Effect of stochasticity in lysis time on fitness of bacteriophage undergoing spatial range expansions

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Except where specific reference is made to the work of others, this work is original and has not been already submitted either wholly or in part to satisfy any degree requirement at this or any other university.

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Abstract

Bacteriophages spreading on bacterial lawns can be used to study spatial range expansions – a ubiquitous process in nature. In this project we explored the effect of stochasticity in lysis time on the fitness of phages undergoing these range expansions. Previous work has modelled different aspects of phage dispersal, but has not yet incorporated stochasticity in lysis time into the models. We used agent-based stochastic simulations adapted from previous work on phage dispersal to simulate range expansions on a one dimensional bacterial lawn. We showed that a larger variance in lysis time increases the fitness of phages, possibly due to the presence of individuals in the population with a lower average lysis time over their history. Our model failed to predict the experimentally observed double ring morphology in bacterial density. This project adds to the general understanding of the various mechanisms that play an important role in spatial range expansions.

Contents

1 Introduction

Bacteriophages (or phages) are viruses that infect bacterial cells. Phages can typically have either lytic or lysogenic life cycles [1], and our focus is on phages with a lytic life cycle. The key steps in the life cycle of a phage undergoing a lytic cycle are the following: infecting the bacterium (host), replicating its genome using the cellular machinery of the host, and breaking open the host cell to release multiple copies of itself (lysis). These processes define the main life-history parameters of the phage: adsorption rate α, i.e. the number of successful viral entries into the host per unit of time; lysis time τ, i.e. the time between adsorption and lysis; and burst size β, i.e. the number of phages released when the cell breaks open. It is common for naturally occurring microbes to live in spatially structured habitats: for example biofilms, or colonies of cyanobacteria in marine environments [2]. Introducing spatial structure of the host population into the system changes the dynamics of phage dispersal significantly. Now in order to reach new susceptible hosts, phages have to diffuse outward from the initial inoculation site. That process is called a spatial range expansion, and it is an example of a process which occurs everywhere in nature: from invasive plant or insect pest expansions to new territories [3]–[5], range expansions of species due to climate change [6], to even human migration out of Africa [7]. This interaction can be studied in the lab using bacterial lawns – two-dimensional bacterial cultures that are macroscopically homogeneous – onto which droplets of phage are inoculated. These droplets give rise to plaques, i.e. visible clearings of dead bacteria on a lawn [8], see Figure 1. Plaque formation is not only restricted to phages, as animal and plant viruses similarly form lesions on cell cultures [9]. Therefore, what we find when studying bacterial plaques can generalise to other types of viruses as well.

The spread of phages on a bacterial lawn can be modelled using reaction-diffusion equations (see Section 2), which admit travelling wave solutions [10]. An interesting feature of these travelling waves is that chance plays a large role in the evolutionary change of the spreading populations [11]: individuals at the very tip of a spreading population have a large advantage in terms of being represented within the founding population in the newly spread-to environment [12]–[14]. In other words, the probability of a phage undergoing a range expansion to have descendants close to the wavefront after some time is much

larger if the current phage is close to the tip of the wave. Stochastic reaction-diffusion systems have been used to study the effect of randomness in selecting which alleles end up in the new population [11]. In this project, we explore how the wave dynamics are modified when stochasticity in lysis time is incorporated into the model, using similar stochastic agent-based simulations (see Section 3) which have previously been used to study range expansions for example in [15]–[17], and which are based on the 'stepping stone' model [18].

A larger plaque size after a fixed amount of time is indicative of a phage which spreads faster. We expect there to exists an *optimal* adsorption rate for plaque growth, because if it was too high, then phages would be spending too much time inside bacteria, hindering diffusion outwards significantly. Also, keeping other parameters equal, we expect a shorter lysis time to give rise to larger plaques [8], [19]. However, it is also known that lysis time and burst size are positively correlated: a longer lysis time results in linearly more new phages produced at lysis[20], [21]. Taking that into account, lysis time will also have an *optimal* value which is dependent on host density, and going below the optimal value would reduce phage fitness [20]–[22] due to the smaller number of offspring produced. By collecting phages from the outer edge of a plaque, using them to inoculate new host colonies, and repeating this process, we can select for faster spreading phages. If we then measure the life history parameters of the evolved phage population, compare them to the initial population, and find a difference in some of the parameters, we could infer that there was selective pressure acting on those parameters. Fusco et al (unpublished results, manuscript in preparation) ran this evolution experiment and found that, while the plaque size went up, the population averages of *none* of the main life history parameters (α, β and τ) had changed significantly, implying that they were already 'optimal' in the original population. We then hypothesise that it is instead the degree of stochasticity (i.e. the variance) in lysis time that was under selective pressure. There are a couple of reasons to expect lysis time stochasticity to play an important role. Firstly, since the optimal lysis time for phages depends on host density and quality [23], [24], it might be good for a phage population to include individuals of varying lysis times, in order to guarantee survival during fluctuations in environmental conditions [25]. Secondly, there is evidence that for λ phage, the mechanism by which the lysis time is controlled is the accumulation of holin proteins up to a threshold within host cell inner membranes, and also that this process allows for stochasticity [24], [26]. On the other hand, Hunter et al's [27] brief exploration of the effect of lysis time stochasticity on the probability of fixation of neutral mutants in well-mixed populations showed no significant change to their systems's behaviour. This was, however, due to the specific turbidostat (phages were constantly provided with new hosts) setup of the experiment. In that case, even average lysis time has no effect on the probability of fixation of neutral mutants. Therefore, because selective pressures depend on the experimental setup, we need to investigate the effect of stochasticity in lysis time explicitly in spatial range expansions, if that's what we are interested in. The results from a turbidostat experiment have no obvious implications on the answers to our problem.

In the evolution experiment described above, another interesting observation was made: the bacterial density within the plaques of faster spreading phages exhibited a double ring morphology, see Figures 2, 3. The current models cannot explain that.

In this project we focus on answering the following questions: 1) Should we theoretically expect stochasticity in lysis time to increase the fitness of bacteriophage? 2) Do we see an increase in fitness in the simulations? 3) What is a plausible mechanism for why (not)? 4) Can this model predict the double ring morphology seen in the evolution experi-

ment?

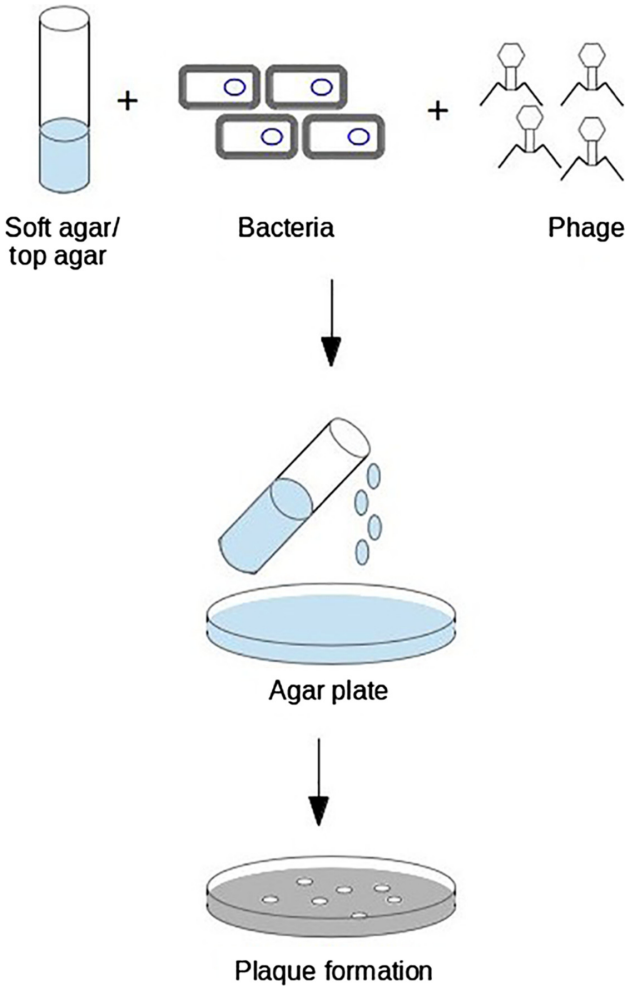

Figure 1: Diagram of plaque formation, from [1].

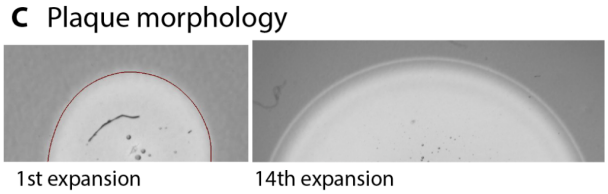

Figure 2: A picture of the double ring structure of bacteria within a plaque.

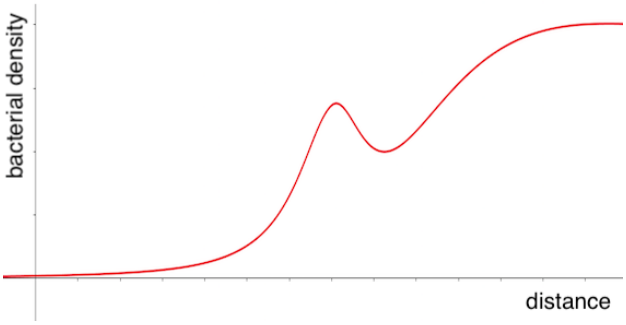

Figure 3: Schematic depiction of bacterial density in the plaque, based on the image from the experiment.

2 Theory

2.1 Spatial range expansions

Consider three populations: the viral population, V, the uninfected bacterial population, B, and the infected bacterial population, I. A model for the interactions between these populations is described by:

$$V + B \xrightarrow{\alpha} I \xrightarrow{\tau} \beta V$$

where α is the adsorption rate of phage into host cells, τ is the lysis time of an infected cell, and β is the burst size. Following [16] and [10], we can write down a set of reaction-diffusion equations which describe plaque growth in 1D for a phage population with a **deterministic** lysis time:

$$\frac{\partial B}{\partial t} = -\alpha V B \tag{1}$$

$$\frac{\partial I}{\partial t} = \alpha V B - \alpha V_{t-\tau} B_{t-\tau} \tag{2}$$

$$\frac{\partial V}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial V}{\partial x}\right) - \alpha V B + \beta \alpha V_{t-\tau} B_{t-\tau} \tag{3}$$

The subscript $t-\tau$ is used to represent that the corresponding value should be evaluated a time τ ago, thereby capturing the time lag

between infection and lysis. For example, in the second equation, the rate of change in the number of infected bacteria is due to uninfected bacteria becoming infected at the current time (from equation 1), and due to the bacteria which became infected time τ ago now lysing. Equation 3 captures the diffusion of phages with diffusion constant D (which we take to be constant, although it has been shown to depend on host cell density [16]), their adsorption into host cells and emergence due to a lysis event.

These PDE-s admit travelling wave solutions with an asymptotically constant velocity [10], [28]–[31]. In a deterministic model, the speed of the travelling wave is approximately given by $\sqrt{D/\tau}$ [10], [29].

2.2 Stochasticity in lysis time

In order to model the effect of incorporating stochasticity into the lysis time, we start by thinking about a toy model: consider a system with a single virus at time t_0. Now, let us draw a random variable T_1 from a normal distribution $\mathcal{N}(\mu, \sigma^2)$[a]. After time T_1 the viral population will be multiplied by β, i.e. T_1 would act as a lysis time if the virus was to immediately infect a host. We keep repeating this process, drawing T_i from the same fixed distribution. We can now consider the expected number of viruses at time t. This will depend on the variance of the distribution, σ^2, and a larger σ will result in a larger expected population size at time t, see Appendix A for a demonstration via numerical simulations. This toy model differs from a real population of viruses in many important ways, and especially because in a viral population, each individual draws its own lysis time, and so the replication events are asynchronous: a virus with $\tau = 400$ will replicate earlier than one with $\tau = 500$. However, the model captures an important idea: if there are individuals in a population who happen to replicate in a shorter amount of time than the average, then the expected size of the population is larger. In the case of a turbidostat experiment in which newly produced phages are immediately provided with new uninfected host bacteria, we would thus expect to see the fraction of phage variants with a higher σ be larger than of those with a lower variance in their distribution of lysis times. (This is not what Hunter et al [27] were measuring, so this does not contradict their results.)

It is also expected that a similar argument works in the case of a spatial expansion. Intuitively, in a travelling wave of phages, if one phage happens to have a short lysis time, its β descendants from the lysis event will emerge from their host before the wave has moved very far. Thus, they will have a larger chance of ending up near the front, which is a good predictor of still being at the front of the expansion some time later. That also means that those phages will have the opportunity to come across new hosts before they are all killed, and therefore themselves replicate. We propose that if the average lysis time $\bar{\tau}$ of a lineage of phages (see Figure 4) was tracked over time during a spatial expansion, then the probability mass distribution of $\bar{\tau}$-s, $f(\bar{\tau})$, of the entire phage population would be shifted towards a mean which is smaller than μ, the mean of the underlying probability distribution, $p(\tau)$. Naively, one would expect the central limit to apply, and thus the probability distribution of $\bar{\tau}$ to have the same mean as $p(\tau)$, but this is not the case, because we are not taking the average of *independent* lysis time events. Once a phage draws a smaller τ, it will replicate sooner than other phages, therefore the proportion of lineages with that phage is larger than before see, Figure 4. Additionally, we would expect $\langle\bar{\tau}\rangle$ to approach an asymptote (as opposed to going to zero[b]), which would be lower for phages with higher σ. Using a relatively simple argument, see Ap-

[a] Technically, it would be a truncated normal distribution, because we restrict T_1 to be positive, but in cases relevant to us, $\langle\tau\rangle$ would be large enough that the probability mass below 0 would be small regardless.

[b] Or the minimum cutoff value of the truncated Gaussian.

pendix B, we can calculate a lower bound for the asymptotic value. Meanwhile, $p(\tau)$ would remain unchanged, and new infection events would still take as much time as initially to reach lysis. Therefore, if we now considered a population with different phage variants with different σ-s, then by picking phages from the front of the wave and using them to start new plaques, we could be selecting for phages with higher σ, while keeping μ constant.

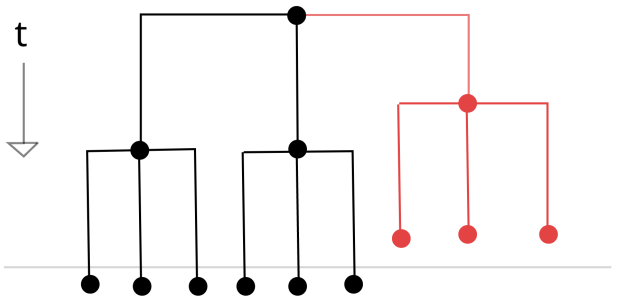

Figure 4: A schematic diagram of a tree representing a viral population. The edge lengths represent lysis time lengths. Each path from the root node to a leaf represents a lineage. A single shorter lysis time on the rightmost branch of the tree means that the proportion of red phages goes from 1/3 to 3/2 for a while.

3 Computational Model

A description of the agent-based stochastic simulation used.

We use agent-based stochastic simulations to investigate the effects of lysis time stochasticity. The code used in this project was largely based on the work of N. Krishnan in [16], where they used the following model to study range expansions of bacteriophage on a bacterial lawn. The system consists of a one dimensional lattice of colonisation sites, called demes. Each deme has a fixed capacity, K_{bac} of either uninfected, infected or dead cells, and is initialised to have K_{bac} uninfected bacteria. At each timestep, the following is carried out (see Figure 5 for an overview and a summary of the parameters): 1) each phage will diffuse with a probability $m/2$ to a neighbouring deme; 2) each phage will infect an uninfected host cell with probability α[c]; 3) the infected hosts who were infected at time $t-\tau$ undergo lysis and release β new phages into the deme. The simulation has a shifting frame that keeps track of the travelling wave, introduces new demes full of uninfected bacteria to the front of the wave, and removes demes where the phage population has reached a steady state from behind the wave front. We adopt the following set of assumptions:

1. The bacterial hosts are motionless.
2. The bacterial hosts do not replicate.
3. Phages cannot adsorb to already infected hosts (superinfection exclusion).
4. Adsorption to uninfected hosts always results in an infection.
5. Within a simulation, α and β are fixed to a single value.
6. Instead of a fixed τ, the phage population has an associated probability distribution $p(\tau)$ from which each lysis time is drawn.
7. τ only takes integer values. Whenever $\bar{\tau}$ is calculated from a sequence of τ-s, it is also rounded to the nearest integer[d].

We will later relax assumption 2 in the double ring morphology experiment. See Section

[c]By this we mean that the number of adsorbing phage is sampled from a binomial distribution with success probability α and B_iV_i number of trials.

[d]This is an arbitrary approximation made so that we could compare values of $\langle\bar{\tau}\rangle$ between phages.

5 for a discussion on the validity and accuracy of assumptions 3, 5. The probability distribution $p(\tau)$ is usually taken to be a normal distribution, with $\sigma \sim \tau/10$, as in [27], [32].

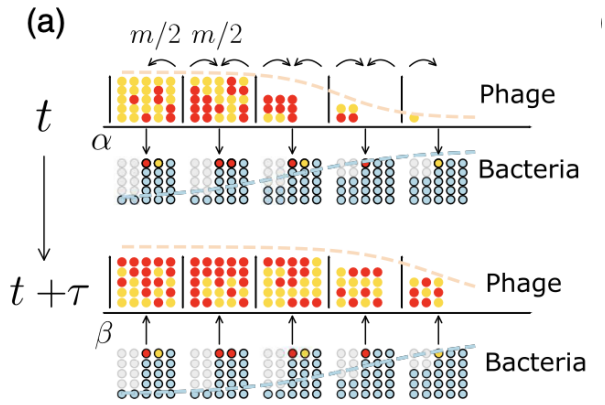

Figure 5: Diagram of the spatial range expansion simulation setup from [16].

We ran experiments of roughly three types:

1. **Competition** of one phage variant versus another with a different $p(\tau)$. A travelling wave is first established, and then all the free and adsorbed phages are randomly labelled either 1 or 2, and their parameters set accordingly. After that, the simulation will keep running for a while, and the "winner" is determined by seeing which variant remains once heterozygosity has gone to 0.
2. Tracking the **history of lysis times** in a population of a single phage variant. Once a phage "falls out" from the moving frame, its $\bar{\tau}$ is recorded. We explore how the distribution $f(\bar{\tau})$ evolves over time.
3. Introducing bacterial replication to see if a **double ring morphology** can be produced. Additionally, a requirement that bacteria can replicate only if another cell has recently lysed in the same deme is introduced.

4 Results

4.1 Competition

We tested whether phages with a higher variance in lysis time outcompete ones with a lower variance. The lysis time distribution of phage 1 is set to $\mathcal{N}(500, 50)$, and the distribution parameters of phage 2 are varied. The results are presented in Figure 6A. Phage 1 will almost certainly outcompete phage 2 if $\sigma_1 \geq 1.2\sigma_2$ if $\mu_1 = \mu_2$.

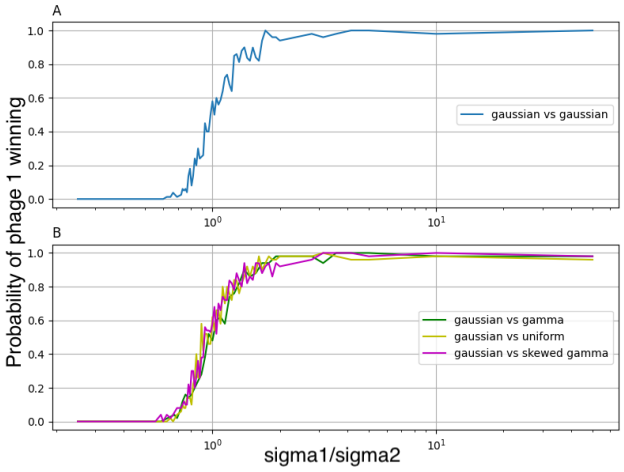

Figure 6: Probability of phage 1 outcompeting phage 2 as a function of σ_1/σ_2 if phage 1 has a Gaussian $p(\tau)$ and phage 2 has 1) a Gaussian distribution (A); 2) a gamma distribution 3) a uniform distribution; 4) a skewed gamma distribution for $p(\tau)$ (B). All the distributions have the same mean $\mu = 500$.

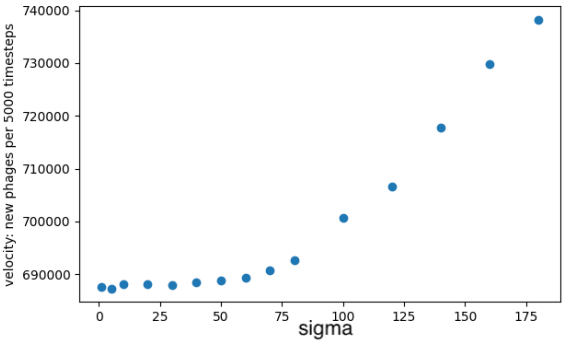

Figure 7: Velocities of spreading phages for different values of σ for phages with a Gaussian $p(\tau)$. Due to the truncation of $p(\tau)$ at $\tau = 100$, higher values of σ result in higher μ, so the velocities above $\tau = 200$ will start decreasing.

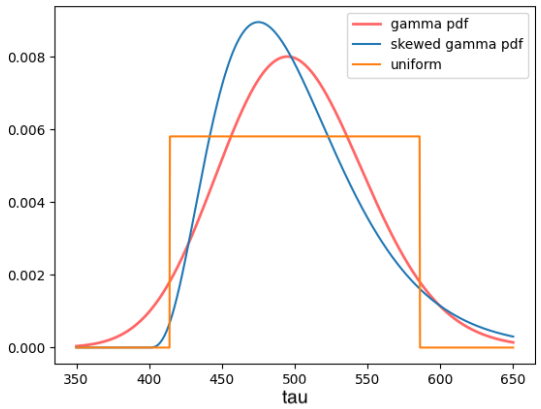

Figure 8: Different probability density functions for the distributions used in the competition experiment.

In addition, we measured the velocities of the waves for phages with Gaussian $p(\tau)$-s with different σ-s, for a separate measure of the fitness. The results are in Figure 7.

We also explored whether the shape of the distribution $p(\tau)$, given that the mean and variance stay fixed, plays a role in the competitive advantage of one phage vs another. The results are in Figure 6B for a competition run between a phage with $\tau \sim \mathcal{N}(500, 50)$ and phages with a 1) uniform, 2) gamma, and 3) skewed gamma distributions (see Figure 8).

4.2 Average lysis time over history

We tracked the average lysis time $\bar{\tau}$ for each phage in a population with $\tau \sim \mathcal{N}(\mu, \sigma^2)$ for two different values of σ. The results for $f(\bar{\tau})$, the probability mass function of $\bar{\tau}$, after 80,000 timesteps are shown in figure 9. We see that both $f(\bar{\tau})$-s are shifted towards a smaller mean and variance. Additionally, the distribution with a larger variance has undergone a larger shift. By tracking how $f(\bar{\tau})$ changes over time as the simulation progresses, we can observe whether $\langle\bar{\tau}\rangle$ tends towards an asymptotic value, and also estimate what that value is. First, we note that the average $\bar{\tau}$ over all phages within each deme only inside the comoving frame is initially[e] lower than the mean of $f(\bar{\tau})$ of the total phage population. We also see that the frame average of $\bar{\tau}$ approached an asymptote, which is similar to the asymptotic population average $\bar{\tau}$, although the population average takes longer to reach that value. The frame average $\bar{\tau} < 500$ demonstrates that picking phages from the edge of a plaque results in picking phages which have on average lysed their hosts faster than μ even in the case of a population of (genetically but not phenotypically) identical phages. The data for the the average $\bar{\tau}$ within the moving frame, and in the entire population are depicted in Figure 11. The results for the asymptotes are collected in Table 1.

σ	theoretical bound	$\langle\bar{\tau}\rangle$ of entire population	$\langle\bar{\tau}\rangle$ of frame
100	200	433.2	425.8
50	350	483.8	482.2

Table 1: The bounds for asymptotic values for $\langle\bar{\tau}\rangle$, and the values from the best fit lines.

[e]By initially we mean that after some time which is sufficiently long enough to establish meaningful data for average lysis times, but not long enough for the system to have reached values close to the asymptotic values.

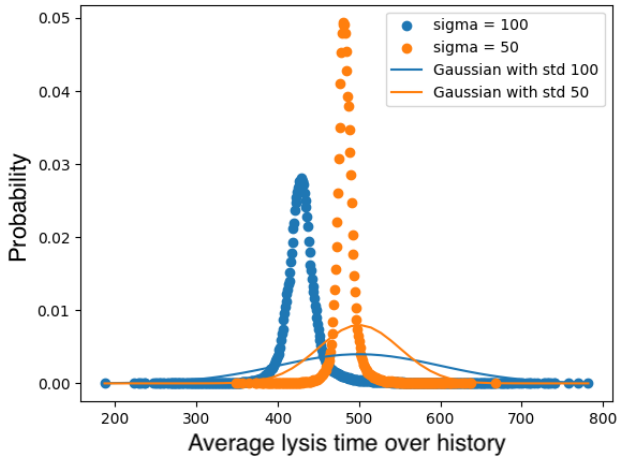

Figure 9: Probabilities $f(\bar{\tau})$ for $\sigma = 100$ and $\sigma = 50$ at time $t = 80,000$. The underlying probability distributions $p(\tau)$ are also depicted.

4.3 Double ring morphology

Altering the model to now include bacterial replication, we explored the parameter space of different diffusion rates, adsorption rates, and bacterial replication rates (see Table 2) and found that none of these result in a double ring morphology (Figure 2). We additionally added the constraint that bacteria can only replicate if other bacteria have lysed very recently (within the last 5 timesteps in this particular case) in the same deme. This assumption makes sense because after a long time, the bacteria have consumed all the nutrients on the lawn, and only the bursting open and release of inner contents of surrounding bacteria can provide them with more food, enabling them to grow. In that case, our findings show curves with peaks, see Figure 10A, however, these do not correspond to a double ring structure because here, the density does not go down again before reaching its final value of 200.

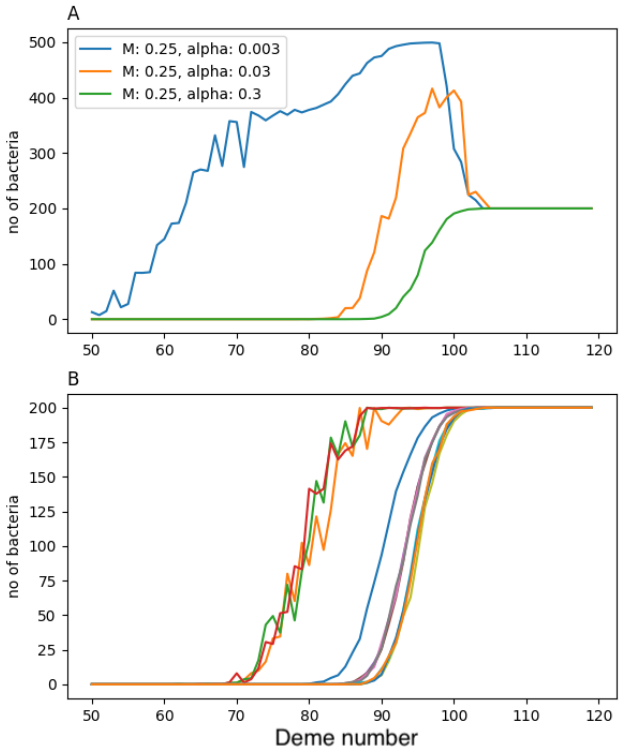

Figure 10: A: A representative sample of data for the number of alive (infected or uninfected) bacteria as a function of position in the moving frame if the carrying capacity of each deme is higher than the initial bacterial population. B: Same as A but the carrying capacity of each deme is equal to the initial bacterial population.

diffusion rates	[0.01, 0.05, 0.1, 0.25]
adsorption rates	[0.0003, 0.003, 0.03, 0.3]
bacterial growth rates	[1, 100, 500, 1000]

Table 2: The parameters explored in the double ring morphology experiments.

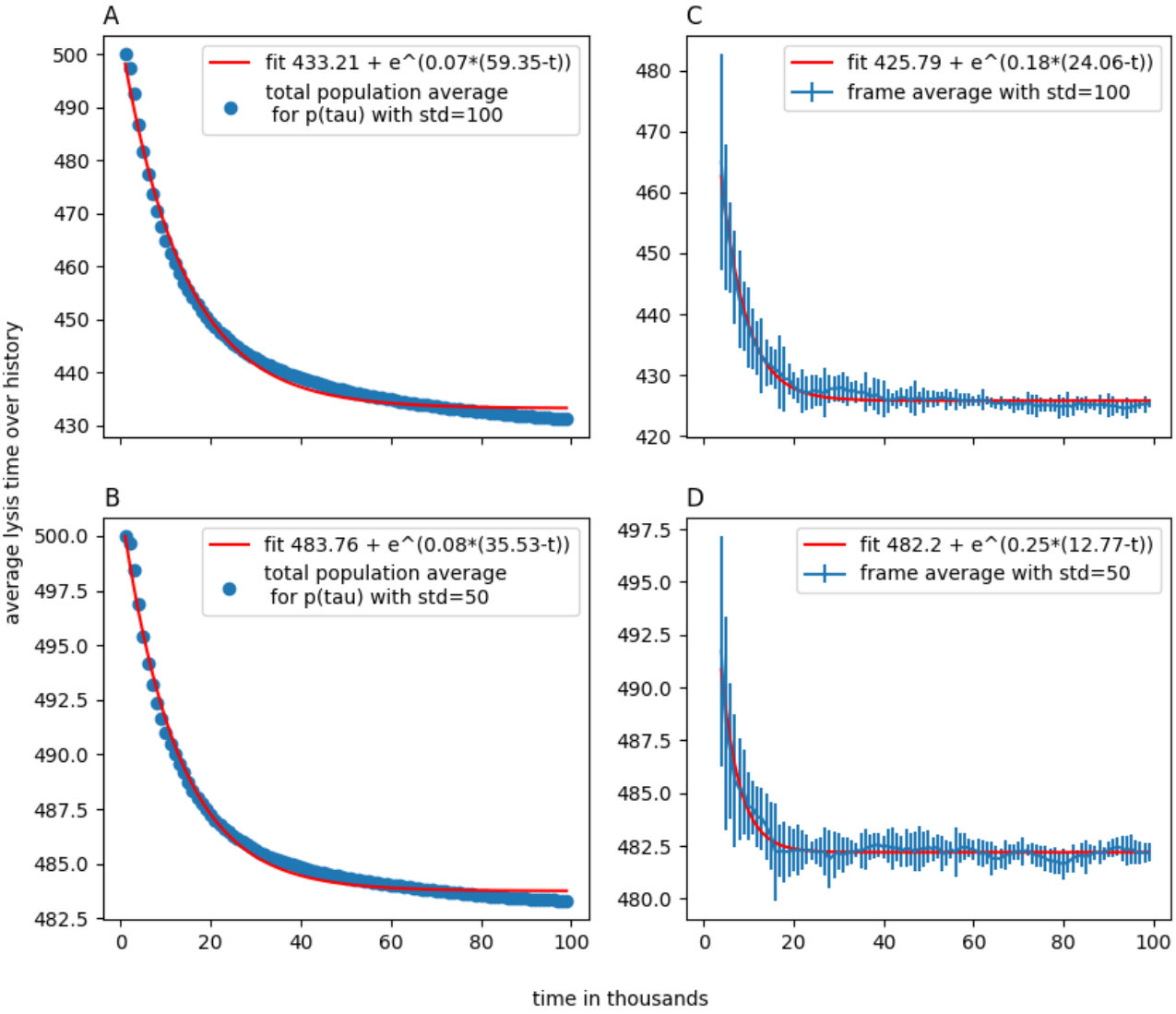

Figure 11: A and B: The average of $\bar{\tau}$ of all free phages over time for $p(\tau)$ with $\sigma = 100$ (A) and $\sigma = 50$ (B). C and D: The average of $\bar{\tau}$ of free phages in the moving frame over time for $p(\tau)$ with $\sigma = 100$ (C) and $\sigma = 50$ (D). The vertical bars are the standard deviations of the data for the average lysis time at time t. All figures include a best fit line of the form $a + e^{b(c-t)}$.

5 Discussion

5.1 Competitive advantage of stochasticity and distribution shape in lysis time

5.1.1 Gaussians

We saw that if two phage variants both have $\tau \sim \mathcal{N}(\mu, \sigma^2)$, and σ was varied for one variant, then for variants with the same mean lysis time, the variant with a higher variance had a higher chance of outcompeting the other one. From this we infer that the speed of spreading on the bacterial lawn is faster for phages with a higher variance in lysis time. We also measured the speed explicitly, and confirmed that result separately. This is already enough to explain the results of the evolution experiment: assuming that in the original population there existed different variants of phage

with different σ-s, and that we were selecting for higher σ, we ended up with a phage population that spreads faster. From just this experiment it might seem like higher variance in lysis time is always good, so it raises the question: why would there exist phages with a low variance at all? In addition to the reasons outlined above in the Introduction, one reason might be that in our simulation, only phage populations that were large compared to the host population were considered. If the opposite was true, and there were only a few phages infecting the bacteria, then a larger variance could also mean that there is a higher chance of one of these few phages having a very long lysis time. Those individuals could then have a higher risk of 'dying out'. This could perhaps be tested in simulations where the focus is not on travelling wave dynamics.

5.1.2 Different distribution shapes

Our results confirm that the shape of the distribution $p(\tau)$ beyond the mean and variance does not play a role in fitness.

5.2 Analysis of average lysis time over the history

Our results on the average historical lysis time generally agree with our theory. We have demonstrated that the average lysis time of a population of phages is lower than the mean of the underlying distribution of lysis times – $\langle\bar{\tau}\rangle \leq \mu$. Over time, $\langle\bar{\tau}\rangle$ approaches an asymptotic value, which is lower for larger σ. In the future, a rigorous mathematical theory could be developed to more tightly bound these asymptotic values. The results so far are confidently within our theoretical bounds of $\langle\bar{\tau}\rangle > 350$ for $\sigma = 50$, and 200 for $\sigma = 100$.

5.3 Double ring morphology

We were unable to produce a bacterial density curve with a clear intermediate peak (which corresponds to a double ring morphology in a 2D experiment) for a wide range of parameters, and different assumptions within the model, see Table 2. It is possible that by tweaking the parameters more, a positive result could be found. However, care must be taken when interpreting promising results which arise due to an arbitrary (and thus possibly unrealistic) set of parameters. Even if a suitable set of parameters was found, the question of why the original population of phages, that hadn't yet been selected for speed, did not exhibit the double ring morphology would remain unanswered.

5.4 Further work

In general, our work contributes to the effort to fully understand the evolutionary dynamics of phage range expansions. With that in mind, we now propose a couple of ways to directly expand on our current results.

In all of our simulations, the burst size β stayed constant. However, there is evidence that burst sizes depend roughly linearly on lysis times [33], [34]. The proposed reason for that is simply that the more time a phage spends inside an infected host, the more time it has to make copies of itself. This could then mean that what phages with a longer lysis time lose from taking longer to replicate, they might gain by producing more copies at once.

Additionally, we know of other properties that phages exhibit, which we have not included in our simulations, but which could affect the spreading dynamics. For example, in our model, we do not allow for superinfection [27], [35]: once a phage has infected a host, it is not possible for other phages to infect the same host. In reality, however, some phages do not have mechanisms to stop superinfection, and therefore allow for the possibility of multiple different variants of phage producing copies of themselves inside a single host at the same time. We could also consider the possibility of simultaneous infections speeding up lysis, due to increased expression of holin proteins [36]. Furthermore, we might explore the

effect of lysis inhibition – a mechanism only known in T4 phages and its relatives, where lysis is *delayed* in the event of superinfection [37].

Other examples of processes to include in the model are bacterial replication, and the possible effect of host growth rate on lysis times [26], or cell debris from lysed bacteria triggering phage adsorption.

6 Conclusions

We have demonstrated that stochasticity in lysis time increases the fitness of bacteriophages in the context of spatial range expansions within bacterial colonies where viruses vastly outnumber the hosts. More specifically, we have presented a general mathematical argument for why we should expect a population of phages with a higher variance in lysis time to grow faster, and shown that this holds true for our particular setup in simulations. In simulations where a steady state wave of phages spreading in a one dimensional bacterial population was split into two variants with σ_1 and σ_2, then given that $\mu_1 = \mu_2$, variant 1 would outcompete variant 2 if $\sigma_1 \geq 1.2\sigma_2$. Additionally, the velocity of the waves increased with σ. Therefore, we have confirmed the theory that in the spatial range evolution experiment where faster phages were selected for, the variable that was under selection pressure could have been σ.

We proposed that the mechanism by which phages with a higher stochasticity in lysis time end up having an advantage had to do with the average lysis time over the history of the phages' evolution. We showed that we expect $\langle\bar{\tau}\rangle$ at time $t \neq 0$ of a population of phages to be lower than the mean of $p(\tau)$. By thinking about the probability of even a single phage having a particularly low $\bar{\tau}$, we bounded the asymptotic value for $\langle\bar{\tau}\rangle$ from below. We tested this in our simulation and found that the asymptote is well within our bound, and in fact much higher than that, see Table 1.

We were unable to show that the bacterial density exhibits a double ring morphology within our model.

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A Effect of larger variance on population size in a toy model

Let there be a single virus at time t_0. Let $X_1, ..., X_n \overset{\text{iid}}{\sim} \mathcal{N}(\mu, \sigma^2)$, and

$$T_n = \sum_{i=1}^{n} X_i \sim \mathcal{N}(n\mu, n\sigma^2).$$

We want to know the expected value of the population size at time t given that X_i is the time it takes between the population going from N_{i-1} to $N_i = \beta N_{i-1}$. First, the probability that there are N_t phages at time t is given by:

$$\begin{aligned} \mathbb{P}(N_t = \beta^n, t) &= \mathbb{P}(T_n < t, T_{n+1} > t) \\ &= \mathbb{P}(T_n < t, X_{n+1} \in [t - t_n, \infty)) \\ &= \int_0^t f_n(s) \int_{t-s}^{\infty} \phi(x) \mathrm{d}x \mathrm{d}s \end{aligned} \tag{4}$$

where $f_n(s)$ is the probability density function of T_n, and $\phi(x)$ is the probability density function of X. We can write down the expressions for the probability density functions to get

$$\mathbb{P}(N_t = \beta^n, t) = \int_0^t \frac{1}{\sigma\sqrt{2\pi n}} e^{-\frac{1}{2}\frac{(s-n\mu)^2}{n\sigma^2}} \int_{t-s}^{\infty} \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\frac{(x-\mu)^2}{\sigma^2}} \mathrm{d}x \mathrm{d}s \tag{5}$$

The expected value of the population size in general:

$$\mathbb{E}(\beta^n) = \sum_i \beta^i \mathbb{P}(\beta^i, t) \tag{6}$$

We don't know of a way to simplify the expression for the probability, so we proceed by running numerical simulations of this model. If we average over 100,000 runs, the expected value of the population size at time $t = 10,000$ is shown in Figure 12. We can see that as σ increases, so does $\mathbb{E}(\beta^n)$.

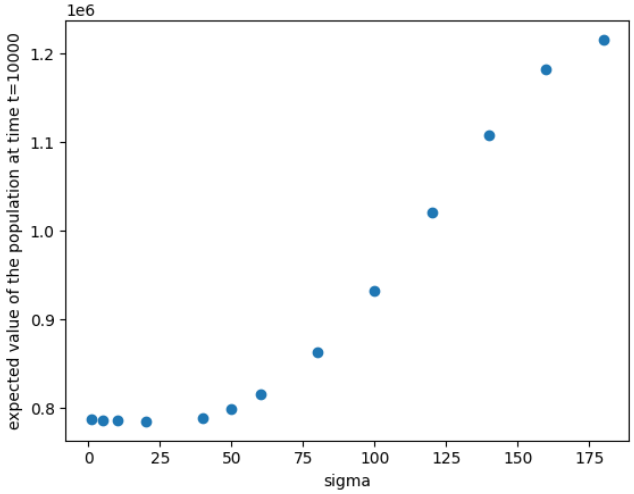

Figure 12: Expected size of a population that is multiplied by β after every X_i time where X_i drawn from $\mathcal{N}(500, \sigma^2)$, as a function of σ.

B Bound for $\langle \bar{\tau} \rangle$

We will bound the mean of the probability distribution of average lysis times over the phages' history by considering the probability of a single virus having a $\bar{\tau}$ which is smaller than some value. We find the largest value for which that probability goes to 0 in the long time limit.

Let the initial viral population have size N_0. If it takes time τ for each virus in the population to replicate and release k copies of itself, then after n replications, there are at most $N_0 k^n$ viruses. The tree representing the growth of the population (see Figure 13) also has at most $N_0 k^n$ branches. If $\tau \sim \mathcal{N}(\mu, \sigma)$, then a branch of length n has an average replication time $\bar{\tau} \sim \mathcal{N}(\mu, \sigma^2/n) = \mathcal{N}(\mu, \sigma'^2)$. Now the probability of $\bar{\tau}$ of a branch being $m\sigma = m\sqrt{n}\sigma'$ away from the mean is at most

$$\frac{e^{-nm^2/2}}{m\sqrt{n}\sqrt{2\pi}}.$$

This can be proven by noting that for $X \sim \mathcal{N}(0, 1)$:

$$\mathbb{P}(X < x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} 1 \cdot e^{-t^2/2} \, \mathrm{d}t. \tag{7}$$

And since for $t \leq x < 0$ we have $1 \leq t/x$,

$$\mathbb{P}(X < x) \leq \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} \frac{t}{x} e^{-t^2/2} \, \mathrm{d}t = \frac{e^{-x^2/2}}{x\sqrt{2\pi}}. \tag{8}$$

The result follows immediately if we scale the probability distribution of X appropriately. We also note that

$$\frac{e^{-nm^2/2}}{m\sqrt{n}\sqrt{2\pi}} \leq e^{-nm^2/2}.$$

According to the union bound in probability theory, the probability that at least one branch has a $\bar{\tau}$ that is $m\sigma$ away from the mean is then

$$\mathbb{P}_{\geq 1} \leq N_0 k^n e^{-nm^2/2} = N_0 (k e^{-m^2/2})^n. \tag{9}$$

We want $ke^{-m^2/2} < 1$ so that $\mathbb{P}_{\geq 1} \approx 0$ for large n, while $m\sigma > 0$ because each lysis time is positive, so the average also has to be positive. For $k = 30$, $\mu = 500$, $\sigma = 50$, we can take $m \geq 3$ for the inequality to hold. Then, the bound for the shortest average lysis time is given by $\bar{\tau} \geq 500 - 3 \times 50 = 350$, which is also a bound for $\langle \bar{\tau} \rangle$. For $\sigma = 100$, we get that $\langle \bar{\tau} \rangle \geq 200$.

Although this argument ignores the fact that not all viruses in the population will replicate exactly n times, we believe that the bounds are still roughly of the right size.

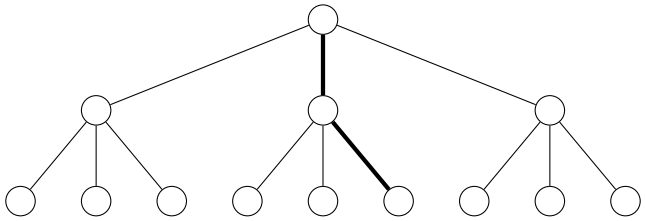

Figure 13: A tree representing the growing phage population. A branch from the founder to one of its descentants is marked in bold.

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