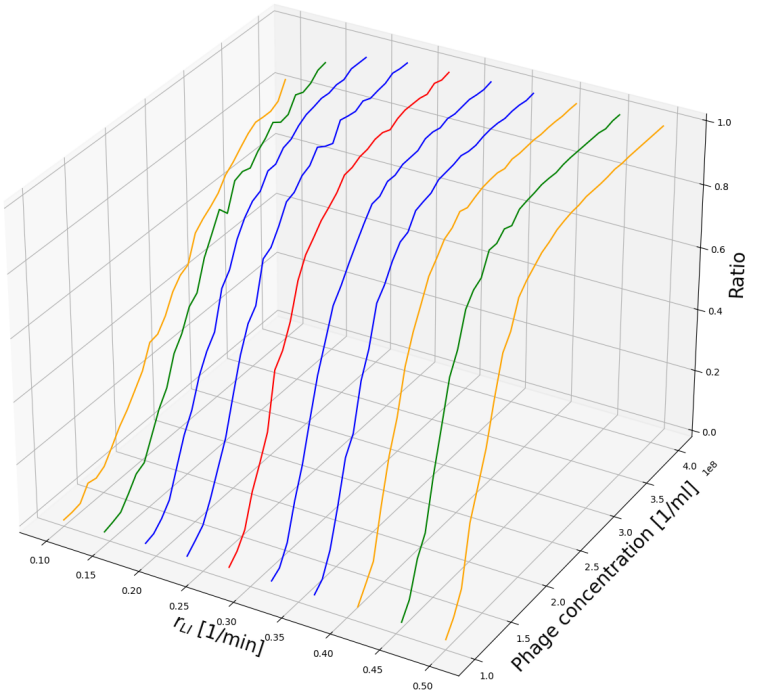

Figure 11: A magnification of the anomolous area in fig. 10. Each curve still contains 30 points, with every point corresponding to a full simulation ran with 500 bacteria.

While the curve shapes still resemble eachother in fig 11, we see that really low values of r_{LI} create environments where LO outcomes are less sensitive to phage concentration variations. In fact for $r_{LI} = 0.01\frac{1}{\text{min}}$, there are still several LI-outcomes with phage concentrations as high as $10^{10}\frac{1}{\text{ml}}$, which tells us that the inhibitory effects of phage superinfections must be greatly weakened for this particularly low lytic rate (fig. 12).

Figure 12: Ratio of lyses from without outcomes as a function of phage concentration in the environment when r_{LI}. Figure is identical to fig. 9 with the exception of r_{LI}-value.

4.3 System dynamics

4.3.1 Progression of the System

There are three distinct ways in which the system usually plays out: (*i*) The phage concentration is so high that all Bacteria lyse from without. (*ii*) The phage concentration is so low that all the bacteria will eventually lyse from within. (*iii*) The system self-organizes into a form of steady state, where lyses occur rarely and the phage concentration remains constant, until enough time has passed, that the system collapses and the remaining bacteria begin lysing from without en masse (fig. 13).

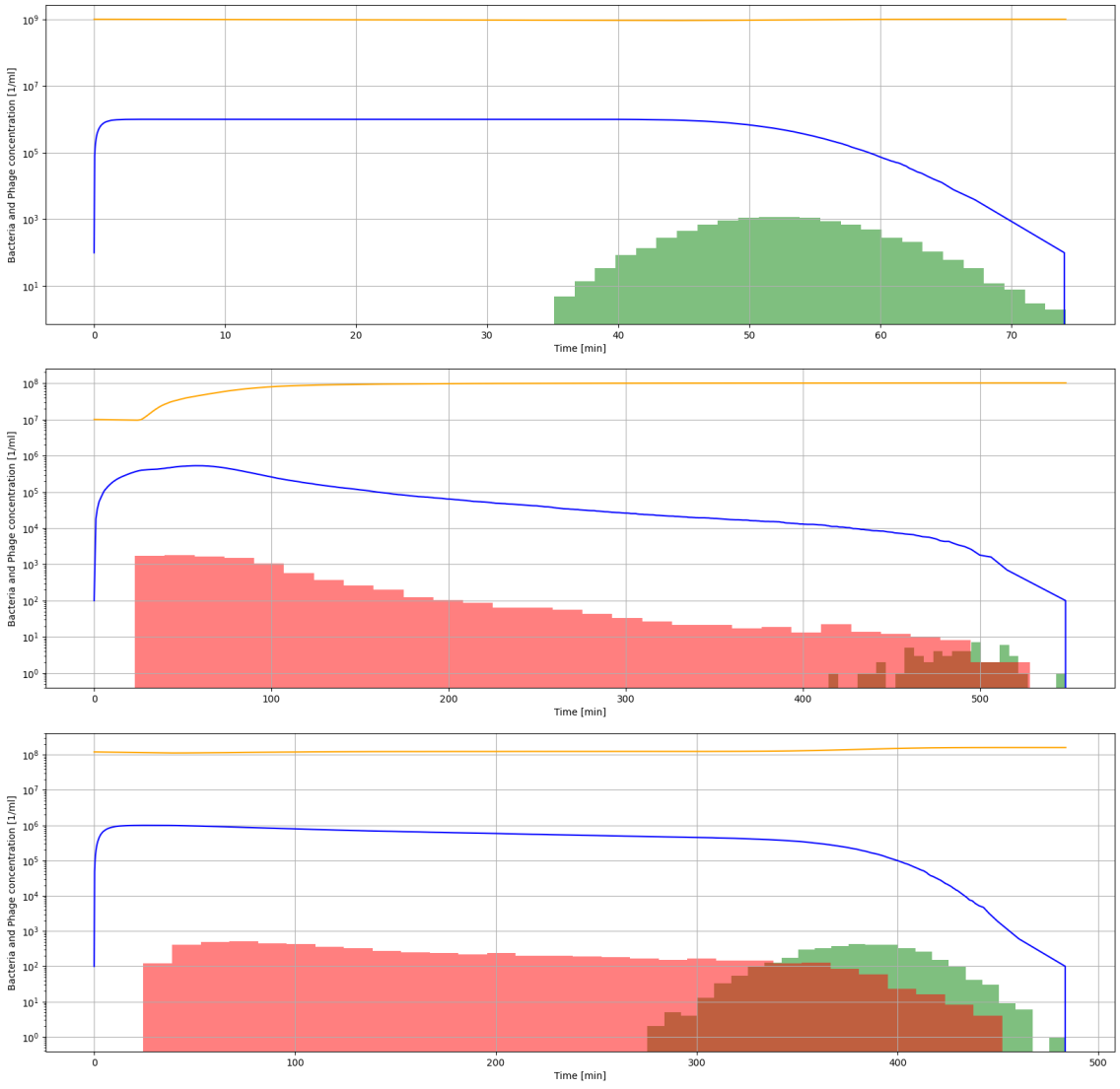

Figure 13: Example variations in initial configurations of the system, that yield three markably different progressions. From top to bottom: (*i*) The majority of bacteria lyse from without due to the high phage concentration. (*ii*) The majority of bacteria lyse from within due to the low phage concentration. (*iii*) The system reaches a steady state and both lysing types are prevalent. Orange: Free phages (/ml), Blue: Infected bacteria (/ml), Red bins: Lysis from within, Green bins: Lysis from without histogram. Note that the histograms are not normalized and display the number of absolute lyses.

4.3.2 Steady state dynamics

The first two cases (i) and (ii) yield straightforward and intuitive results but the third case begs further inquisition. To properly showcase the steady-state, we proceeded in the following way: Instead of letting the simulation run its full course, we terminated it every 100 minutes in simulation-time. This let us check if the system had reached the steady state yet. If it had not, we ran the simulation again, from whence it was terminated. Additionally we prolonged the steady state artificially, by increasing T_{LO}, so that we would not accidentally skip past and miss it.

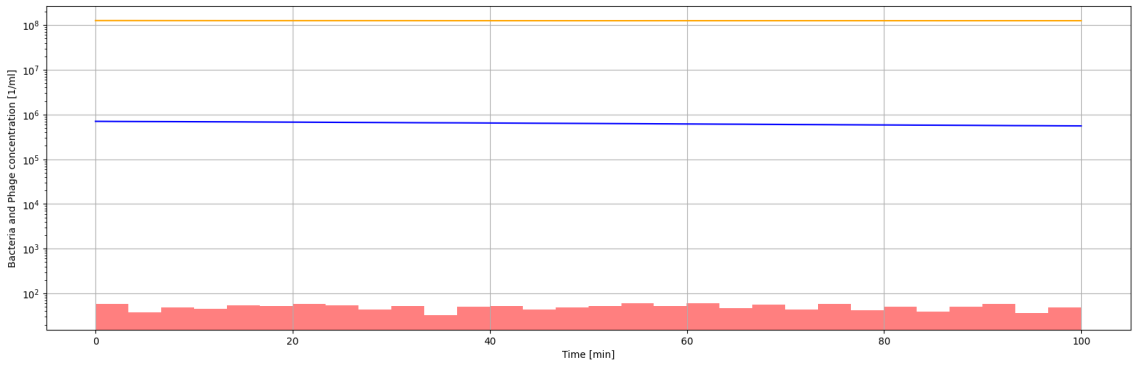

Figure 14: Snapshot of the system amidst its selforganizing process, showcasing the methodology used to identify a steady state. The initial conditions of this system are identical to the ones depicted in Fig. 13 (iii), except for the fact that T_{LO} has been increased significantly.

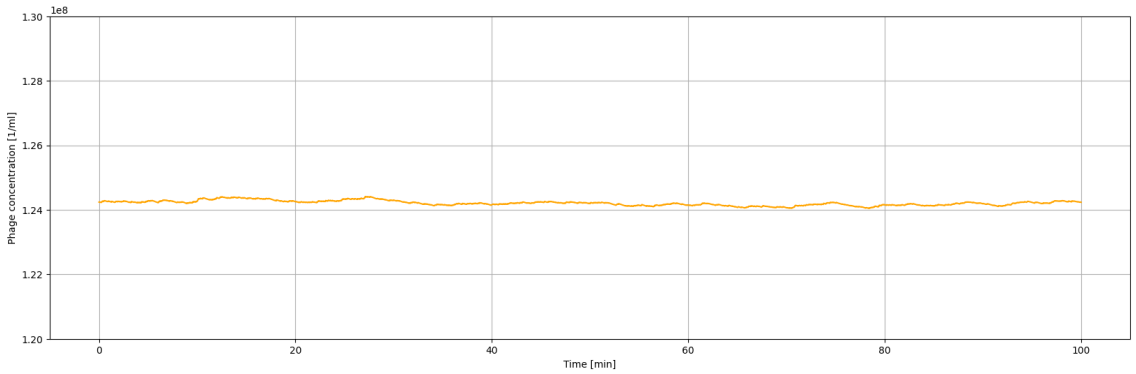

Figure 15: Phage concentration in the steady state.

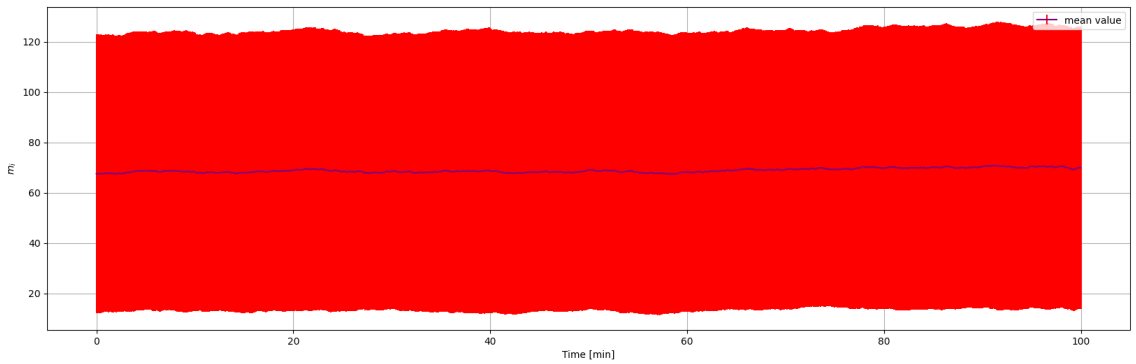

Figure 16: Mean value of m_i of non-lysed bacteria in the steady state. Errorbars show a single standard deviation σ_m.

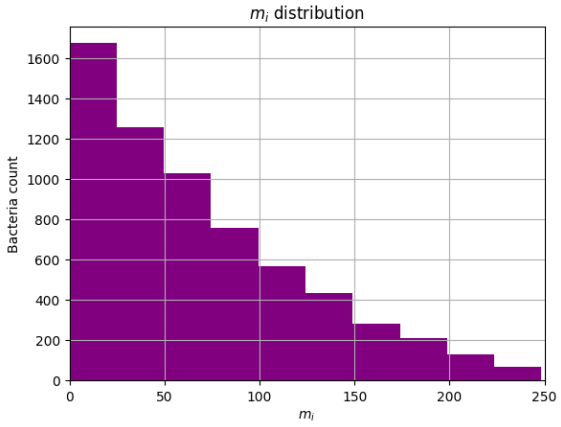

Figure 17: Distribution of m_i-values at the end point of fig. 16

The standard for when the system had reached a steady state was determined qualitatively by observing the phage concentration plot as depicted in fig. 15. If it were constant, we had reached the steady state, and if it were not, we would let the system play out for another 100 minutes.
A very interesting discovery is that the mean of m_i also hovers around a constant value in the steady state. Since the steady state is maintained until LO-collapse happen, we are motivated to assume that the average of m_i is decreasing from when the steady state is entered. Consider then the relation:

$$\begin{aligned} \frac{d\langle m_i \rangle}{dt} &= r_{LI} - \Delta r_{LO} \leq 0 \\ r_{LI} - \Delta\eta P &\leq 0 \\ P &\geq \frac{r_{LI}}{\Delta\eta} \\ P &\geq \frac{1}{\tau_d \eta} \end{aligned} \tag{12}$$

We tested if this relation actually holds, by varying τ_d, which due to eq. (9), is possible in two of the following ways:

1. Varying Δ.
2. Varying r_{LI}, while ensuring $\frac{T_{LI}}{r_{LI}} = \tau_{LI} = 27\text{min}$.

While the first method is straightforward, the latter approach may have unforeseen effects on the steady state, due to the fact that T_{LI} is inversely related to the variance of m_i, σ_m^2. Since the bulk of m_i-values are concentrated at its lower bound, we expect that if the steady state is to be maintained, that σ_m^2 needs to be sufficiently high, so that only a handful of bacteria lyse in a given time interval. We tested this hypothesis by varying the parameters for the same values of τ_d. Once a steady state was reached we extracted the average value of P and plotted the relation (12).

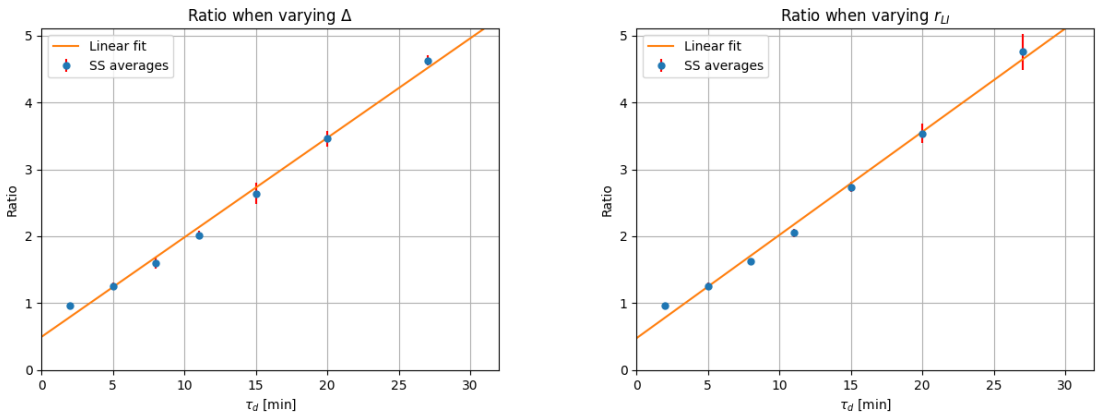

Figure 18: The results of varying the two parameters Δ and r_{LI}. On the y-axis the ratio $P/\frac{1}{\tau_d \eta}$ is measured, while the corresponding τ_d-value is shown on the x-axis. Averages of P were used to collect the y-axis values, and their standard deviations, magnified by a factor 20, are shown at each point. Each plot is overlayed by an individual linear fit.

As seen in fig. 18, contrary to our initial belief, there is little discreprancy in the two variation methods. In hindsight this may be explainable by the fact that, since T_{LI} was changing alongside r_{LI}, which may have resulted in the ratio between T_{LI} and σ_m staying constant.

Furthermore fig. 18 tells us that the relation (12) does not hold, since the ratio of the two values falls below 1 at $\tau_d = 2$. We overlayed the two diagrams with a linear fit to show that the correlation is not linear, and that the steepness does in fact fall off for smaller values of τ_d. It was however not possible for us to measure the ratio for smaller values of τ_d, due to most of the bacteria lysing before a steady state was reached, regardless of initial phage concnetration. A steady state should in principle still be possible, but may require higher bacteria concentrations, than what we were able to simulate with our limited computation power. Memory errors were a common occurrence when exceeding bacteria concentrations of $10^6 \frac{1}{\text{ml}}$, which made us abandon this endeavor.

5 Closing remarks

An important thing to note is that our model had several simplifications attached to it, that one may otherwise find in different models, such as the one presented in [3]. We do not account for phenomena such as resistance to LO, increased burst sizes for longer inhibitions or the spatial diffusion dynamics of newly released phage progeny. Our model is however far from useless and several key insights are to be gained.

The main goal has been to present a stochastic framework, in which we could better understand lysis inhibition and its effects on lysis outcomes. We succeeded in presenting a cohesive model, that initially yielded intuitive and expected results, such as a predictable distribution of first passage times for the LO-process and the overall different progressions of the system. Other times however we were surprised by the outcomes of our simulations: It was unexpected that a lower value for r_{LI} may actually decrease LO-outcomes and yet fig. 10 shows just that. The steady state also proved to be rather unpredictable and violated the relation (18) we had otherwise hoped to confirm. We currently lack a clear explanation for these results.

The Gillespie algorithm proved very useful for our purposes, as most of our initial simulations ran unproblematically. However, it later became clear that this was not sustainable once we reached higher bacteria concentrations, which was necessary to maintain a steady state for low values of τ_d. It may be better in the future to sacrifice the precision that the Gillespie algorithm offers, for the efficiency offered by other stochastic algorithms, such as the tau-leaping method. That way it may be much more manageable to run the larger simulations and we can gain further insight to the steady state that was studied.

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6 Appendix

6.1 Erlang distribution

An intuitive way to derive the Erlang distribution for the first passage times of the poisson process is considering the fact that the probability of leaving a state was given by the negative derivative of the survival probability:

$$P_{0\to 1}(\tau)d\tau = \omega e^{-\omega\tau}d\tau$$

$$P_{0\to 1}(\tau) = \omega e^{-\omega\tau}$$

Now consider the calculation when we want to pass two states:

$$P_{0\to 1\to 2}(\tau) = \int_0^\tau \omega e^{-\omega t}\omega e^{-\omega(\tau-t)}dt$$

$$P_{0\to 1\to 2}(\tau) = \int_0^\tau \omega^2 e^{-\omega t}e^{-\omega(\tau-t)}dt$$

$$P_{0\to 1\to 2}(\tau) = \omega^2 e^{-\omega\tau}\int_0^\tau dt$$

$$P_{0\to 1\to 2}(\tau) = \omega^2 e^{-\omega\tau}\tau$$

Through induction one finds that for a total of k transitions and transition rate ω, is given by the Erlang distribution:

$$P_{0\to\ldots\to k}(\tau, k, \omega) = \frac{\omega^k \tau^{k-1} e^{-\omega\tau}}{(k-1)!}$$

A full proof for first passage times of poisson processes can be found in [6].