Host Physiology–Dependent Lysis Timing Shapes Bacteriophage Competition Under Nutrient Fluctuations

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ABSTRACT

When bacteriophages infect starved host bacteria, the restrictive host physiology may lead to prolonged latent periods and/or reduced burst sizes, compared to infection of a fast-growing bacterium. Using a mathematical model, we explore a system of two types of virulent phages that have distinct host physiology dependencies and are infecting a shared bacterial host population. We consider different environmental regimes to test whether they can compete and coexist under fluctuating conditions, putting emphasis on phases with limited resources for bacterial growth. We find that phages capable of delaying lysis in response to nutrient limitations can outcompete fast-replicating phages in feast-famine environments. This advantage mainly stems from increased mortality of free phages due to abortive adsorption to already infected hosts during starvation phases. We identify specific system dynamics that either support or suppress the propagation of the delayed lysis phage. This theoretical analysis highlights the competitive benefits and the limitations of delayed lysis as a phage propagation strategy. Our results underscore importance of considering the bacterial physiology dependence of bacteriophage replication in order to correctly predict phage fitness and population dynamics in complex environments.

IMPORTANCE

Bacteriophage replication depends strongly on the physiological state of their hosts, yet most ecological and theoretical studies treat phage life histories as fixed traits. This overlooks how nutrient limitation, starvation, and fluctuating growth conditions reshape infection outcomes. By examining competition between phages with different responses to host physiology, our work shows how environmentally driven changes in the latent period can alter which phages persist, spread, or are lost. These insights clarify when delayed lysis is a beneficial strategy and when it becomes a liability. More broadly, our results highlight the need to integrate host physiology into models of phage–host dynamics to better understand microbial ecosystems and to guide applications such as rational phage therapy design.

INTRODUCTION

Bacteriophages are gaining increased attention due to their central role in shaping the dynamics of microbial ecosystems and their potential application as therapeutic agents. Considering that the infection dynamics of different types of phages vary widely, even among strictly lytic phages, we can expect to observe complex interactions and environmental dependencies when multiple phages with overlapping host specificity are present in the same system. Understanding phage replication and competition across diverse environmental contexts is essential for predicting microbial ecosystem dynamics.

Phages are effective agents of managing bacterial communities and change growth dynamics, community composition and metabolic activity of different ecosystems [1, 2, 3]. In a community without phages, and under the assumption of one shared, limiting growth substrate, the fastest growing bacterial species will dominate the population quickly and drive other strains to extinction through competitive exclusion. However, the introduction of phages to the system can alter these dynamics and even reverse them [4, 5, 6, 7]. The phage species infecting the fastest growing strain will replicate quickly and therefore suppress its host bacterium's growth, opening opportunities for slower growing strains to thrive.

In complex microbial ecosystems, phages must navigate multiple factors that can promote or inhibit successful infection and replication. Phages and bacteria are engaged in a continuous "arms race", with bacteria developing resistance to infection and phages evolving to circumvent these defenses [8, 9, 10, 11, 12]. Additionally, phages compete against other phages and mobile genetic elements for available hosts, and must "defend" their host cell against superinfection after the successful takeover of a host cell [13, 14].

It is assumed that bacteria spend most of the time under conditions of nutrient limitation in their natural environments [15, 16, 17, 18, 19]. Consequently, phage infections often occur under conditions that differ significantly from the pure cultures and rich growth media that serve as the default experimental model to study phage infection in the laboratory. The parameters that characterize phage replication (adsorption rate, burst size, latent period) are commonly used to define phage fitness, but these parameters can vary significantly depending on the physiological state of the host bacterium. Phage production relies on the infected host's gene expression machinery, so that slow bacterial growth will lead to slower or even completely halted phage production [20, 21, 22].

Despite this variability, theoretical analyses often treat these traits as constant parameters[4, 5, 6], or assume simple linear relations to the growth rate in cases where the growth physiology dependence is important for the system [23, 24, 25]. While some studies have characterized how phage replication parameters change with host physiology for selected model phages [20, 21, 26, 27], and others have documented the stochastic variability of these parameters [28, 29, 22], broader datasets on phage infection dynamics under suboptimal conditions are lacking. Similarly, the consequences of different host physiology dependencies for community dynamics remain underexplored.

Even though the available data is limited, remarkably different responses to infection of starved *Escherichia coli* cells have been observed. For instance, phage T4 is capable of delaying lysis when infecting a non-growing starved cell. In this situation, T4 initiates the early infection steps but halts replication before assembling progeny [30]. The viral life cycle resumes when nutrients are restored, often yielding larger burst sizes compared to infection of exponentially growing cells. Note that this observation is a separate

phenomenon from the T-even phages' lysis inhibition triggered by the adsorption of multiple phages to the same host [31], though the phenotypic consequence, delayed lysis, is similar. The observation of lysis delay in T-even phages has previously inspired investigations into the selective advantage of a delayed lysis mechanism and into the optimal tradeoff between a short latent period and a large burst size [31, 32, 33, 34]. These studies have found that the optimal length of the latent period depends on both host density and the physiological state of the host [35, 36, 37, 38]. Both of these factors are under constant variation in an active ecosystem with nutrient fluctuation, predation, and competition.

Other phages, e.g. T7, maintain a strictly lytic strategy, continuing to replicate and lyse host cells even during starvation [39, 40]. The burst size of T7 has been shown to be dependent on the host growth rate under steady-state growth (similar to T4) [21]. However, the extent to which T7's burst size is reduced when a previously fast-growing host enters stationary phase/starvation remains an open question [21, 40]. The ability to produce phage progeny from starved hosts has also been observed for other phages, e.g. phages UT1 and ACQ of *Pseudomonas aeruginosa* [40]. Conversely, infection of a stationary phase host is detrimental to virulent mutants of phage λ, with no functional progeny produced [22].

In this study, we draw inspiration from the replication strategies of phage T4 (hibernation) and phage T7 (continuous bursting) to model two otherwise identical virulent phages in direct competition for a single host population experiencing cycles of abundant and limited resources (feast-famine cycles). These two approaches represent fundamentally different life-history strategies for coping with resource limitation. By modeling two abstract phages only loosely inspired by replication strategies observed in natural phages, we try to isolate the specific conditions under which lysis delay proves to be an advantage, even without a direct compensation through larger burst sizes.

The delayed lysis strategy we consider is one form of "pseudolysogeny" where infected cells neither proceed towards the lysis pathway nor replicate with the host [41, 42]. This strategy may provide better survival of phages in environments harsh to free

phage particles, similar to the advantage of lysogenization [43, 44, 45]. On the other hand, continuous lysis enables the phages to spread even in a starved population, as long as enough progeny is produced even in the diminished lysis, as demonstrated in the continuous enlargement of T7 phage plaque in a stationary lawn [46]. Such a behavior will allow the phage to keep relatively high number of free phage particles in the system, allowing them to be ready to infect newly available cells all the time, and to continue diffusing in space, searching for other available hosts.

Yet, it remains unclear which strategy confers a competitive advantage when phages compete for hosts under recurrent nutrient fluctuations, inducing variability in host physiology. Understanding this competition is crucial for predicting phage dynamics in natural ecosystems and for designing robust phage-based therapeutic interventions in complex environments.

MODEL

Substrate dependent host growth and two types of phages

We present a mathematical model for two virulent phages infecting a population of susceptible host bacteria in a well-mixed environment. In the first version of the model, we simulate a chemostat culture with constant influx of substrate for bacterial growth and constant dilution of the culture at the same flow rate. In the second model, we simulate repeating cycles of batch cultures, resulting in alternating conditions of abundant growth substrate (feast) and starvation conditions (famine). We model the growth of the uninfected bacterial population B under the assumption that the growth rate follows Monod's growth law [47] as

$$\mu = \mu_{max} g(S) \quad \text{with} \quad g(S) = \frac{S}{K_s + S}. \tag{1}$$

Here μ_{max} is the maximum growth rate when the nutrient availability is unlimited, and K_s is the half-saturation constant. One unit of the growth substrate S is defined as the

amount needed to support the duplication of one bacterial cell. In order to contrast the two phage strategies, we consider two types of virulent bacteriophages that are modeled with identical characteristics, except for how their lysis behavior depends on the bacterial growth state.

Delayed lysis phage

We call one of the phages DL (delayed lysis) and assume that the lysis timing is directly proportional to the bacterial doubling time, as previously proposed in [24], while the burst size remains constant. More precisely, the latent period of the host cell infected by a DL phage is given by $\tau_{DL}(S)$ as follows:

$$\tau_{DL}(S) = \frac{\tau_{DL_{min}}}{g(S)}. \tag{2}$$

τ_{DLmin} is set so that $\tau_{DL}(S_0) = \tau_{OB}$ where S_0 is the maximum substrate concentration that the system experience at the beginning of the feast cycle, and τ_{OB} is the latent period of the competing obligatory bursting phage (see below). This ensures that both phages have identical lysis dynamics at the maximum substrate concentration.

Obligatory bursting phage

In contrast, the latent period of phage OB (obligatory bursting) τ_{OB} is independent of the bacterial growth and remains constant. In order to modulate the competitive strength of phage OB relative to phage DL, we couple the burst size to the substrate concentration through $g(S)$ with a step-function in the following manner:

$$\beta_{OB}(S) = \begin{cases} \gamma_{stat}\, \beta_{OB_{max}}, & g(S) < 0.2 \\ \beta_{OB_{max}}, & g(S) \geq 0.2 \end{cases} \tag{3}$$

Here, the parameter $\gamma_{stat} < 1$ defines the burst size reduction factor when the growth rate of the host is slow enough. The threshold nutrient concentration S_{th} for the reduction of

phage OB's burst size is defined by $g(S_{th}) = 0.2$, resulting in $S_{th} = K_s/4$. The characteristic lysis behavior of the two phages is visualized in Figure 1.

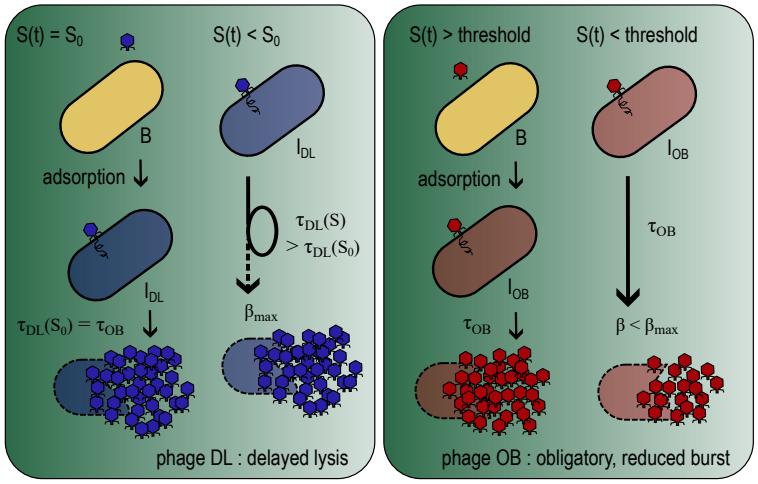

FIG 1 Visual representation of the replication properties of the two phages in the model. The latent period of phage DL (left panel) depends on the host physiology according to eq. 2 so that lysis is delayed relative to phage OB whenever $S(t) < S_0$. When the infected cells lyse, they lyse with the full burst size β_{max}. The latent period of phage OB (right panel) is constant, but the burst size is coupled to the host physiology. If $S(t)$, and therefore the host growth rate, drops below a threshold, the burst size is reduced to $\gamma_{stat}\beta_{max} < \beta_{max}$ (eq. 3).

Model 1 - Chemostat

We consider a well-mixed environment with a constant influx of growth substrate S and a constant dilution of the culture at rate ω. Within the system we consider the concentration of the bacterial population B, the free OB (DL) phage particles P_{OB} (P_{DL}), the bacteria infected by either OB or DL phage I_{OB} (I_{DL}) and the concentration of the growth substrate S. We assume that the infection of host bacteria follows a Lotka-Volterra type interaction and that the free phage particles adsorb to both uninfected and already infected cells with the adsorption rate η. When an already infected cell adsorbs a phage, the phage particle is inactivated and the status of the cell does not change; in other words, the first infection determines the eventual fate of the infected cell. This is particularly important for phage DL which may experience a long latent period, and is consistent with

the T-even phages' superinfection exclusion mechanism, where DNA injected by secondary adsorbing phages gets trapped and degraded in the periplasm [48, 49, 50]. A bacterium primarily infected by OB (DL) phage will produce $\beta_{OB}(S)$ (β_{DL}) new OB (DL) phage particles that will be released after the latent period of τ_{OB} ($\tau_{DL}(S)$), respectively. Functional forms of $\beta_{OB}(S)$ and $\tau_{DL}(S)$ are described in eqs. 2 and 3. The full chemostat model is given as follows:

$$\frac{dS}{dt} = \underbrace{\omega(S_{influx} - S)}_{in/outflow} - \underbrace{\mu_{max}\frac{S}{K_s + S}B}_{consumption} \tag{4}$$

$$\frac{dB}{dt} = \underbrace{\mu_{max}\frac{S}{K_s + S}B}_{cell\ division} - \underbrace{\eta B(P_{OB} + P_{DL})}_{infection} - \underbrace{\omega B}_{outflow} \tag{5}$$

$$\frac{dP_{OB}}{dt} = \underbrace{\beta_{OB}(S)\frac{I_{OB}}{\tau_{OB}}}_{production} - \underbrace{\eta P_{OB}(B + I_{OB} + I_{DL})}_{adsorption} - \underbrace{\omega P_{OB}}_{outflow} \tag{6}$$

$$\frac{dP_{DL}}{dt} = \underbrace{\beta_{DL}\frac{I_{DL}}{\tau_{DL}(S)}}_{production} - \underbrace{\eta P_{DL}(B + I_{OB} + I_{DL})}_{adsorption} - \underbrace{\omega P_{DL}}_{outflow} \tag{7}$$

$$\frac{dI_{OB}}{dt} = \underbrace{\eta B P_{OB}}_{infection} - \underbrace{\frac{I_{OB}}{\tau_{OB}}}_{lysis} - \underbrace{\omega I_{OB}}_{outflow} \tag{8}$$

$$\frac{dI_{DL}}{dt} = \underbrace{\eta B P_{DL}}_{infection} - \underbrace{\frac{I_{DL}}{\tau_{DL}(S)}}_{lysis} - \underbrace{\omega I_{DL}}_{outflow} \tag{9}$$

Model 2 - Feast-Famine

To simulate a system with fluctuating substrate availability that alternates between phases of exponential growth and a stationary starvation phase, we modify the model as

follows: We consider a batch culture system, where B_0 bacteria, P_0 phages, and S_0 nutrients added to the system at $t = 0$. We simulate this system for one growth cycle that lasts t_{end} time units, which is set long enough in comparison to the initial bacteria and nutrient concentration that nutrients can be fully consumed and bacteria experience starvation (famine). At the end of one growth cycle, all bacteria and phages are diluted by a factor 1:10. Then, to restart a new "feast" phase, the concentration of the growth substrate is reset to the value S_0 and a set amount of susceptible host bacteria B_{add} is added to the system. We repeat this procedure (usually 80 times) and follow the dynamics of the two phage populations.

During each cycle, the dynamics of the system are described by the same set of equations as the chemostat system, but with $\omega = 0$. At the end of each cycle, the system components are adjusted in the following manner to serve as initial conditions for the next feast-famine cycle:

$$\begin{aligned} S_0^i &= S_0 \\ B_0^i &= 0.1\, B_{end}^{i-1} + B_{add} \quad \text{with} \quad B_{add} = \alpha\, S_0 \\ P_{OB_0}^i &= 0.1\, P_{OB_{end}}^{i-1} \\ P_{DL_0}^i &= 0.1\, P_{DL_{end}}^{i-1} \\ I_{OB_0}^i &= 0.1\, I_{OB_{end}}^{i-1} \\ I_{DL_0}^i &= 0.1\, I_{DL_{end}}^{i-1} \end{aligned} \tag{10}$$

Here, the superscript i denotes the number of the feast-famine cycles, and the subscript 0 (*end*) denotes the start (end) of the next (previous) feast-famine cycles, respectively.

The Monod constant K_s in eq. (1) was set relatively low ($K_s = \frac{S_0}{10}$) to permit rapid substrate consumption and entering of a starvation phase for a host population under attack. This simulates a true “feast” influx of excess nutrient which is rapidly consumed.

The numerical integration was performed using solve_ivp from the scipy.integrate package with the fourth-order Runge-Kutta method. A time unit $t = T_g$ equals the generation time of the host bacterium at the maximum growth rate μ_{max}, i.e.,

$T_g = 1/\mu_{max}$. For *E. coli* in rich medium, this corresponds to about 30 min. The maximum time step for the solver was set to 1.

TABLE 1 Default parameter values and initial values for the simulation.

Parameters and Initial Conditions

Parameter	Description	Default value	Notes
μ_{max}	maximum bacterial growth rate	1	Time unit, see caption.
K_s	half maximum growth constant	10^5	$K_s = S_0/10$
η	phage adsorption rate	$1.5 \cdot 10^{-8}\ \frac{ml}{T_g}$	Adapted from adsorption rate reported for T4 [51] $3 \cdot 10^{-8}\ \frac{ml}{h}$
$\beta_{OB_{max}}$	maximum burst size, phage OB	150	
β_{DL}	burst size, phage DL	150	Adapted from burst size reported for T4 [51]
τ_{OB}	latent period, phage OB	$0.8\ T_g$	approximately 24 min, adapted from latent period reported for T4 [51]
$\tau_{DL_{min}}$	adjusted minimum latent period, phage DL	$0.8\ T_g \cdot \frac{S_0}{K_s+S_0}$	adjusted so that $\tau_{DL}(S_0) = \tau_{OB}$, see equation 2
t_{end}	Length of feast-famine cycle	100	

TABLE 2 Initial values for the simulation.

Parameter	Description	Default value
Initial variable values chemostat system		
S_0	Initial concentration of substrate	10^6 ml^{-1}
B_0	Initial concentration of bacteria	10^4 ml^{-1}
P_0	Initial concentration of phage OB and phage DL	10^4 ml^{-1}
I_0	Initial concentration of infected cells	0 ml^{-1}
Initial variable values feast-famine system		
S_0^1	Initial concentration of substrate	10^6 ml^{-1}
B_0^1	Initial concentration of bacteria	10^6 ml^{-1}
P_0^1	Initial concentration of phage OB and phage DL	10^6 ml^{-1}
I_0^1	Initial concentration of infected cells	0 ml^{-1}

RESULTS

In a chemostat system, delayed lysis gives only a limited competitive advantage

We first compete the two phages against each other in a chemostat system defined by equations (4)-(9). Important assumptions in the model are (i) phage OB has reduced burst size if the substrate $S < S_{th} = 2.5 \cdot 10^4$ ml^{-1}, (ii) phage DL has prolonged latent period proportional to the host growth rate for the given S, and (iii) phages are adsorbed by both uninfected and infected cells, but the fate of the infection is determined by the primary infecting phage.

Figure 2A shows one example of the population dynamics with the flow rate $\omega = 0.05\ T_g^{-1}$ and a stationary phase burst size for phage OB of $\gamma_{stat}\beta_{max} = 75$. In the default case, we add the same amount of phage DL and phage OB at the start of the simulation ($P_0^{DL} = P_0^{OB} = 10^4$ ml^{-1}). We observe oscillations due to the negative feedback between the bacteria and phage, known as predator-prey oscillations. For this parameter set, the substrate concentration remains generally above S_{th}, hence the burst size of phage OB is not reduced (eq. 6), while the latent period of phage DL increases periodically

following the fluctuations in substrate concentration. This slight disadvantage leads to phage DL eventually being outcompeted by phage OB.

The increased latent period of phage DL generally presents a disadvantage, and phage DL can only exclude phage OB if the competitor phage suffers an even bigger disadvantage from the reduced burst size during host starvation. In our system, the burst size of phage OB is only reduced for significant time periods when the flow rate ω is less than 0.03 T_g^{-1} (Figure 2C). For $\omega < 0.03\ T_g$ phage DL can outcompete phage OB with $\gamma_{stat}\beta_{max}$ of up to 75 (Figure 2B).

The boundary of the maximum $\gamma_{stat}\beta_{max}$ that phage DL can compete with at $\omega < 0.03\ T_g^{-1}$ weakly depends on the initial conditions of the simulation. When we increase the initial concentration of one of the phages, the speed at which phage DL excludes phage OB in advantageous conditions is altered. If phage OB is invading a system already dominated by phage DL, a value of $\gamma_{stat}\beta_{max} > 100$ is necessary for successful invasion (Supplementary Figure S1). For high flow rates ($\omega > 0.03\ T_g^{-1}$), the nutrient S does not drop below the starvation threshold irrespective of the initial conditions and the outcome is unaffected. Overall, in the chemostat setup, the outcome of the competition is strongly limited by the flow rate and the burst size of the competitor phage under starvation.

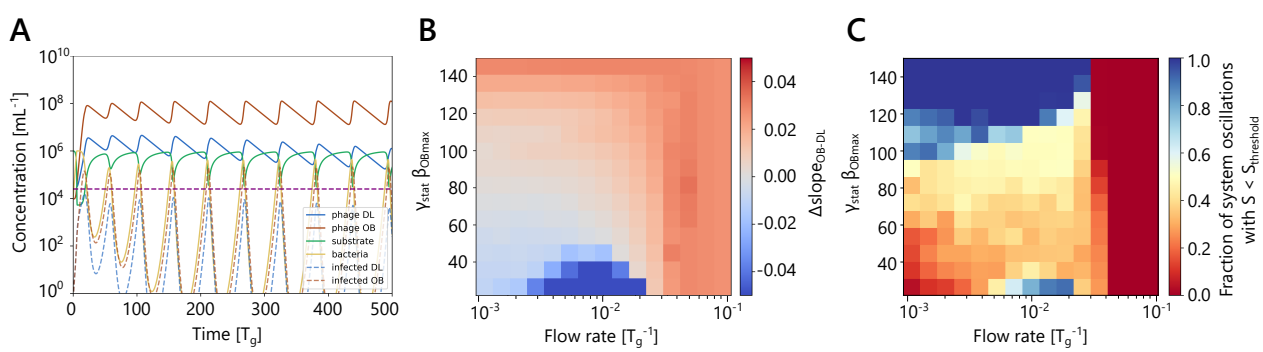

FIG 2 Chemostat system, A: Overview/Example of system dynamics, with flow rate $\omega = 0.05\ T_g^{-1}$ and phage OB burst size reduction factor $\gamma_{stat}\beta_{max} = 75$. B: Outcome of phage competition in a chemostat environment for different values of ω and $\gamma_{stat}\beta_{max}$. The outcome is defined as the difference of the slopes (Δs) of a log-linear fit to each phage concentration over time, normalized by the flow rate ω. Each simulation was evaluated for $50,000\ T_g$. C: Relative number of

oscillations in which the condition $S < S_{th} = 2.5 \cdot 10^4$ ml^{-1} is met, measured during the first 1/3 of the time series, normalized to total number of oscillations in that time period for each parameter set.

Repeated feast-famine cycles increase the fitness of a delayed lysis strategy

In most natural ecosystems, substrate influx is not continuous and bacteria spend much of their time in nutrient depleted conditions [15, 16, 17, 18, 19]. We therefore next compare the infection dynamics of the two phages targeting the same host bacteria type in a series of feast-famine cycles. We consider a batch culture where a limited amount of nutrients supports populations of bacteria and phages. After a set time period, the end product of this cultivation is diluted using a fixed dilution factor and added to a new batch culture. More specifically, phages and bacteria (uninfected and infected) are diluted 1:10 at the end of the respective growth cycle, which lasts for 100 T_g time units, equivalent to approximately 48 hours for a fast growing bacterium like *Escherichia coli*. To restart a new "feast" phase, the concentration of the growth substrate is reset to S_0 and a set amount of susceptible host bacteria B_{add} is added to the system (Figure **3**A). We define the ratio of B_{add} and S_0 as α (eq. (10)), and explore the effect of α on the competition. Since the nutrient is measured as a unit required for doubling of one bacterium, $1/\alpha = S_0/B_{add}$ quantifies the potential bacterial growth fold per feast phase. Typically, we simulate 80 such feast-famine cycles for a certain parameter combination.

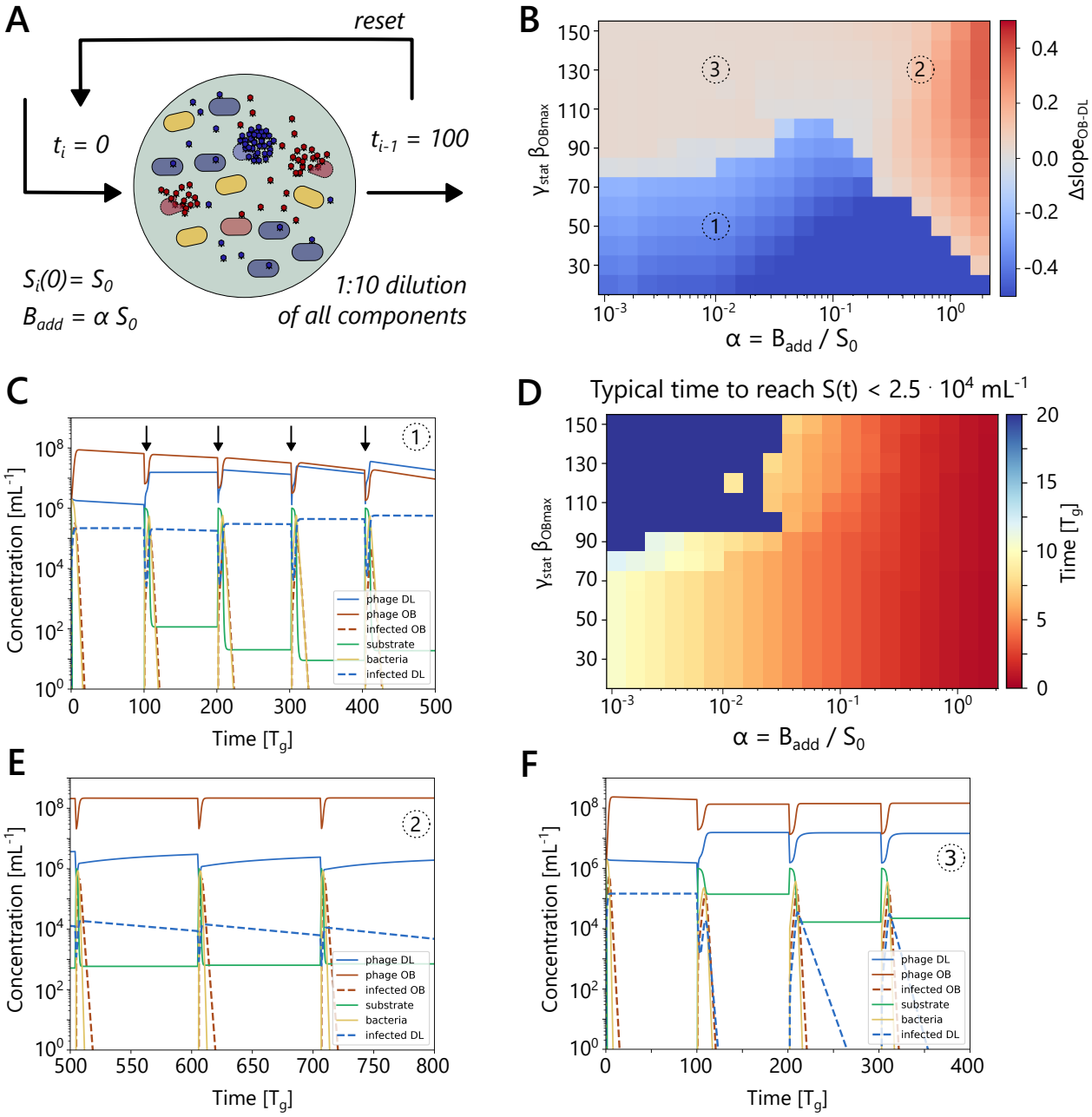

FIG 3 A: Schematics illustrating the feast-famine system. B: Result of phage competition in the feast-famine system for different values of γ_{stat} and α. The result is shown as the difference of the slopes of a log-linear fit to each phage concentration over time. A positive value (red) indicates that phage OB is outcompeting phage DL and *vice versa*. The dynamics of the indicated examples are shown in panel C, E and F. C: Dynamics of the feast-famine system (cycle 1 - cycle 5) for $\gamma_{stat}\beta_{max} = 50, \alpha = 0.01$. Arrows indicate time points of system dilution and replenishment of S and B. D: Time index of the time point where S

typically drops below S_{th} for different values of γ_{stat} and α. E: System dynamics for $\gamma_{stat}\beta_{max} = 130, \alpha = 0.5$ (highlighted case 2 in panel C). Cycle 5 - cycle 7. F: System dynamics for $\gamma_{stat}\beta_{max} = 130, \alpha = 0.01$ (highlighted case 3 in panel C). Cycle 1 - cycle 4.

We screened the dynamics of the feast-famine system for different values of the parameters $\gamma_{stat}\beta_{max}$ and α and observed a number of possible outcomes (Figure 3B). We characterized the outcome by the difference between slopes of a long-term population log-linear fit; negative values (blue) denote that phage DL outcompetes phage OB, and *vice versa* for positive values (red). The tested parameter space can be separated into multiple regions that produce the outcome of the competition by different mechanisms.

The dynamics for case (1), with relatively small α and $\gamma_{stat}\beta_{max}$, is represented in Figure 3C with $\gamma_{stat}\beta_{max} = 50$ and $\alpha = 0.01$. After the addition of fresh substrate and host bacteria, the substrate is consumed as the bacteria grow. Then the concentration of susceptible bacteria drops rapidly due to phage infection. Those infected by phage OB lyse quickly and produce new phage OB, while the concentration of bacteria infected by phage DL plateaus as the substrate concentration decreases towards its minimum level typically in less than 12 T_g time units, and lysis comes to a halt. The decrease in both phage populations until the next dilution event is mainly driven by adsorption to DL-infected cells that are still in the system. At the end of the cycle, phage OB, phage DL, and DL-infected bacteria are present in the system, and 1/10 of them continue to the next feast round (eq. (10)).

In this parameter region (1), the reduction of the free phage concentration via adsorption by DL-infected cell is critical for phage DL's competitiveness in the feast-famine system, and specific for DL's competitiveness in case (1) (Supplementary Figure S2A). The carry-over of DL-infected cells has a second beneficial effect for phage DL. After the carry-over, the DL-infected cells experience nutrient rich conditions and lyse quickly while the susceptible host B is at its maximum concentration. The freshly produced phages can capture a large amount of the newly available host population. These dynamics result in a steady increase of phage DL relative to phage OB in the system.

In the end, phage DL outcompetes phage OB for this parameter combination. Note that the phage loss by adsorption is not important in chemostat system in the studied parameter range, instead the continuous flow strongly contributes to the phage decay (Supplementary Figure S2B).

In the contrasting case of (2), represented in panel E with $\gamma_{stat}\beta_{max} = 130$ and $\alpha = 0.5$, the available substrate is immediately consumed by the incoming host and the system enters the famine phase very quickly. Without phages present, the time to consume all of the substrate S_0 by newly added bacteria $B_{add} = \alpha S_0$ would be $T_{sub} = \ln(1+\alpha)/\alpha T_g$, which satisfies $T_{sub} < 2.5T_g$ for $\alpha > 0.1$. Even though the presence of phages somewhat slows down substrate consumption, the timing of the entry into starvation depends little on γ_{stat} for this parameter region (Figure 3D).

The extremely short growth window in the feast period results in a disadvantage for phage DL. Under these conditions, the lysis of the carried-over population of lysis-delayed cells cannot proceed efficiently, and any newly infected cells are immediately affected by a strong lysis delay. Hence, phage DL loses the opportunity to build a large population of free phage to compete against phage OB in claiming susceptible hosts, and this disadvantage becomes more severe the shorter the growth period is (larger α, panel D). Phage OB is also affected by the short growth window, leading to many OB-infected cells bursting with the reduced burst size $\gamma_{stat}\ \beta_{OB_{max}}$. Larger α values lead to shorter growth windows, which means that phage DL gets outcompeted by phage OB with progressively smaller γ_{stat} values. This results in a downward slope of the boundary between phage-DL and phage-OB advantageous parameter regions in the α-$\gamma_{stat}\beta_{OBmax}$ space (Figure 3B).

For the same $\gamma_{stat}\beta_{max} = 130$ but smaller $\alpha = 0.01$ (case 3), the substrate would be consumed within 4.6 T_g without phages present. However, infection and lysis of bacteria by phages alters the growth dynamics significantly and the time to enter the famine phase becomes dependent on $\gamma_{stat}\beta_{max}$ in addition to α (Figure 3D). As can be seen in the time course in the panel F, a high concentration of phage OB after the first cycle leads to immediate infection of the small host population in the following cycles, preventing full

substrate consumption. The substrate concentration never reaches below the threshold to activate the reduced burst size for phage OB, and phage DL continues to lyse over the whole cycle, removing the ability to both capture free phage through secondary adsorption and to carry-over infected cells to the next cycle, leading to phage DL eventually being outcompeted by phage OB, however, due to different population dynamics than in case (2).

The outcome in case (3) is different from that in case (1) due to the initial conditions that we set. In Figure 3B, We used the same initial conditions in all cases: $P_0 = B_0 = S_0 = 10^6$ ml^{-1}, effectively setting $\alpha = 1.0$ for the first cycle. Due to the immediate consumption of the substrate by the initial host population, most of the phage OB infected cells will lyse with the reduced burst size, leading to a γ_{stat} dependent phage OB concentration at the end of cycle 1 (Supplementary Figure S3A), which then determines the dynamics in the following cycles. If we instead initialize with an increased concentration of phage DL ($P_{DL_0} = 10^8\ mL^{-1}$), the bacterial growth and substrate consumption dynamics in the first few cycles of case (3) are changed in a way that activates delayed lysis and carry-over for DL-infected cells similarly to case 1 (Supplementary Figure S3C). For the region of the parameter space exemplified by case (1) and case (2), the outcomes do not change by increasing P_{DL_0}, except that the boundary between advantageous conditions for either phage is shifted in advantage for phage DL (Supplementary Figure S3C). In the reverse case of setting $P_{OB_0} = 10^8$ ml^{-1}, the outcome is the same as with the default initial conditions (Supplementary Figure S3B), highlighting that we are effectively analyzing the ability of phage DL to invade an established population of phage OB.

Fluctuating environments support the coexistence of competing phages

The effect of pairwise alternating host feeding rates

The feast-famine system introduces a cyclic variation between periods of rapid microbial growth and starvation. However, the variation follows a regular pattern that favors either one of the phages in the system and leads to gradual competitive exclusion

of the other. We next introduce additional environmental variation in the system by either alternating between two α values (mode II in Figure 4A) or by choosing a random α value at each reset event (mode III). We investigate how the different parameter regimes affect the fitness of each phage species and if it allows for long-term coexistence of phage DL and phage OB.

There is a vast foundation of both theoretical and experimental research that shows that environmental fluctuations can stabilize the coexistence of species which could otherwise not thrive alongside each other [52, 53, 54, 55]. The key mechanisms for the fluctuation-dependent coexistence include the presence of relative nonlinearities in the response to the fluctuating environment [56, 57, 58] and the storage effect [59]. Often, multiple mechanisms are contributing to coexistence simultaneously [60, 61, 62]. In some systems, the coexistence in a fluctuating environment may be explained by fluctuation-independent mechanisms, i.e., the coexistence in a fluctuating environment can be predicted by the coexistence in the time-averaged, constant environment [63, 64]. The relevance of each mechanism depends on the system at hand, and specifically if the per capita growth rate is dependent on competitive factors in a linear or nonlinear manner. Our current model assumes nonlinear substrate dependence of the phage growth rate through either burst size or latent period variation, and it is not trivial to map the model to previously studied analytically tractable models [63, 64]. Hence, we here study the model outcome in fluctuating environments numerically to highlight if and how phage coexistence can be realized in fluctuating environments.

First, we evaluate a regime of environmental fluctuation in which the parameter α alternates between two values α_1 and α_2 within the previously tested parameter range. Which phage wins in this scenario strongly depends on the stationary phase burst size reduction for phage OB, i.e., its competitive strength. Figure 4B shows the outcome of various combination of α_1 and α_2 for $\gamma_{stat}\beta_{max} = 65$ and $\gamma_{stat}\beta_{max} = 95$. The diagonal cut-off line of these plots is equivalent to the corresponding horizontal section in 3C showing data for a non-alternating α value.

When $\gamma_{stat}\beta_{max} = 65$ and $\alpha = 0.347$ (left plot, cross symbol) the system falls on the border where the competitive advantage changes from phage OB to phage DL, and the two phages can coexist in the feast-famine system over the tested time scales (Supplementary Figure S4A). On this basis, we can then construct cases with alternating α values where the geometric mean falls on $\alpha = 0.347$. Examples are $(\alpha_1 = 0.246, \alpha_2 = 0.491)$ or $(\alpha_1 = 0.872, \alpha_2 = 0.138)$, which are shown in Figure 4B (left) as filled circles and dotted lines. We use the geometric mean as the effective constant α because, in the Lotka–Volterra system studied by Abreu et al. [64], alternating dilution factors produce long-term dynamics equivalent to those under a constant dilution equal to the geometric mean. In our model, α plays an analogous multiplicative role, setting the fold-change permitted by the ratio of initial nutrients to initial bacterial density. Although Abreu's analytical equivalence relies on the linear structure of the LV equations and does not directly extend to our more nonlinear system, the geometric mean remains the natural choice for comparing alternating and constant-parameter scenarios.

We find that switching between these two α values results in phage coexistence over the tested time scales (at different phage titers, see details in Supplementary Figure S4B, C). However, this effect is quite unstable. Pairs of α values further away from the mean do not result in co-existence, and even some combinations of intermediate α values result in competitive exclusion (e.g., $\alpha_1 = 0.088, \alpha_2 = 1.393$, but also $\alpha_1 = 0.195, \alpha_2 = 0.617$; see open circles in Figure 4C(left) and Supplementary Figure S4D and G).

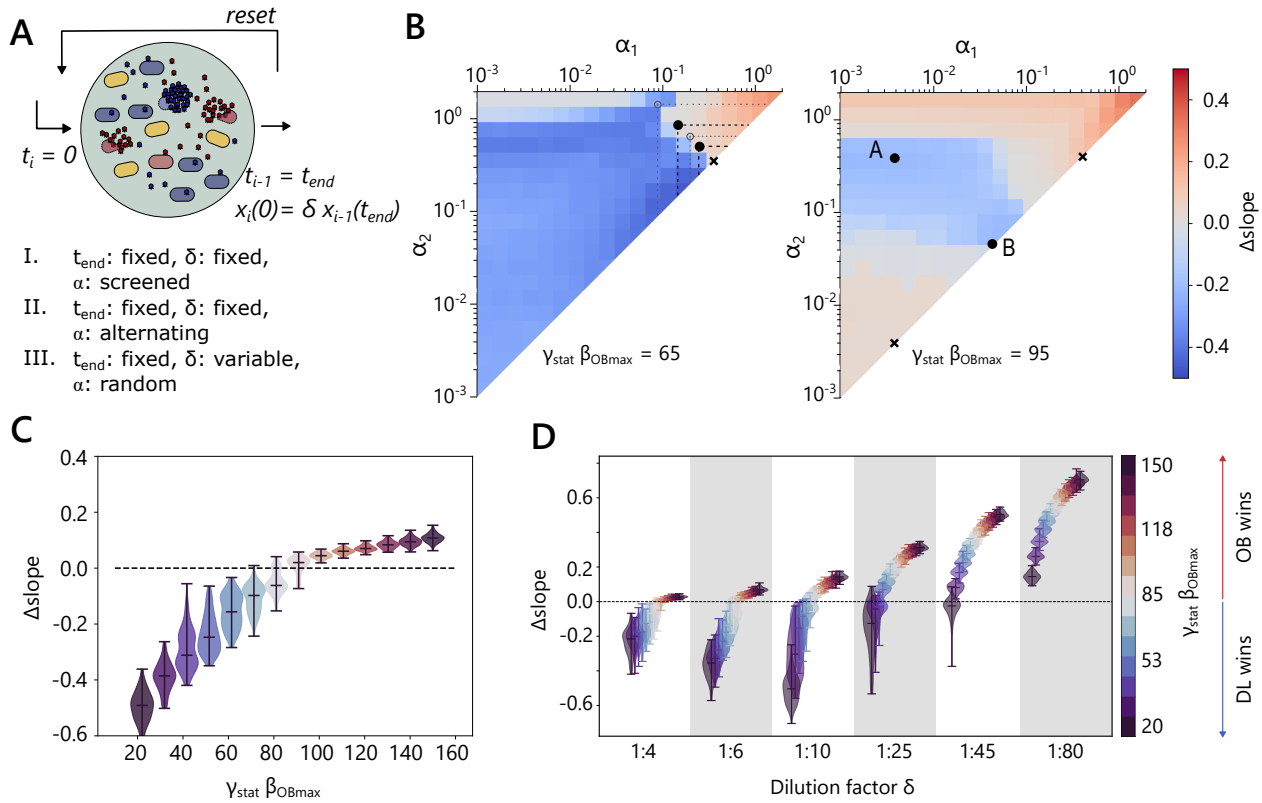

FIG 4 A: Overview of different modes of controlling the environment in the feast-famine system. B: Results from mode II. Alternating between a pair of α values broadens the parameter range in which the two phages can coexist, and can change the outcome of the competition. Cross: At $\alpha = 0.347$, $\gamma_{stat}\beta_{max} = 65$ the two phages coexist over the simulated time scales. Certain pairs of α_1 and α_2 lead to coexistence (black circle, black lines: $(\alpha_1 = 0.246, \alpha_2 = 0.491); (\alpha_1 = 0.872, \alpha_2 = 0.138)$. In those cases the average is still $< \alpha >= 0.347$. This finding is, however, not generalizable for the whole parameter space (grey circles and lines indicate counterexamples). At $\gamma_{stat}\beta_{max} = 95$ we observe that alternating between two environments that are advantageous for phage OB ($\alpha_1 = 0.004, \alpha_2 = 0.4$) leads to phage DL excluding phage OB, again predicted by the outcome of the averaged environment $< \alpha >= 0.04$. C: Results from mode III, drawing a random α value. Each violin plot represents the results from 100 simulations using a randomly selected value for α at each reset event and a specific stationary phase burst size for phage OB. D: The dilution factor at the reset event is an important environmental variable of the system. As in C, which shows a more detailed version of the simulations using $\delta = 1 : 10$, each violin plot shows the results from 100 simulations using a

series of randomly selected α values. Phage DL can only competitively exclude phage OB in systems with sufficiently low dilution factors, akin to lower flow rates in the chemostat system.

We can use a similar logic to find cases in this system where averaging over two alternating values of α changes the outcome of the phage competition. If we set $\gamma_{stat}\beta_{max} = 95$ and let α alternate between 0.004 and 0.4, phage DL outcompetes phage OB in the simulation (circle A, right plot). A fixed α of either 0.004 or 0.4, on the other hand, leads to phage OB excluding phage DL from the system (cross symbols, Supplementary Figure S5). However, a simulation using the geometric mean of these two values $< \alpha >= 0.04$ results in an advantageous environment for phage DL (circle B). This draws our attention back to Figure 3C and the different conditions that can support the competitiveness of phage DL in the feast-famine system. Both constant $\alpha = 0.004$ and $\alpha = 0.4$ lead to a win for phage OB. In one case because the growth substrate is not sufficiently depleted for phage OB to experience the reduced burst size (case 3), and in the other due to too short growth and lysis windows (case 2). However, alternating between them means that situations that support the propagation of phage DL are created, e.g., when a lysis inhibited population of DL infected cells is carried-over to a growth cycle where slow depletion of the substrate allows for full lysis and high production of phage DL (Detailed dynamics shown in Supplementary Figure S5E).

Randomly selected host feeding rates allow a broader examination of environmental parameters

We showed that alternating between two distinct conditions can promote coexistence of two phage types or enhance the competitive strength of phage DL. We next extend this idea by allowing α to vary at random (option III in Figure 4A). At every refeeding, a random value of α from within the range $0.001 \leq \alpha < 2$ is uniformly drawn. We ran 100 simulations for each of the 14 values of γ_{stat}. The results are presented as distributions of Δslope outcomes in Figure 4C. As before, a positive Δslope value means that phage OB has an advantage over phage DL. Under these conditions, we see that phage DL can only outcompete phage OB if $\gamma_{stat}\ \beta_{OB_{max}} < 85$. We also found that phage OB and phage DL

can frequently coexist over long time periods when $80 < \gamma_{stat}\beta_{max} < 90$ (Example dynamics shown in Supplementary Figure S6).

The random draw of a host feeding rate α removes this parameter as the key environmental variable, and leaves the dilution factor at each reset event as another controllable parameter, which has been kept constant as $1:10$ so far. To evaluate the role of this parameter in determining the outcome of the phage competition, we systematically changed the dilution factor and simulated the competition outcome (Figure **4**D). The dilution factor corresponds to a system wide mortality rate that effects both phages and hosts equally. A high dilution factor, representative of a very harsh external environment, favors the faster replicating phage OB, just like a high flow rate ω is favorable for phage OB in the chemostat system. The length of the starvation period also impacts the outcome of the competition, since abortive adsorption of phages to already infected cells during this period is an important contribution to phage DL fitness (see Figures **3** and S2). However, the effect of increasing or decreasing the time scale of each feast-famine cycle is much smaller than the effect of changing the dilution factor (Supplementary Figure S7).

In the previous examples, we have seen that the outcome of the competition with alternating α values can in some cases be predicted by analyzing the system with the averaged, static α value, pointing towards fluctuation-independent mechanisms determining the system outcome [64]. This observation was, however, only made within a limited parameter range. In the case of the random selection of α values, we observe clear deviation from the outcome of simulations with a static, averaged α value (Supplementary Figure S8).

DISCUSSION

Just like any other living organism, bacteriophages must evolve strategies to overcome adverse environmental conditions [22] and compete with other organisms that occupy the same ecological niche. Phage evolution and growth strategies are often evaluated under the premise of co-evolution in an arms race with their host [8, 3, 9, 10]. However, before

they encounter potential host defenses, they first have to compete with other phages in claiming a susceptible host.

In this study we explore the dynamics between two virulent phages infecting the same host population under the pressure of varying availability of the bacterial growth substrate. We find that repeated feast-famine cycles improve the competitive strength of a phage that has a mechanism to delay lysis in response to host starvation against a fast lysing phage, and we identified several mechanisms that contribute to this phenomenon. We also find that increased variation in the environmental conditions can support the long term co-existence of two phage types with different lysis behaviors.

These results evoke some similarity to findings of classical ecological modeling concerning coexistence of species on shared resources. The delayed lysis/pseudolysogeny could be interpreted as a form of buffered population growth, one of the essential contributors to coexistence through the storage effect [59]. Our model does not directly fit into the theoretical frame work of analytically trackable modeling concerning coexistence on shared resources [63, 64], e.g. we assume that interspecies and intraspecies competition for the limited resource has the same magnitude, but we observe some of the hallmarks of both fluctuation-dependent and fluctuation-independent mechanisms driving coexistence in the conditions where we observe it. We found examples where the geometric mean of an alternating pair of α values could predict the outcome of the competition, even though explicit nutrient dependence makes the current model highly nonlinear. This observation is consistent with the previously reported usefulness of such approach in understanding complex communities [64] and can be interpreted as a good approximation if the fluctuation amplitude is sufficiently small.

Our model is limited by the assumptions. We consider two virulent phages that adjust their lysis behavior in two different ways depending on the host physiology. These relationships do not directly follow experimentally tested data, but are loosely inspired by the behavior of two well-studied model phages of *Escherichia coli* (T4 and T7). The variety of system dynamics we observe even with this simple model demonstrates the need for more experimental study of phage response to host starvation and determination of

phage replication parameters along the whole growth curve. Many of these experiments would be very laborious with the current standard methodologies, especially if systematic study across many conditions is planned. This prompts the development of new high-throughput methodologies for phage characterization (cf. [65]), which are trailing behind compared to bacteria characterization [66].

Despite the limitations, the overall qualitative outcome of this study are experimentally testable. We can think of setting up a series of batch cultures equivalent to the feast-famine system presented. If such a system were simultaneously infected with a phage with a delayed lysis mechanism (e.g. T4) and a continuously lysing phage (e.g. T7), the winner of the competition following different feeding schemes could be determined by classical plaque assays, due to the difference in plaque morphology of these two phages. It should, however, be noted that the experimental testing would be complicated by the development of resistance to phage infection, which was not considered in the model. Development of resistance and therefore divergence in the host population and phage host range can increase the potential for coexistence of similar phages [67, 68, 69, 7]. In the model, we can tune the fitness of the competitor phage to test the limits of the fitness of the delayed lysis phage and its response to various environmental disruptions in a very fine-grained matter. An experimental test will be limited by the replication characteristics of available model phages.

The delayed lysis mechanism of phage T4, which served as an inspiration for phage DL in the model, is a very intricate system that gives phage T4 multiple options to regulate its response to environmental and host information. The classically known mechanism is the lysis inhibition, where lysis halts in response to adsorption of multiple same phages [31]. Delayed lysis was also observed after T4 infection of non-growing, starved cells, independent of MOI [30]. In our model, we did not consider secondary-infection triggered lysis inhibition, but we observed that the adsorption of free phage particles to already infected cells is crucial for the fitness of a delayed lysis phage in a feast-famine environment. Interestingly, in our previous theoretical work of competition between a lysis inhibiting wild type T4 phage and a non-lysis inhibition mutant phage, we also reported that adsorption of phages to the lysis inhibited cells contribute to the

competitiveness of the wild type T4 phage [70]. The lysis delay is therefore not just a mechanism for the phage to hibernate in an environment when the outside conditions might be harsh for free phage particles, but an active competitive strategy to gain advantage over competitors in poor resource environments. Such a mechanism is of course beneficial only if the secondary adsorption does not prevent the eventual production of primary infecting phage. We therefore hypothesize that the ability to delay lysis for a virulent phage should in many cases co-occur with mechanisms of superinfection exclusion across different phage types.

The ability to modulate lysis timing in response to host physiology comes with a cost to short-term replication but can substantially enhance phage persistence in resource-limited and fluctuating environments. Our simulations highlight the specific ecological conditions under which delayed lysis is favored or suppressed, and show how the presence of competing phages reshapes infection dynamics for the entire system. These findings underscore that phage life-history traits cannot be evaluated in isolation from the surrounding biotic and abiotic context. A deeper understanding of how physiological cues, competition, and environmental variability jointly govern phage replication strategies will be essential for improving predictive models of microbial ecosystems and for guiding the rational design of phage cocktails in therapeutic settings.

DATA AVAILABILITY STATEMENT

All code used for simulations and figure generation is available on GitHub https://github.com/AnjaEh/Ehrmann_Mitarai_2025_FeastFamine

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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