OPTIMIZING PHAGE λ SURVIVAL IN A CHANGING ENVIRONMENT: STOCHASTIC MODEL PREDICTIONS

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Abstract— **Bacteriophages - viruses that infect and replicate inside bacteria - undergo rapid degradation outside their hosts. Thus, a common expectation is that phages will minimize environmental exposure by maximizing their adsorption rate, i.e., infection rate. Here we show that, while maximized adsorption is a good strategy when bacterial host cells are healthy, situations exist where bypassing hosts may be beneficial, such as when host cells are not productive for infection. In these situations, optimal adsorption rates may take on intermediate values, thereby increasing phage dispersal. We aim to develop a theoretical understanding of the intermediate, optimal adsorption rate for phage λ, in environments where changing conditions lead to either good or poor quality hosts. We develop a Markov chain model and define optimal adsorption as the adsorption rate that maximizes the probability of survival. We impose experimentally-achievable periodicity in environmental change and derive novel analytic results for the probability of phage λ survival, from which optimal adsorption is computed. We then discuss the sensitivity of the phage survival probability to relevant biological parameters and environmental conditions. Finally, we extend these results to approximate the probability of phage λ survival when environment change is random, which better represents of natural dynamics, and show that stochasticity facilitates phage λ survival in sub-optimal conditions.**

I. INTRODUCTION

Following its release from a lysed host cell, a bacteriophage - a virus that infects and replicates within a bacterium - enters a dangerous and unpredictable phase of its lifecycle. Having no ability to direct its motion, a phage is at the mercy of the surrounding environment, and vulnerable to chemical, photolytic and thermal degradation. Because of this, researchers often assume that phages should always attempt to infect the first bacterial host they encounter in order to escape a volatile environment. That is, phages should maximize their adsorption rate, which is a function of phage attachment-protein binding avidity. This assumption may be valid when bacterial host cells are healthy and growing exponentially, but there many situations when host cells are not productive for infection. Because phages cannot differentiate between good- and poor-quality hosts, or even cells from cell fragments, it may be beneficial for phages to bypass some potential hosts, and thereby increase dispersal, when poor-quality hosts are common.

Several situations may lead to high frequencies of poor-quality hosts. One common situation occurs when bacterial populations reach the carrying capacity of the habitat, and enter stationary phase, such as when nutrients are exhausted. In stationary phase, bacterial cells stop dividing, and are generally unable to support phage reproduction [1]–[3]. Binding to a stationary-phase cell could entail phage death if the host should die before good conditions return. Similarly, phage infection can drive the host's acquisition of resistance [4]. Some mechanisms of phage resistance entail the destruction of phage following host entry [5]. If such resistant hosts are abundant, it may be beneficial for phages to practice restraint in host binding.

Another situation that could lead to selection against adsorption rate maximization is the accumulation of cell fragments resulting from bacterial cell lysis in phage-infected cultures. Since phage can bind receptors on the cell debris just as they would on intact cells, debris shielding can limit phage growth and protect bacterial cells from infection [6], [7]. In this scenario, we expect that adsorption rates will not be maximized such that receptor binding and dissociation can be effected.

To summarize, a wide range of situations can result in the environment shifting from favoring maximal adsorption rates to favoring intermediate adsorption rates. By not maximally binding host cells, phages may increase dispersal, and increase the probability of encountering a viable host population elsewhere.

Evidence for the benefits of an intermediate adsorption rate comes from phage λ, which lost its side tail fibers (stf-) during early lab culturing [8]. Side tail fibers play a role in attachment of phage λ to host bacteria receptors. In agar, λ stf- shows reduced adsorption rates, but increased fitness, relative to λ stf+ [9]. Further work on this system found evidence that isogenic phage populations contain a residual fraction of low attachment rate phages, which provides a mechanism of bet hedging against extinction [10].

Our aim is to develop a theoretical understanding of the intermediate, optimal adsorption rate for phage λ, which infects *Escherichia coli* bacteria, assuming that it is favored by selection imposed by a shifting environment. In the following we discuss results from our first model. We derive a time-dependent Markov chain model and define optimal adsorption as the adsorption rate that maximizes the probability of survival.

Dynamics of Markov chains in changing environments

*JJD is supported by National Science Foundation Early Career Development Award #1148879. AS is supported by a National Science Foundation Grant (DMS-1312926).

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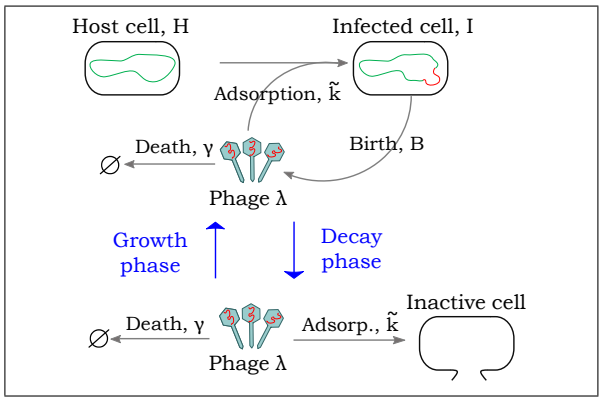

Fig. 1. Model schematic. In the growth phase, a phage λ can either die at rate γ or adsorb at rate $\tilde{k}$ into a host bacterium H rendering it infected I. Infected bacteria produce B λ phages before dying at rate δ. In the decay phase, a phage λ can either die at rate γ or adsorb into a host bacterium at rate $\tilde{k}$, but since bacteria are inactive, no viral production follows. In the decay phase, adsorption is equivalent to clearance.

are not fully resolved, although there are asymptotic and approximate results, for example [11]–[13]. Numerical simulation of Markov chain models [14], in which we must account for the time-dependent parameters associated with environment change [15], can be time consuming, even when using acceleration methods [16], [17]. We will seek an analytic solution. In experimental conditions, the change in environment can be prescribed; we exploit the imposed periodicity of a prescribed environment to derive an analytic expression for the probability of survival. We then extend the analytic solution to derive an approximation for the optimal adsorption rate in the case where environment change is random, which better represents of natural dynamics. In both cases we discuss optimal adsorption rate predictions and sensitivity to biological parameters and environmental conditions.

II. MODEL 1: OPTIMAL ADSORPTION IN A PRESCRIBED ENVIRONMENT

A. Model

Our underlying model schematic is shown in Fig. 1. Phage λ virus can either die at rate γ or infect host, *E. coli* bacteria, to make infected cells with adsorption rate $\tilde{k}$. Λ gives the number of phage λ particlesm H the number of host bacteria, and I the number of infected bacteria. In the growth phase (environment favorable to good hosts), phage λ replicates in the infected cells. Infected cells die at rate δ, producing more phage λ virus. In the "decay phase" (environment favoring poor hosts), for example the stationary phase described above, phage does not replicate and adsorption results in viral death.

We assume that the phage λ infection dynamics correspond to a standard viral dynamics model [18] assuming a constant number of host bacteria H. Average behavior of this system is given by the equations $\dot{I} = \tilde{k}H\Lambda - \delta I$ and $\dot{\Lambda} = B\delta I - (\gamma + \tilde{k}H)\Lambda$, where B is the number of phage produced by an infected bacterium before dying at rate δ. Importantly we define $k \equiv \tilde{k}H$, the actual adsorption rate multiplied by the constant number of host, *E. coli* cells. We will maximize survival probability with respect to this rescaled adsorption rate k.

We can simplify the model with the quasi-steady equilibrium $I = k\Lambda/\delta$ to obtain $\dot{\Lambda} = (k(B-1) - \gamma)\Lambda$ in the growth phase. In the decay phase, however, conditions prevent the infected bacteria from producing virus, for example if there are no nutrients and their metabolism is slowed. Thus the average behavior would correspond to $\dot{\Lambda} = -(k+\gamma)\Lambda$.

We are interested in optimal, scaled, adsorption rate k, which we define as the rate that maximizes the probability of survival. We must therefore consider the stochastic dynamics. In the growth environment, we model dynamics with a birth and death process with birth rate $k(B-1)$ and death rate γ,

$$\Lambda \xrightarrow{k(B-1)} \Lambda + 1 \quad \text{and} \quad \Lambda \xrightarrow{\gamma} \Lambda - 1, \tag{1}$$

where the time between birth or death events are drawn from exponential distributions with rates $k(B-1)$ or γ respectively. Mean behavior of this processes corresponds to the differential equation $\dot{\Lambda} = (k(B-1) - \gamma)\Lambda$. In the decay environment, we model dynamics with a pure death process, with death rate $k+\gamma$,

$$\Lambda \xrightarrow{k+\gamma} \Lambda - 1, \tag{2}$$

where the death rate $k+\gamma$ is exponentially distributed in time. Mean behavior of this processes corresponds to the differential equation $\dot{\Lambda} = -(k+\gamma)\Lambda$.

We first investigate optimal adsorption when the environment switches between growth and decay phases. For example, the environment cycles between a growth phase for fixed time t_1 and a decay phase for fixed time t_0. This scenario replicates experimental conditions, thus our analysis can predict experimental outcomes.

In the following, we compute the probability of extinction starting with n phage λ and use that probability to study optimal adsorption k. For simplicity, we assume that $B = 6$ λ phages, so that the birth rate during the growth phase is $5k$. While $B = 6$ is a low estimate, this assumption should not alter our qualitative results. We then briefly discuss sensitivity to remaining parameters.

B. Analysis

In order to calculate the probability that an infection chain initiated by n phage λ goes extinct as $t \to \infty$, we exploit the periodicity of the prescribed environment. One period consists of a growth phase followed by a decay phase, or vice versa. We will compute $\Psi(x)$, the probability generating function (PGF) [19] for the progeny distribution, i.e., for the distribution on the number of viral particles at the end of one period, starting with a single phage λ. The probability that the infection chain will go extinct, q, is given by the smallest non-negative root of $q = \Psi(q)$ [20]. The survival probability is given by $1-q$ and the optimal adsorption k_* is the adsorption that maximizes the survival probability. From $\Psi(x)$ we can also compute the basic reproduction number

$R_0 = \Psi'(1)$, which we can use to predict conditions under which extinction is guaranteed, i.e., when $R_0 < 1$ [20].

Our results depend on the initial environment. That is, the probability of extinction will differ if the period consists of a growth phase followed by a decay phase, or vice versa.

Progeny PGF - process initiated in decay phase: We first consider dynamics initiated in the decay phase, modeled by the pure death process eq. (2), for fixed time t_0, followed by growth phase, modeled by the birth-and-death process eq. (1), for fixed time t_1.

To compute the PGF for the number of virus particles at the end of one period, starting with a single phage λ, we require the distribution on the number of virus particles surviving to time t_0, at which point the growth phase is initiated. If we assume that at $t = 0$ there is a single virus particle, then at the switching time $t_0 \geq 0$, the probability that the particle remains is given by

$$p(t_0) = e^{-(k+\gamma)t_0},$$

since the time to the next death event is exponentially distributed with rate $k+\gamma$. For the rest of the period, $t_0 < t < t_1 + t_0$, the stochastic process is a birth and death process, eq. (1). The forward Chapman-Kolmogorov differential equation (master equation) associated with this process is

$$\frac{dP_j}{dt} = 5k(j-1)P_{j-1} + \gamma(j+1)P_{j+1} - (5k+\gamma)jP_j, \quad (3)$$

where $P_j(t,t_0) = \text{Prob}(j \text{ phage } \lambda \text{ at } t | n \text{ phage } \lambda \text{ at } t_0)$ [19]. We can multiply eq. (3) by x^j and sum over j to derive a partial differential equation for the PGF $G_n(x;t,t_0) = \sum_{j=0}^{\infty} P_j(t,t_0)x^j$ [19],

$$\frac{\partial G_n}{\partial t} = (x-1)(5kx-\gamma)\frac{\partial G_n}{\partial x} \quad (4)$$

with initial condition $G_n(x;t_0,t_0) = x^n$. We can solve eq. (4) analytically to find the PGF $G_n(x) \equiv G_n(x;t_1+t_0,t_0)$ at the end of the period, i.e., time $t = t_0 + t_1$, associated with the birth-and-death process eq. (1) initiated by n λ phage, is

$$G_n(x) = \left(\frac{(x-1)\gamma e^{(5k-\gamma)t_1} - 5kx + \gamma}{(x-1)5ke^{(5k-\gamma)t_1} - 5kx + \gamma} \right)^n. \quad (5)$$

We start the birth and death process with a single viral particle $n = 1$ with probability $p(t_0)$, at time t_0, and we end the cycle at time $t_0 + t_1$. Therefore the generating function for the number of viral particles at time $t_0 + t_1$ is

$$\begin{aligned}\Psi_d(x) =& G_0(x)(1-p(t_0)) + G_1(x)p(t_0) \\ =& 1 - e^{-(k+\gamma)t_0} \\ &+ e^{-(k+\gamma)t_0}\left(\frac{(x-1)\gamma e^{(5k-\gamma)t_1} - 5kx + \gamma}{(x-1)5ke^{(5k-\gamma)t_1} - 5kx + \gamma} \right), \end{aligned} \quad (6)$$

where the subscript d indicates that this is the PGF for the number of particles at the end of one period if we start in the decay phase.

Progeny PGF - process initiated in growth phase: We next consider dynamics initiated in the growth phase, modeled by the the birth-and-death process eq. (1), for fixed time t_1, followed by a decay phase, modeled by the pure death process, eq. (2), for fixed time t_0.

Let r_n be the probability that there are n viral particles at the end of the growth phase, time t_1, starting with a single viral particle. Using the PGF for the birth and death process $G_1(x;t,0)$ from eq.(5), we can compute r_n,

$$r_n = \frac{1}{n!}\left.\frac{\partial^n G_1}{\partial x}\right|_{x=0},$$

to find

$$r_n = \begin{cases} \frac{(5k-\gamma)^2 e^{(5k-\gamma)t}}{5k\left(e^{(5k-\gamma)t}-1\right)\left(5ke^{(5k-\gamma)t}-\gamma\right)} \left(\frac{5k\left(e^{(5k-\gamma)t}-1\right)}{5ke^{(5k-\gamma)t}-\gamma} \right)^n, & n > 0 \\ \frac{\gamma e^{(5k-\gamma)t}-\gamma}{5ke^{(5k-\gamma)t}-\gamma}, & n = 0. \end{cases}$$

For the rest of the period, $t_1 < t < t_1 + t_0$, stochastic dynamics are given by a pure death process. The PGF for the pure death process is

$$H_n(x) = \left(1 - (1-x)e^{-(k+\gamma)t_0}\right)^n,$$

which we can obtain from eq. (5) replacing t_0 with t_1, $5k$ with 0, and γ with $\gamma + k$. Alternatively, following our derivation of eq. (5), one can use the pure death process master equation to derive a partial differential equation which one can solve for $H_n(x)$.

Therefore the generating function for the number of phage λ particles at the end of the period is

$$\begin{aligned}\Psi_g(x) =& \sum_{n=0}^{\infty} r_n H_n(x) \\ =& -\frac{5k - \gamma e^{Dt_1}}{5kC} + \frac{D^2 e^{Dt_1}}{5kC\left[D - 5k(x-1)e^{-(k+\gamma)t_0}C\right]}, \end{aligned} \quad (7)$$

summing the series, where $C = (e^{Dt_1} - 1)$ and $D = (5k - \gamma)$. The subscript g indicates that this is the PGF if we start in the growth phase.

Probability of extinction: The probability that the process will go extinct as $t \to \infty$ is the root of the equations $q = \Psi_{d,g}(q)$ with $\Psi_d(q)$ given by eq. (6) and $\Psi_g(q)$ given by eq. (7) [20]. The extinction probability depends on the phase in which you initiate dynamics. The probability of extinction for the process initiated by a single viral particle in a decay phase is

$$q_d = \min\left[1, \frac{5ke^{(5k-\gamma)t_1} - \gamma - (5k-\gamma)e^{-(k+\gamma)t_0 + (5k-\gamma)t_1}}{5k\left(e^{(5k-\gamma)t_1} - 1\right)}\right], \quad (8)$$

and the probability of extinction for the process initiated by a single viral particle in the growth phase is

$$q_g = \min\left[1, \frac{e^{-(k+\gamma)t_0}\left(\gamma e^{(5k-\gamma)t_1} - 5k\right) + (5k-\gamma)}{5ke^{-(k+\gamma)t_0}\left(e^{(5k-\gamma)t_1} - 1\right)}\right]. \quad (9)$$

Optimal Adsorption k_*: The survival probability of an infection chain initiated by n virions is given by $1-q_d^n$ and $1-q_g^n$ for processes initiated in the decay and growth phases, respectively. The optimal adsorption rate is the value $k=k_*$ that maximizes these survival probabilities or, conversely, minimizes the probabilities of extinction q_d and q_g, respectively. We will compute these minima numerically from transcendental eqs. (8) and (9).

Basic reproduction number: The basic reproduction number R_0 gives the average number of progeny, at the end of one period, starting with a single phage λ. We can immediately compute the R_0 from the PGFs $\Psi_{d,g}(x)$: $R_0=\Psi'_d(1)=\Psi'_g(1)$, since the average number of viral particles produced is unaffected by the phase in which you start. We find

$$R_0 = e^{-(k+\gamma)t_0+(5k-\gamma)t_1}. \tag{10}$$

From eq. (10) we can predict thresholds below which the phage λ infection chains will die out, i.e., when $R_0<1$. In particular we can find the minimal adsorption rate $k>0$ below which our model predicts no growth, $k_{min}=\gamma(t_1+t_0)/(5t_1-t_0)$ assuming $5t_1>t_0$, with no growth permitted otherwise, as $R_0<1$ for $5t_1\le t_0$.

C. Results

We first compute the survival probability for a process initiated by a single phage λ viral particle as (1- probability of extinction), i.e., $1-q_d$ or $1-q_g$, with q_d and q_g given by eq. (8) and (9), for the process initiated in the decay or growth phase, respectively. The survival probabilities as a function of the adsorption rate k are shown in Fig. 2. Note that for processes initiated in both the growth and decay phase, there is a minimum adsorption rate below which the survival probability is zero regardless of the phase in which the process is initiated, which corresponds to $k_{min}=\gamma(t_1+t_0)/(5t_1-t_0)$ computed from $R_0<1$ (cf. eq. (10)). k_{min} is an increasing function of γ, shown in Figs. 2a and b, which is consistent with our biological intuition: if phage λ die more rapidly, the infection/adsorption rate should be larger to ensure survival.

For processes initiated in the decay phase, as shown in Fig. 2a, there is a maximum adsorption rate k_{max} above which we do not expect survival. The chain of infection initiated by phage in the decay phase dies off at rate $k+\gamma$ before rescue in the growth phase. We observe from the probabilities of survival shown in Fig. 2a that, as a result, the range $k_{min}<k<k_{max}$ wherein survival is possible, shrinks.

We note no such k_{max} if we initiate the process in the growth phase. Fig. 2b shows that for large $k>\gamma$, survival is guaranteed: the death rate during the decay phase is not significant enough to eliminate the viral population following growth at ≈ 5 times the death rate.

However, in natural circumstances one would expect the decay phase (duration t_0) to last much longer than the growth phase (duration t_1). To investigate the role of the durations t_0 and t_1 we consider the survival probabilities depending on the fraction of time spent in the growth phase, $\sigma=t_1/(t_0+t_1)$,

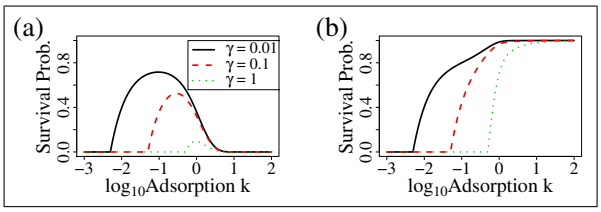

Fig. 2. Probability of survival as a function of the adsorption rate k in a process initiated with a single phage λ viral particle, for different values if the phage λ death rate γ. Time spent in the growth and decay phases is set to $t_0=t_1=1$ day. (a) Process initiated during decay phase; (b) process initiated in the growth phase.

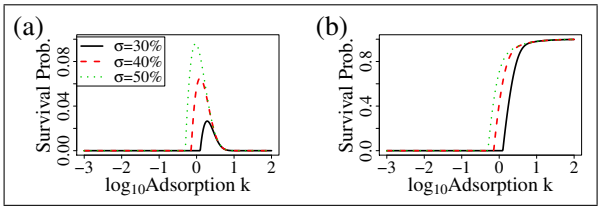

Fig. 3. Probability of survival as a function of the adsorption rate k in a process initiated with a single phage λ viral particle, for different ratios of time spent in the growth phase $\sigma=t_1/(t_0+t_1)$, assuming the phage λ death rate $\gamma=1$ day^{-1} and duration of the decay phase $t_0=1$ day. (a) Process initiated during decay phase; (b) process initiated in the growth phase.

see Fig. 3. Using R_0, eq. (10), one can show that for $\sigma<1/6\approx 17\%$, there can be no growth, since $R_0<1$ for $5t_1\le t_0$. We note that the qualitative results observed for $t_0=t_1=1$ day, Fig. 2, remain: for large adsorption rate $k>k_{max}$, processes initiated in the decay environment can't survive (Fig. 2a), while processes initiated in the growth environment are guaranteed to survive (Fig. 2b). In both cases there is a minimum k_{min} below which survival is impossible; from $R_0<1$ (eq. (10)), $k_{min}=(\gamma t_0-(1-\sigma))/(t_0(6\sigma-1))$, which decreases with increasing σ. The decrease is unsurprising: larger σ indicates more time spent in the growth phase, improving odds of survival.

Note that, for processes initiated in the decay environment, the k_{max} above which survival is impossible seems insensitive to σ, see Fig. 3a. Therefore, as σ decreases, i.e., as the time spent in the growth phase decreases, the range of adsorption rates k that permit survival decreases.

Since we expect $t_0>t_1$ outside of experimental contexts, it is more likely that the process initiates during a decay phase. For processes initiated in the decay phase, there is an optimal adsorption rate $k=k_*$ for which the probability of survival is maximized, see Figs. 2a and 3a. We can compute these optima k_* numerically by maximizing the probability of survival $1-q_d$ or minimizing the probability of extinction q_d, where q_d is given by eq. (8).

The optimal adsorption rate k_* is plotted against the phage λ death rate γ for different fractions of time spent in the growth phase, σ, in Fig. 4a. We observe, for fractions σ considered, that the optimal adsorption rate is not very sensitive to σ. Far more significant is the phage λ death rate γ. For larger, more rapid γ, the adsorption rate k, and therefore the optimum k_*, must increase for the infection expansion during the growth phase to outpace the probability

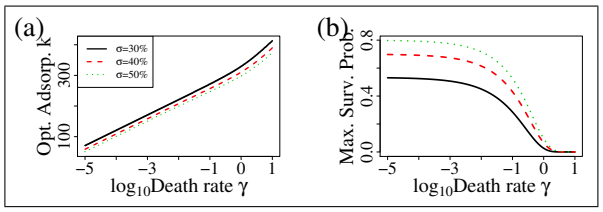

Fig. 4. Maximal survival probability and optimal adsorption rate as a function of the phage λ death rate γ for processes initiated in the decay phase, for different ratios of time spent in the growth phase $\sigma = t_1/(t_0+t_1)$. (a) Optimal adsorption rate k, defined as the optimal adsorption rate that maximizes the probability of survival. (b) Maximum probability of survival.

that the phage will die first. But observe from Figs. 2a that as γ increases, the survival probability decreases. For γ very large, the optimal adsorption rate k_* is moot: Fig. 4b shows the maximum survival probability permitted by the optimum k_*, which goes to zero for γ large. Thus, from a practical perspective the optimal k_* is only of value for phage λ death rate γ sufficiently small (for our parameters, $\gamma \lesssim 1$ per day).

III. MODEL 2: OPTIMAL ADSORPTION IN A RANDOM ENVIRONMENT

A. Model

In Sec. II, we assumed that the times spent in the growth and decay phases are fixed. We now assume that the time spent in each phase is sampled from a continuous probability density function, more representative of phage λ dynamics in a random environment.

As in the prescribed environment case, we compute the probability of extinction starting with n phage λ and use that probability to study optimal adsorption k. Again we assume the burst size $B = 6$ phage λ. We then briefly discuss sensitivity to remaining parameters.

B. Analysis

In order to calculate the probability that an infection chain initiated by n phage λ goes extinct as $t \to \infty$, we exploit the cyclic nature of the changing environment. We follow the same approach as above, computing the probability generating function for the number of viral particles produced in a single growth-then-decay or decay-and-growth time window, with the important difference that the time spent in each of these phases is not fixed. Though the calculations in the prescribed environment case were exact, in this random environment case, our predictions will be approximations. We consider the period consisting of a decay phase followed by a growth phase, and vice versa.

Expected progeny PGF: Let $f_d(t)$ be the probability density function for the time spent in the decay phase, and $f_g(t)$ be the probability density function for the time spent in the growth phase, nonzero for $0 \le t < \infty$. Assume these are independent. $\Psi_g(x;t_0,t_1)$ and $\Psi_d(x;t_0,t_1)$, in eq. 7 and 6 respectively, are the PGFs for the for the number of viral particles at the end of one period, starting with a single phage λ, given a decay phase duration t_0 and growth phase duration t_1. Note that we've made the dependence of the PGFs on the durations t_0 and t_1 explicit. Since now t_0 and t_1 are random variables, with corresponding probability densities $f_d(t)$ and $f_g(t)$, we can compute the expected value of the PGF at the end of one period. The expected PGF can be used to compute the expected distribution on the number of viral particles at the end of one period.

The PGF for the expected distribution on the number of phage λ, at the end of one period starting in the decay phase ($0 \le t < t_0$) followed by a growth phase ($t_0 \le t < \infty$), is

$$\begin{aligned}\Phi_d(x) &= \int_0^\infty \int_{t_0}^\infty \Psi_d(x;t_0,\tau-t_0) f_d(t_0) f_g(\tau-t_0)\, d\tau dt_0 \\ &= \int_0^\infty \int_0^\tau \Psi_d(x;t_0,\tau-t_0) f_d(t_0) f_g(\tau-t_0)\, dt_0 d\tau, \quad (11)\end{aligned}$$

exchanging the order of integration, where $\Psi_d(x;t_0,t_1)$, given by eq. (6), taking times t_0 and t_1 spent in the decay and growth phases, respectively, as random variables. As before the subscript d indicates initialization in the decay phase.

If we start instead in the growth phase, so the period consists of a growth phase ($0 \le t < t_1$) followed by a decay phase ($t_1 \le t < \infty$), the PGF for the expected distribution on the number of viral particles is

$$\begin{aligned}\Phi_g(x) &= \int_0^\infty \int_{t_1}^\infty \Psi_g(x;\tau-t_1,t_1) f_d(\tau-t_1) f_g(t_1)\, d\tau dt_1 \\ &= \int_0^\infty \int_0^\tau \Psi_g(x;\tau-t_1,t_1) f_d(\tau-t_1) f_g(t_1)\, dt_1 d\tau, \quad (12)\end{aligned}$$

again exchanging the order of integration, where the subscript g indicates initialization in the growth phase. $\Psi_g(x;t_0,t_1)$ is given by eq. (7), taking times t_0 and t_1 as random variables.

Probability of extinction: The probability that the process will go extinct as $t \to \infty$ is the root of the equations $q = \Phi_{d,g}(q)$. Here we find the approximation: the PGFs eq. (11) and (12) are for the expected number viral particles produced at the end of a decay/growth or growth/decay period, respectively. The roots of $q = \Phi_d(q)$ and $q = \Phi_g(q)$ are therefore "expected" probabilities of extinction.

This extinction probability q depends on the phase, decay or growth, in which the process is initiated. Unlike the prescribed environment case, we cannot compute an analytic form for q, except for in special case densities $f_d(t)$ and $f_g(t)$ (e.g. uniform density). Therefore to compute the probability of extinction starting in a decay environment, $q_d^{(r)}$, or starting in a growth environment, $q_g^{(r)}$, we solve the equations $q_d^{(r)} = \Phi_d(q_d^{(r)})$ and $q_g^{(r)} = \Phi_g(q_g^{(r)})$ numerically.

Optimal Adsorption k_*: As in the prescribed environment case, we can compute the optimal adsorption rate k_*. We compute $k_* = k$ that minimizes $q_d^{(r)}$ and $q_g^{(r)}$ numerically from the roots of $q_d^{(r)} = \Phi_d(q_d^{(r)})$ and $q_g^{(r)} = \Phi_g(q_g^{(r)})$, respectively.

Basic reproduction number: Using eqs. (11) or (12) we can compute the expected number of progeny, R_0, at the end of one period. For example if we assume that that $t_0 \sim \text{Exp}(k_0)$ and $t_1 \sim \text{Exp}(k_1)$, from $R_0 = \Phi_b'(1) = \Phi_g'(1)$ we recover

$$R_0 = \frac{k_0 k_1}{(k_1 - 5k + \gamma)(k_0 + k + \gamma)} \quad \text{for } k_1 > 5k - \gamma \qquad (13)$$

with R_0 not finite for $k_1 < 5k - \gamma$. The condition $k_1 < 5k - \gamma$ arises from the different exponential rates: the mean exponential growth rate during the growth phase, $5k - \gamma$, is greater than the mean exponential switching rate to the decay phase k_1 and therefore, the average number of particles at the end of a period is not finite.

As before, from eq. (13) we can predict parameter thresholds below which we predict that the phage λ infection chains will die out. In particular we can find the minimal adsorption rate k below which our model predicts no growth, $k_{min} = ((k_1 - 5k_0 - 4\gamma) + \sqrt{(k_1 - 5k_0 - 4\gamma)^2 + 20\gamma(k_1 + k_0 + \gamma)})/5$.

C. Results

In the analysis, Sec. III-B, we made no assumption on the probability density associated with time spent in the growth or decay environments (with the exception of the calculation of R_0 in eq. (13)). For the following results we assume $t_0 \sim \text{Exp}(k_0)$ and $t_1 \sim \text{Exp}(k_1)$, where k_0 and k_1 are the exponential rates of switching from the decay to growth, and growth to decay, phases respectively. Thus $f_d(t) = k_0 e^{-k_0 t}$ and $f_g(t) = k_1 e^{-k_1 t}$ in eqs. (11) and (12). We leave more realistic densities, e.g. lognormal or gamma, for future investigation.

We recapitulate results from the prescribed environment change case (Figs. 2-4), now assuming random environment change (Figs. 5-7). We use $k_0 = k_1 = 1$ per day in Fig. 5, so the mean time spent in each phase is 1 day, matching the prescribed environment change parameters (cf. Sec. II), so that results are comparable. We now define σ as the fraction of the average times spent in the growth phase, $\sigma = (1/k_1)/(1/k_0 + 1/k_1) = k_0/(k_0 + k_1)$, keeping $k_0 = 1$ per day, and consider $\sigma \leq 0.5$ since in natural circumstances one would expect the decay phase (mean duration $1/k_0$) to last much longer than the growth phase (mean duration $1/k_1$).

We note one important qualitative change in the phage λ survival results. If we initiate the process in the growth environment and compare the fixed and random environment models, Figs. 2b and 5b, respectively, we note that stochasticity guarantees extinction (Fig. 5b) for large adsorption rates k that previously guaranteed survival (Fig. 2b). Likely the primary cause of this difference is the assumption of an exponential density on time spent in the growth or decay phases, since there is non-zero probability that the duration is 0. Note that the behavior of the survival probability for large k is not sensitive to choice of γ.

However stochasticity induces quantitative changes in our predictions of phage λ survival as well.

(1) Stochasticity permits phage λ survival at a greater breadth of adsorption rates k (note that the x-axis ranges are different in Figs. 2 and 5), since the median time spent in the decay environment is $\ln(2)/k_0 \approx 0.69$ days, less than the mean time of $1/k_0 = 1$ day. That is, for more than half the realizations, the duration spent in the decay environment is less than the mean, improving the probability of survival.

(2) If the process is initiated in the growth or decay phase, the probability of survival decreases with σ, as shown in Fig. 6a and b. However we note that stochasticity lessens this sensitivity, with maximum survival probabilities increasing $\approx 1.3\times$, comparing $\sigma = 30\%$ to $\sigma = 50\%$ (Fig. 6); the comparable increase is nearly 10-fold in the prescribed environment (Fig. 3).

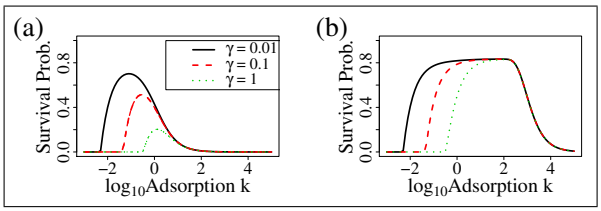

Fig. 5. Probability of survival as a function of the adsorption rate k in a process initiated with a single phage λ viral particle, for different values if the phage λ death rate γ. Rates of switching between the growth and decay phases set to $k_0 = k_1 = 1$ per day. (a) Process initiated during decay phase; (b) process initiated in the growth phase.

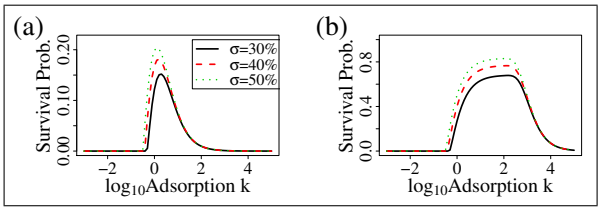

Fig. 6. Probability of survival as a function of the adsorption rate k in a process initiated with a single phage λ viral particle, for different ratios of time spent in the growth phase $\sigma = k_0/(k_0 + k_1)$, assuming the phage λ death rate $\gamma = 1$ day^{-1} and mean duration of the decay phase $1/k_0$=1 day. (a) Process initiated during decay phase; (b) process initiated in the growth phase.

Our main objective is the optimal adsorption rate k_*, now assuming the environment switching occurs at exponentially-distributed times. Note that if we initiate the process in the growth phase, k_* is not very sensitive to either phage λ death rate γ (Fig. 5b) nor to the average fraction of time spent in the growth phase σ (Fig. 6b). Further, outside of experimental contexts, we expect the duration of decay phases, when bacteria are not metabolically active, to be longer than the duration of the growth phase. We therefore focus on the optimum k_* for processes initiated during the decay phase.

To compute the optimum, we numerically calculate the value $k_* = k$ that minimizes $q_d^{(r)}$ and $q_g^{(r)}$, the numerically-computed roots of $q_d^{(r)} = \Phi_d(q_d^{(r)})$ and $q_g^{(r)} = \Phi_g(q_g^{(r)})$, with $\Phi_d(x)$ and $\Phi_g(x)$ given by eqs. (11) and (12), respectively.

Stochasticity induces qualitative changes in our optimal adsorption rate predictions (cf. Figs 4 and 7):

(1) While the maximum survival probabilities occur at approximately the same values of k, for small γ, decaying to zero for large gamma, stochasticity extends the range of phage λ death rates γ over which survival is possible: for our parameters, the probability of survival goes to zero for γ just above 1 per day assuming a prescribed environment (Fig. 4a), which stochasticity extends to $\gamma \gtrsim 100$ per day (Fig. 7a). We attribute this increase to the exponential density assumption, since median time spent in the decay environment is $\ln(2)/k_0 \approx 0.69$ days is less than the mean of $1/k_0 = 1$ day.

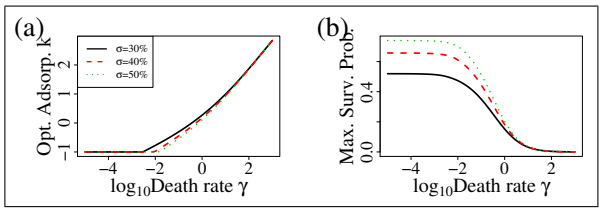

Fig. 7. Maximal survival probability and optimal adsorption rate as a function of the phage λ death rate γ for processes initiated in the decay phase, for different ratios of time spent in the growth phase $\sigma = k_0/(k_0+k_1)$. (a) Optimal adsorption rate k, defined as the optimal adsorption rate that maximizes the probability of survival. (b) Maximum probability of survival.

(2) Stochasticity introduces sensitivity in optimal adsorption rate k_*. For large γ, assuming exponentially-distributed environment change times, the optimal k_* is $O(10^2)$, as it is in the prescribed case for our range $10^{-5} \leq \gamma \leq 10$ per day (cf. Fig. 4b and Fig. 7b). However for small γ, $\gamma \lesssim 10^{-2}$ per day, the optimal k_* is very small and approximately fixed, increasing to $O(10^2)$ for $\gamma \gtrsim 10^{-2}$ per day (Fig. 7b), before the probability of survival goes to zero (Fig. 7a).

IV. CONCLUSIONS

Our aim is to develop a theoretical understanding of the optimal, intermediate adsorption rates of phage λ in changing environments. We created a simple branching process model to approximate phage λ dynamics. We define the optimal adsorption rate k_* as the rate which maximizes the probability of survival, and derived probabilities of survival from a simple, branching process model. In the case where environment change is random, modeling natural conditions, our probability of survival (1 - probability of extinction) only approximates model outcomes. However, in the case where environment change is prescribed and periodic, modeling experimental conditions, our probability of survival is exact. To our knowledge these are novel calculations for branching processes in changing environments.

In deriving our model, we assumed that host cell availability is constant. Recall that we actually maximize the re-scaled adsorption rate $k = \tilde{k}H$, where H is the number of host cells. Thus the scale of optimal adsorption rates k_*, up to $O(10^2)$ per day, is reasonable. Constant host cell availability is a key assumption, which may be built into an experimental setup, but is unlikely in a natural context. Indeed, bacterial populations may enter a decay, stationary, phase by reaching carrying capacity, when nutrients are exhausted, cells stop dividing, and are generally unable to support phage reproduction [1]–[3]. Large viral populations should also lead to dwindling host bacteria populations, which may in turn alter the optimal adsorption rate for phage λ virus survival. Future models will account for these dynamics, for example relaxing the constant host cell assumption, using a logistic growth model and mass-action infection of host cells.

Future investigations will also examine sensitivity of results to infected bacterial death rate δ, in particular making the more realistic assumption that bacterial cell death occurs at a higher rate in the decay phase, and infected bacterium viral burst size B. Since increasing viral burst size B enhances the probability that there remains virus at the end of a decay phase, realistic, larger values of B will yield non-zero survival probabilities over a larger range in re-scaled adsorption rate k, and decrease the optimal k_*. We will also consider alternative probability densities for environment switch and investigate the goodness of our approximations.

Nonetheless, even with this simple model we recovered optimal, intermediate adsorption rates k_* (see Figs. 2a, 3a, 5, 6), reproducing observations. Our results assuming prescribed environment change can be verified experimentally, for example with serial passage experiments. We showed that stochasticity improves survival probabilities and also the breadth in adsorption rates over which survival is possible. We therefore anticipate this difference when comparing experimental results with observations.

REFERENCES

[1] M. Adams, *Bacteriophages*. New York: Interscience Publishers, 1959.
[2] M. Woody and D. Cliver, "Effects of temperature and host-cell growth-phase on replication of F-specific RNA coliphage Q-Beta," *Appl. Environ. Microbiol.*, vol. 61, pp. 1520–1526, 1995.
[3] S. Gross, "Nutritional requirements for the reproduction of coliphage T2 in a strain of Escherichia coli." *J. Bacteriol.*, vol. 68, pp. 43–49, 1954.
[4] J. Dennehy, "What can phages tell us about host-pathogen coevolution?" *Int. J. Evol. Biol.*, vol. 2012, p. 396165, 2012.
[5] S. Labrie, J. Samson, and S. Moineau, "Bacteriophage resistance mechanisms," *Nat Rev Microbiol*, vol. 8, pp. 317–327, 2010.
[6] I. Aviram and A. Rabinovitch, "Dynamical types of bacteria and bacteriophages interaction: Shielding by debris," *J Theor Biol*, vol. 251, pp. 121–136, 2008.
[7] A. Rabinovitch, I. Aviram, and A. Zaritsky, "Bacterial debris - an ecological mechanism for coexistence of bacteria and their viruses." *J Theor Biol*, vol. 224, pp. 377–383, 2003.
[8] R. Hendrix and R. Duda, "Bacteriophage lambda PaPa - not the mother of all lambda phages," *Science*, vol. 258, pp. 1145–1148, 1992.
[9] R. Gallet, Y. Shao, and I. Wang, "High adsorption rate is detrimental to bacteriophage fitness in a biofilm-like environment," *BMC Evol Biol*, vol. 9, p. 241, 2009.
[10] R. Gallet, T. Lenormand, and I. Wang, "Phenotypic stochasticity protects lytic bacteriophage populations from extinction during the bacterial stationary phase," *Evolution*, vol. 66, pp. 3485–3495, 2012.
[11] J. D'Souza and J. Biggins, "The supercritical Galton-Watson process in varying environments," *Stoch Process Their Appl*, vol. 42, pp. 39–47, 1992.
[12] H. Cohn and P. Jagers, "General branching processes in varying environment," *Ann Appl Probab*, 1994.
[13] V. Vatutin, E. Dyakonova, P. Jagers, and S. Sagitov, "A decomposable branching process in a Markovian environment," *Int J Stoch Anal*, vol. 2012, p. 694285, 2012.
[14] D. Gillespie, "Exact stochastic simulation of coupled chemical reactions," *J Phys Chem*, vol. 81, pp. 2340–2361, 1977.
[15] A. Alfonsi, E. Cances, G. Turicini, B. D. Ventura, and W. Huisinga, "Exact simulation of hybrid stochastic and deterministic models for biochemical systems," *INRIA Report No. 5435*, 2004.
[16] Y. Cao, D. Gillespie, and L. Petzold, "Efficient step size selection for the tau-leaping simulation method," *J Chem Phys*, vol. 124, p. 044109, 2006.
[17] S. Wu, J. Fu, and L. Petzold, "Adaptive deployment of model reductions for tau-leaping simulation," *J Chem Phys*, vol. 142, p. 204108, 2015.
[18] M. Nowak and R. May, *Virus dynamics: Mathematical principles of immunology and virology*. Oxford University Press, 2001.
[19] S. Karlin and H. Taylor, *A First Course in Stochastic Processes*. Academic Press, 1975.
[20] T. Harris, *The Theory of Branching Processes*. Dover, 1989.