Viral Fitness Across a Continuum from Lysis to Latency

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The prevailing paradigm in eco-evolutionary studies of viruses and their microbial hosts is that the reproductive success of viruses depends on the proliferation of the "predator", i.e., the virus particle. Yet, viruses are obligate intracellular parasites, and the virus genome – the actual unit of selection – can persist and proliferate from one cell generation to the next without lysis and the production of new virus particles. Here, we propose a unified theory of virus-microbe dynamics that addresses the inherent tension between horizontal and vertical modes of viral reproduction. In doing so we propose a cell-centric metric for quantifying the 'fitness' of viruses that infect microorganisms. This cell-centric metric takes an epidemiological perspective that enables direct comparison of viral strategies characterized by obligate killing of hosts (e.g., via lysis), persistence of viral genomes inside hosts (e.g., via lysogeny), and strategies along a continuum between these extremes (e.g., via chronic infections). As a result, we can identify those environmental drivers, life history traits, and key feedbacks that govern variation in viral propagation in nonlinear population models. For example, we identify threshold conditions given relatively low cell densities and relatively high cell growth rates in which lysogenic and other persistent strategies have higher potential viral reproduction than lytic strategies. By focusing on the proliferation of viral genomes inside cells instead of virus particles outside cells, the present theory unifies the study of eco-evolutionary drivers of viral strategies in natural environments.

I. INTRODUCTION

Viral infections begin with the physical interaction between a virus particle (the "virion") and the host cell. Infection dynamics within the cell often culminate in lysis, i.e., the active disruption of the integrity of the cell surface, leading to the death of the host cell and the release of virus particles [1, 2]. At population scales, virus-induced lysis can be a significant driver of microbial mortality, whether in the oceans, lakes, soil, extreme environments, or in plant and animal microbiomes [3–9]. As a result, studies of the ecological influence of viruses of microorganisms have, for the most part, focused on the lytic mode of infection. However, the spread of viruses through microbial populations need not involve the immediate lysis of the infected cell.

Indeed, many viruses have alternative strategies. Temperate phage – like phage λ – can integrate their genomes with that of their bacterial hosts, such that the integrated viral DNA, i.e., the prophage, is replicated along with the infected cell, i.e., the lysogen [10]. Filamentous phage, like M13, infect cells and persist episomally [11, 12], whereby the genome of M13 is replicated inside infected cells and then packaged into particles which are released extracellularly without necessarily inducing cell death [13, 14]. An analogous mode of "chronic" infection has been observed in archaeal infections [15]. These examples raise a critical question (see [16–18]): are temperate or chronic modes prevalent or rare in nature?

More than a decade ago, studies of marine, hydrothermal, and soil environments suggested that lysogeny could be more prevalent than assumed based on culture-based analysis of virus-microbe interactions [19–22]. This evidence has been augmented by recent studies identifying viral dark matter - including integrated and extrachromosal viral sequences - in microbial genomes [23–26]. Yet, despite increasing evidence of the relevance of persist infections *in situ* there is no common metric to compare the context-dependent fitness of lytic, temperate, and other chronic viral strategies.

A landmark theoretical study provides a setting off point for investigating the potential benefits of non-lytic strategies [27]. This study proposed that temperate phage, like phage λ could persist over the long term if prophage integration directly enhanced host fitness or enhanced resistance to infections by other lytic phage ("superinfection immunity"). The same study predicted that oscillations in population abundances could provide an ecological "niche" for temperate phage. In essence, if bacterial densities were too low to support the spread of lytic phage, then temperate phage already integrated into lysogens could persist until "conditions become favorable for the bacteria to proliferate" [27]. Yet this finding does not exclude the possibility that lytic strategies could out-compete temperate strategies – even if lysis at low densities leads to population collapse.

More recently, efforts to understand why viruses should be temperate have drawn upon the mathematical theory of portfolio balancing [28]. According to portfolio balancing theory, the temperate strategy enables viruses to expand rapidly during stable periods for hosts (via

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lysis) and mitigate risks of population collapse, particular during unfavorable periods for hosts (via lysogeny). Such arguments rely on generalized estimates of long-term growth rates without invoking the nonlinear feedback mechanisms underlying virus-microbe interactions. Moreover, a focus on *long-term* estimates of growth does not directly address whether killing a microbial host cell is the advantageous strategy for a virus at a given *moment* in time. As noted by [28], ecological models that incorporate feedback mechanisms of virus-host interactions are required to understand the viability of realized viral strategies.

Viruses have evolved many mechanisms to propagate with microbial hosts. Here, we use the word "strategies" to denote the *type* of mechanism underlying viral propagation. Comparing the relative fitness of viral strategies requires some means to quantify reproduction and survival across an entire viral life cycle, even if the molecular details, host strain, or virus strain differs. Drawing upon the foundations of mathematical epidemiology, here we propose a theory to quantify viral fitness in which viral proliferation is measured in terms of *infected cells* instead of virus particles. In doing so, we show how this theory can predict and explain a continuum of infection strategies observed in different environmental contexts.

II. ON HORIZONTAL AND VERTICAL TRANSMISSION

Viruses are obligate intracellular parasites. As such, virus-microbe dynamics can be re-cast in terms of the spread of an infectious disease through a microbial population. The risk for the spread of an infectious disease can be quantified in terms of the basic reproduction number, $\mathcal{R}_0$, "arguably the most important quantity in infectious disease epidemiology" [29]. In mathematical epidemiology, $\mathcal{R}_0$ is defined as the average number of new infected individuals caused by a single (typical) infected individual in an otherwise susceptible population [30]. Measuring $\mathcal{R}_0$ is the *de facto* standard for assessing pathogen invasion, *e.g.*, when $\mathcal{R}_0 > 1$ then a pathogen is expected to increase its relative abundance in a population [31, 32]. Thus far, estimates of $\mathcal{R}_0$ have had limited application in the study of the ecology of viruses of single-celled microorganisms, in part because counts of the number of *virus particles* have been used as a proxy for eco-evolutionary success (e.g., [33]). However, the production of new virus particles does not, in and of itself, constitute a new infection. In addition, particle production is not the only way for viruses of microbes to proliferate at the population scale.

The virocell paradigm provides a path forward towards a unified notion of viral fitness [34, 35]. The paradigm centers on the idea that the "real living [viral] organism" [34] is an infected cell actively producing new virions, i.e., the "virocell". In contrast, conventional definitions of a virus refer to the physical properties of the virus particle, e.g., nucleic acids surrounded by a protein coat. As a consequence, it would seem logical to surmise that the viability of a viral strategy should be measured in terms of the number of new virocells produced.

Here we reconcile the virocell and conventional paradigms by adapting definitions of $\mathcal{R}_0$ to the study of viruses of microorganisms. Specifically, we propose the following definition:

> $\mathcal{R}_0$: *the average number of new infected cells produced by a single (typical) infected cell and its progeny virions in an otherwise susceptible population.*

This definition counts viral reproduction in terms of infected cells, *i.e.*, with progeny viral genomes in them, rather than in terms of virus particles. For reasons that we will make clear in subsequent sections, this definition of $\mathcal{R}_0$ includes a critical asymmetry: we use infected cell, and not virion, production to measure viral spread. Characterizing the dynamics of virus genomes inside cells and virus particles outside of cells also enables comparisons amongst viruses with different life cycles. In particular, this definition accounts for infections caused by "vertical" transmission (i.e., from mother to daughter cell) and those caused by "horizontal" transmission (i.e. from an infected cell to another susceptible cell in the population). Next, we explain how to calculate $\mathcal{R}_0$ and conditions for invasion within nonlinear models of virus and microbial population dynamics.

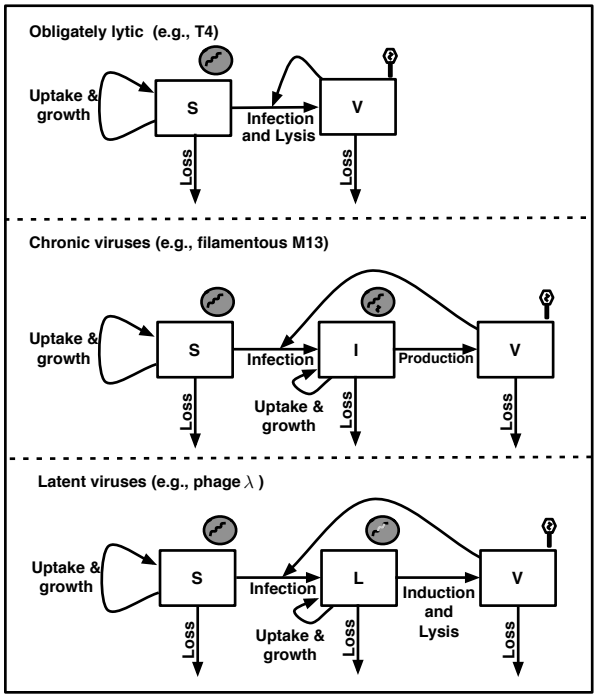

FIG. 1: Population models for three types of viral strategies: obligately lytic, chronic viruses, and latent viruses. The top and bottom panels are modified from [36].

III. OBLIGATELY LYTIC VIRAL STRATEGIES – A BASELINE FOR COMPARISON

We begin our examination of obligately lytic strategies given a virion-centric perspective. Obligately lytic viruses infect and lyse their microbial hosts, thereby modifying the population densities of viruses and cells. Virus-host interactions can be represented via the following nonlinear differential equations (see Figure 1 for this and other model schematics):

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \overbrace{bS\left(1-S/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell washout}} \\ \frac{\mathrm{d}V}{\mathrm{d}t} &= \overbrace{\beta\phi SV}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}\end{aligned} \tag{1}$$

This system of equations represents changes in the density of virus particles, V, and susceptible microbial cells, S, using a resource-implicit model of bacterial growth. Model variants include terms representing nutrient uptake, fixed delays between infection and lysis, and other forms of cell mortality, e.g., due to grazing [36–38]. Given the model in Eq. (1), we are interested in determining the likelihood that a virus will spread when introduced to a susceptible cellular population.

The linearized virus population dynamics near the virus-free steady state are:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \left(\beta\phi S^* - \phi S^* - m\right)V \tag{2}$$

where the steady-state density is $S^* = K(1-d/b)$. This equation represents the potential exponential growth or decay of viruses. The growth constant is the term in the parentheses, $\beta\phi S^* - \phi S^* - m$. When this constant is greater than 0 then virus particles should increase in number, whereas when this constant is less than 0 then virus particles should decrease in number. In other words, viruses should spread when $\beta\phi S^* > \phi S^* + m$ or, alternatively, when $\mathcal{R}_{hor} > 1$ where

$$\mathcal{R}_{hor} \equiv \beta\left(\frac{\phi S^*}{\phi S^* + m}\right) \tag{3}$$

is the (exclusively) horizontal contributions to the basic reproduction number. This inequality can be understood in two ways (see Figure 2).

First, consider a single virion. Virions successfully adsorb to susceptible hosts at a rate ϕS^*. In contrast, virions decay at a rate m. When two independent, random processes take place concurrently, the probability of one event - in this case adsorption - taking place before the other - in this case decay - is the ratio of one process relative to the sum of the rates of all processes. The factor $\phi S^*/\left(\phi S^* + m\right)$ denotes the probability that a virion is adsorbed before it decays. The present model assumes that adsorption implies successful infection and lysis. Hence, this probability must be multiplied by the burst size β, i.e., the number of new virions released, to yield the average number of new infectious virions produced by a single virion in a susceptible host population. This product is equal to the basic reproduction number, $\mathcal{R}_{hor}$. When the basic reproduction number is greater than 1, then a single virion produces, on average, more than one virion, of which each in turn produces, on average, more than one virion and so on. This process leads to exponential proliferation of virus particles, at least initially (see [36] for a similar derivation). As is evident, the spread of an obligately lytic virus depends on its life history traits and the ecological conditions (see Figure 3).

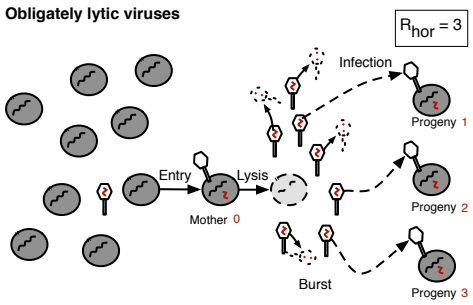

FIG. 2: Schematic of cell-centric counting of the reproduction of obligately lytic viruses. Here, the mother virus generates dozens, if not hundreds of virions, most of these decay or are otherwise removed from the environment. Only three virions infect cells, these are progeny viruses, aka new mothers. Hence, the horizontal $\mathcal{R}_0$ of this virus is 3.

Second, we can revisit this same calculation beginning with an assumption that there is a single infected cell in an otherwise susceptible population. In that event, the infected cell produces β virions, of which only a fraction $\phi S^*/\left(\phi S^* + m\right)$ are adsorbed before they decay. The product represents the number of newly infected cells produced by a single infected cell in an otherwise susceptible population. The product is the same, but in this alternative approach we have counted proliferation in terms of a viral life cycle that starts and ends inside cells, requiring that contributions "complete the cycle". More generally, Figure 3 shows how viral proliferation varies with life history traits (in this case, the burst size) and the ecological context (in this case, the initial cell density). As is apparent, there is a threshold between regimes of viral extinction and proliferation corresponding to the transition of $\mathcal{R}_0$ from below to above one.

Thus far, we have not considered the explicit population dynamics of infected cells. In the Appendix we show that including an explicitly modeled infectious cell state leads to the same qualitative result. The only change is that the horizontal spread includes another factor: the probability that an infected cell releases virions before it dies or is washed out of the system by some other means. If η is the reciprocal of the average latent period and d' is the loss rate of infected cells, then only a fraction $\eta/(\eta+d')$ of infected cells will release virions before being

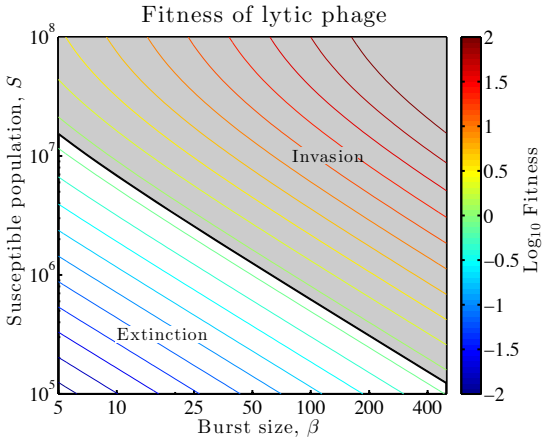

FIG. 3: Virus reproduction as a function of burst size and susceptible cell density.The contours denote the $\log_{10}$ of $\mathcal{R}_0$, as measured using Eq. (3), given variation in burst size, β, and susceptible cell density, S. Viruses invade when $\mathcal{R}_{hor} > 1$ or, equivalently when $\log_{10} \mathcal{R}_{hor} > 0$. Contours denote combinations of (β, S^*) of equivalent $\mathcal{R}_{hor}$. Additional parameters that affect viral reproduction are $\phi = 6.7 \times 10^{-10}$ ml/hr and $m = 1/24$ hr^{-1}.

washed out of the system. As such, the corrected basic reproduction number for obligately lytic viruses is:

$$\mathcal{R}_{hor} = \beta \left(\frac{\phi S^*}{\phi S^* + m} \right) \left(\frac{\eta}{\eta + d'} \right) \tag{4}$$

Although both interpretations - the virion-centric and the cell-centric - lead to equivalent estimates of $\mathcal{R}_0$ for obligately lytic viruses, we will use the cell-centric definition to unify comparisons across a spectrum of viral strategies.

IV. LATENT VIRAL STRATEGIES

In this section we consider the dynamics of latent viral strategies, such as temperate phage, in which proliferation may be either horizontal or vertical (but not both simultaneously). We model the dynamics of latent viruses using the following set of nonlinear differential equations:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \overbrace{bS\left(1 - N/K\right)}^{\text{logistic growth}} - \overbrace{\phi S V}^{\text{infection}} - \overbrace{dS}^{\text{cell death}} \\
\frac{\mathrm{d}L}{\mathrm{d}t} &= \overbrace{qb'L\left(1 - N/K\right)}^{\text{lysogen growth}} + \overbrace{\phi S V}^{\text{infection}} - \overbrace{p\eta L}^{\text{lysis}} - \overbrace{d'L}^{\text{cell death}} \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \overbrace{\beta p \eta L}^{\text{lysis}} - \overbrace{\phi S V}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}
\end{aligned} \tag{5}$$

This system of equations represents changes in the density of virus particles, V, lysogens, L, and susceptible microbial cells, S, in which the total density of cells is denoted as $N = S + L$. In this formulation, the relative rate of lysogenic growth and cellular lysis is controlled by the scaling factors q and p. When $q = 1$ and $p = 0$ then all infections are strictly latent and only lead to lysogenic growth. In contrast, when $q = 0$ and $p = 1$ then all infections are strictly lytic and only lead to cellular lysis. This is a variant of a nutrient-explicit formulation considered as part of an analysis of the tradeoffs underlying lysis and lysogeny for marine viruses [39]. Note that this model includes only a single infected state for cells; analysis of a related model, including detailed processes of integration and induction, will be the subject of follow-up work.

Using Eq. (5), we first consider the case $p = 0$ and $q = 1$ to focus on the vertical pathway. In the vertical pathway, virus genomes exclusively integrate with host cell genomes which can then be passed on to daughter cells. We use the cell-centric interpretation as before, and consider infection dynamics given a single lysogen in an otherwise susceptible population with no virus particles:

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \left(b' \left(1 - \frac{S^*}{K} \right) - d' \right) L \tag{6}$$

This exponential growth equation predicts that lysogens will spread in abundance as long as $\left(b' \left(1 - \frac{S^*}{K} \right) - d' \right) > 0$. We can rewrite this condition for proliferation as:

$$\mathcal{R}_{ver} = \frac{b' \left(1 - \frac{S^*}{K} \right)}{d'} > 1. \tag{7}$$

Here, the subscript denotes the fact that $\mathcal{R}_0$ is entirely derived from *vertical* transmission of viral genomes among lysogens.

The basic reproduction number also has a mechanistic interpretation. The term $b'(1 - S^*/K)$ represents the birth rate of lysogens, which decreases with increasing number of cells - whether susceptibles or lysogens. Given that d' is the death rate of lysogens, the term $1/d'$ denotes the average lifespan of an individual lysogen. Therefore, this reproduction number is equal to the average number of newly infectious cells produced in the lifetime of the original infection (see Figure 4). If this number is greater than one, then a single lysogen will beget more than one lysogen, on average, and those lysogens will do the same, and so on.

Measuring reproduction in this way also provides a mechanistic interpretation to the value of vertical transmission without invoking environmental fluctuations or other long-term measures of fitness. As is evident, lysogens reproduce more frequently when they are subject to less competition with hosts, i.e., when S^* is small relative to K. Given the value of S^* in the particular ecological model of Eq. (5), the basic reproduction number can be written as $\mathcal{R}_{ver} = (b'/d') \Big/ (b/d)$. Hence, if lysogens have more advantageous life history traits than do susceptible cells (as measured by a higher birth to death

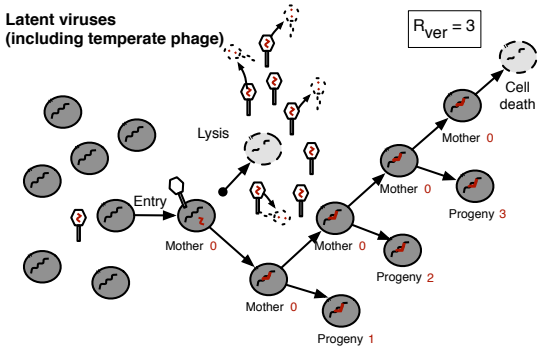

FIG. 4: Schematic of cell-centric counting of the reproduction of latent viruses, e.g., temperate phage. The mother virus could, in principle, lyse the cell or integrate its genome with that of the host. Here, the mother virus integrates and forms a lysogen. The lysogen divides three times before it is removed, thereby producing three daughter cells with virus genomes. The vertical $\mathcal{R}_0$ of this virus is 3.

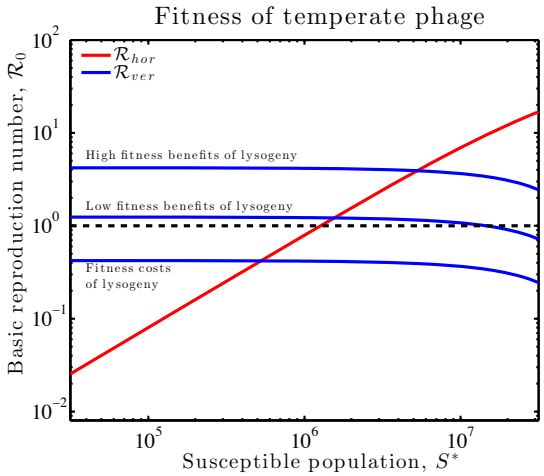

FIG. 5: Basic reproduction number of temperate viruses as a function of susceptible cell density. The increasing (red) line denotes the horizontal $\mathcal{R}_0$ if temperate phage infect then always lyse cells. The decreasing (blue) line denotes the vertical $\mathcal{R}_0$ if temperate viruses always integrate with their hosts. Relevant parameters are $\beta = 50$, $\phi = 6.7 \times 10^{-10}$ ml/hr, $K = 7.5 \times 10^7$ ml^{-1}, and $b' = 0.32$, 0.54 and 1 hr^{-1} as well as $d' = 0.75$, 0.44, and 0.24 hr^{-1} for the three lysogeny curves from bottom to top respectively.

rate ratio, i.e., b'/d' larger than b/d), then viruses can spread exclusively via vertical transmission. This benefit of lysogeny applies in the immediate term and provides direct support for how a lysogen that benefits its host can also benefit the virus. However, if lysogeny comes with a cost (i.e., b'/d' lower than b/d), then vertical transmission alone will not be enough for $\mathcal{R}_{ver} > 1$. More generally, note that $\mathcal{R}_{ver}$ is a monotonically decreasing function of S^*, such that increased abundances – all things being equal – diminishes the advantage for vertical transmission.

To consider horizontal transmission, consider the case where $p = 1$ and $q = 0$. In that case, analysis of the full model in Eq. (5) reduces to that of the obligately lytic virus already presented in Eq. (A5). This raises the question: does a strictly lytic or strictly lysogenic strategy have a higher basic reproduction number? Recall that the horizontal $\mathcal{R}_0$ is an *increasing* function of susceptible cell density, i.e., when there are more hosts then the value of horizontal transmission increases. The value of $\mathcal{R}_{hor}$ and $\mathcal{R}_{ver}$ cross at a critical value, S_c, which satisfies

$$\frac{b'\left(1-\frac{S_c}{K}\right)}{d'} = \frac{\beta\phi S_c}{\phi S_c + m} \tag{8}$$

For $S > S_c$, then $p = 1$ and $q = 0$ has the higher basic reproduction number, (i.e., horizontal transmission is favored) whereas for $S < S_c$, then $p = 0$ and $q = 1$ has the higher basic reproduction number, (i.e., vertical transmission is favored). Extending prior analysis, we identify threshold conditions separating out when lysis should be favored at high density vs. when lysogeny should be favored at low density (see Figure 5). The use of a cell-centric metric makes it evident that vertical transmission can be evolutionarily advantageous given low densities of permissive hosts without invoking group selection or long-term fitness (see [40]).

V. CHRONIC VIRAL STRATEGIES

Finally, we consider the dynamics of "chronic" virus strategies, or what have been termed "chronic" or "producer" strains in other contexts. We use the term chronic to denote those viruses that infect cells, are propagated along with the cell, and produce virions that are released from the cell without lysis, e.g, like filamentous phage M13. The dynamics of viruses, V, chronically infected cells, I, and susceptible microbial cells, S, can be modeled using the following system of nonlinear differential equations:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \overbrace{bS\left(1-N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}} \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \overbrace{b'I\left(1-N/K\right)}^{\text{logistic growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{d'I}^{\text{cell death}} \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \overbrace{\alpha I}^{\text{virion production}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}
\end{aligned} \tag{9}$$

in which the total number of cells is denoted as $N = S+I$. Although it can be remapped to the latency model, this system of equations represents distinct mechanistic processes, including establishment of a chronically infected cell and release of virions from chronically infected cells without lysis at a per-capita rate α. As such, we expect that both vertical and horizontal transmission can take place concurrently.

As before, consider a newly infected cell in an environment in which all other cells are susceptible and there are no additional virus particles. The chronic cell will remain viable for an average duration of $1/d'$. In that time, the chronic cell will produce new virions at a rate α, of which only $\phi S^*/(\phi S^* + m)$ will survive to enter another cell. This is the horizontal component of reproduction for the chronic cell. Concurrently in that time, the chronic cell will divide at a rate $b'(1 - N/K)$. This is the vertical component of reproduction for the chronic cell. Hence a chronic virus will spread at the population scale, on average, as long as

$$\mathcal{R}_{chron} \equiv \overbrace{\frac{\alpha}{d'}\left(\frac{\phi S^*}{\phi S^* + m}\right)}^{\text{horizontal}} + \overbrace{\frac{b'(1 - S^*/K)}{d'}}^{\text{vertical}} > 1. \quad (10)$$

This decomposition of reproduction into horizontal and vertical components (see Figure 6) enables simple and interpretable calculations (see Appendix for the next-generation matrix method and derivation).

This analysis shows how the spread of chronic viruses depends on both infected cell traits and virion-associated traits. As a consequence, it would suggest that chronic viruses should evolve adaptations to improve the sum of horizontal and vertical reproduction. Without trade-offs, this would lead to chronic viruses with arbitrarily high virion release rates and arbitrarily low cell death rates. Yet, there will likely be trade-offs. For example, increasing the virion production rate, α, may improve horizontal reproduction, but if doing so increases cell death, d', then the overall change in $\mathcal{R}_{chron}$ may be negative. As a result, it is possible that chronic viruses could have the largest reproduction number in an intermediate density regime (see example in Figure 7). Understanding the pleiotropic effects of changes to chronic virus genotypes may provide one route to characterizing the evolution of viral strategies in which both horizontal and vertical transmission rates operate concurrently [41].

VI. DISCUSSION

We have proposed a unified theoretical framework to calculate the spread of viral strategies across a continuum from lysis to lysogeny. By defining viral reproduction in terms of infected cells, we are able to directly compare the spread of obligately lytic viruses, latent viruses, and chronic viruses in the context of nonlinear population models (see Figure 1). The invasibility of a newly introduced viruses is measured in terms of the basic reproduction number, specifically adapted to the life cycle of viral infections – in which new cellular infections can arise through horizontal and vertical transmission.

At its core, the theoretical framework re-envisions life history theory for viruses that infect microorganisms. In our calculations, a focal virus genome inside a cell can be thought of as a "mother virus". These mother viruses

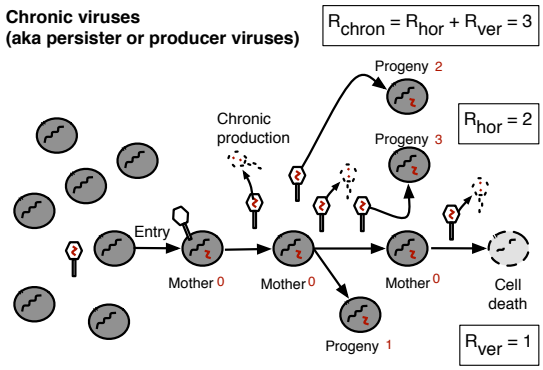

FIG. 6: Schematic of cell-centric counting of the basic reproduction number of chronic viruses. In this example, the mother virus divides once, yielding a vertical $\mathcal{R}_0$ of 1. The mother virus chronically produces multiple virions of which 2 infect new cells, yielding a horizontal $\mathcal{R}_0$ of 2. The total is 3, i.e., the sum of horizontal and vertical components.

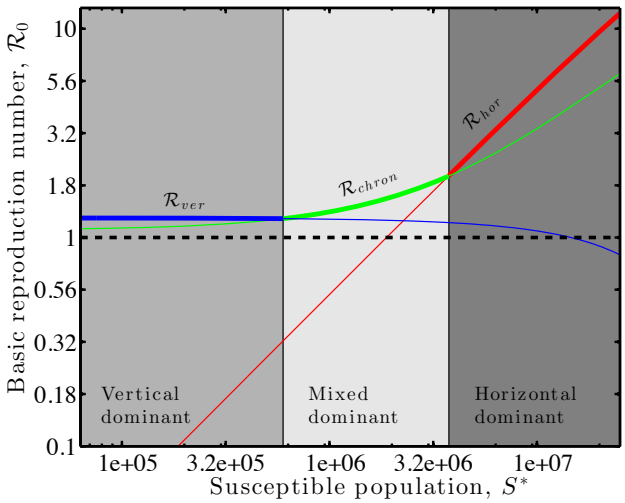

FIG. 7: Viral strategies with the highest $\mathcal{R}_0$ vary with susceptible host density, including exclusively vertical (bold blue, left), mixed (bold green, middle), and horizontal (bold red, right) modes of transmission. Relevant parameters are (i) for obligately lytic viruses (red): $\beta = 100$, $\phi = 6.7 \times 10^{-10}$ ml/hr, and $m = 0.13$ hr^{-1}; (ii) for chronic viruses (green): $b' = 0.68$ hr^{-1}, $d' = 0.63$ hr^{-1}, $\alpha = 20$ hr^{-1}, $\phi = 3.4 \times 10^{-10}$ ml/hr, and $m = 0.04$ hr^{-1}; (iii) for temperate viruses, given vertical transmission (blue) $b' = 0.54$ hr^{-1}, $d' = 0.44$ hr^{-1}, where $K = 7,5 \times 10^7$ ml^{-1} in all three scenarios given variation in S^*.

may lyse cells and produce "juvenile" offspring, i.e., virus particles. When a virion successfully infects a susceptible host this new infection becomes, once again, a mother virus. This is an example of horizontal transmission. For latent and chronic viruses, the viral genome inside an infected cell may be passed on to both cells upon division. This division is equivalent to direct reproduction

of a mother virus, bypassing the juvenile state. This is an example of vertical transmission. These two scenarios are precisely those that emerge in applying next-generation matrix theory for calculating the basic reproduction number of viral strategies (see the Appendix).

As a guide to our calculations of viral reproduction within nonlinear population models, we constructed examples of obligately lytic, latent, and chronic virus with an equivalent $\mathcal{R}_0$ equal to 3 (see Figures 2, 4, and 6). The reproduction in each case is partitioned differently in terms of horizontal and vertical components. Critically, the basic reproduction number of a particular viral genome includes only the number of newly infected cells that arise as a direct result of the first sequence of horizontal or vertical transmission. The fitness of new mother viruses are then their own. Moreover, in partitioning reproduction through horizontal and vertical pathways, this framework also eliminates the dichotomy between paradigms that emphasize the centrality of either virions or virocells. We contend that virion production should be understood as the initiation of horizontal transmission and not its culmination.

The approach to measuring viral fitness focuses on a particular ecological scenario: in which either a single virus particle or a single infected cell is added to an otherwise susceptible population. Yet, the framework is more general – and could apply to partially susceptible populations. The critical invasion fitness of a virus strategy – as calculated in terms of $\mathcal{R}_0$ – depends on life history traits as well as ecological context. As we showed, obligately lytic viruses have increasing values of $\mathcal{R}_0$ in populations with larger numbers of susceptible hosts. This trend is consistent with experimental findings that fitness of virulent phage λcI857 declines with decreasing susceptible cell density [42] (see discussion in [43]). Our theory predicts that the reproductive successes of different strategies differentially depend on susceptible cell density. For example, we demonstrated that latent, chronic, and lytic strategies could have higher potential reproductive success at low, intermediate, and high susceptible cell densities, respectively (Figure 7). By extension, strictly vertically transmitted viruses may have a $\mathcal{R}_{ver}$ above 1 if the ratio of infected cell growth and death rates exceed that of susceptible hosts. This provides a rationale for the evolution of viral traits that directly benefit host competitive fitness, e.g., toxin production and antibiotic resistance.

Despite our focus on short-term invasions, principled understanding of the evolution of viral traits and strategies also requires analysis of long-term dynamics and changes in the Malthusian growth rate of viruses. Such analysis is likely to draw upon a substantial body of work on the evolution of virulence (e.g., [44–51]), and in particular on the evolution of transmission mode [52]. For example, there can be tension and even conflicts at different scales of selection between viral genotypes that are effective at spreading within hosts but relatively ineffective at spreading between hosts [53–55]. In leveraging the insights of prior work, it is important to recall that virus-host dynamics unfold as part of complex ecosystems, whether in animal-associated or environmental microbiomes. As such, drivers of viral fitness will include spatial effects [56–59], temporal variation [60, 61], interactions with other strains [62–64], as well as feedback with other components of multi-trophic systems [65–67].

In moving forward, one immediate opportunity is to assess how viruses of microbes evolve virulence levels, or even strategy types, when co-infecting the same microbial population. For example, the cell-centric approach suggests new mechanisms of coexistence among viruses, e.g., viral-induced lysis may reduce niche competition between cells and enable invasion by latent/chronic viruses given context-dependent increases in $\mathcal{R}_{ver}$ [68]. In addition, competition by multiple viruses within the same host cell could lead to emergent new strategies, e.g., as seen in a prisoner's dilemma in an RNA virus [69]. Finally, analyzing the evolution of temperate phage in the present theoretical framework may also shed light on plastic strategies in which infection outcome depends on the multiplicity of infection [43, 70–74]. How viruses sense cellular state, and perhaps even modify the state of cells prior to infection [75, 76], remains an open question.

Altogether, the theory presented here provides an additional imperative to develop new measurement approaches to assess the entangled fates of viruses and cells. Measurements of the fitness of viruses with latent and chronic strategies should prioritize estimates of the life history traits of infected cells. Screening for viral genomes and their expression inside cells – whether integrated or persisting episomally – may reveal benefits of viral strategies that have thus far remained hidden when utilizing lysis-based assays or virion counts. By combining new measurements and theory, we hope that the present framework provides new opportunities to explore how viruses transform the fates of populations, communities, and ecosystems.

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Appendix A: Next-generation matrix approach for calculating viral invasion

The next-generation matrix (NGM) approach can be used to calculate $\mathcal{R}_0$ in mathematical models of interactions between cells and viruses. We follow the convention of Dieckmann and colleagues in analyzing the subset of the model including infected subclasses [32]. In the case of viruses of microbes, we denote those infected subclasses to include any population type that has an infectious viral genome, i.e., both infected cells and virus particles.

1. Obligately lytic interactions

The main text considers a model of interactions between obligately lytic viruses and cellular hosts. Here, we modify this model to consider the dynamics of susceptible cells, infected cells, and virus particles:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \overbrace{bS\left(1-N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}} \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \overbrace{\phi SV}^{\text{infection}} - \overbrace{\eta I}^{\text{lysis}} - \overbrace{d' I}^{\text{cell death}} \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \overbrace{\beta\eta I}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}
\end{aligned} \tag{A1}$$

We linearize the dynamics around the virus-free equilibrium, $(S^*, 0, 0)$ where $S^* = K(1 - d/b)$, and focus on the infected subsystem of $X(t) = [I(t)\ V(t)]^\intercal$. The linearized infected subsystem dynamics can be written as $\dot{X} = (T + \Sigma)X$ where

$$T = \begin{bmatrix} 0 & \phi S^* \\ 0 & 0 \end{bmatrix} \tag{A2}$$

denote transmissions events (i.e., corresponding to epidemiological births) and

$$\Sigma = \begin{bmatrix} -\eta - d' & 0 \\ \beta\eta & -\phi S^* - m \end{bmatrix} \tag{A3}$$

denote transition events (i.e., corresponding to changes in the state of viral genomes, including loss of infections). Via the NGM theory, the basic reproduction number $\mathcal{R}_0$ corresponds to the largest

eigenvalue of the matrix $-T\Sigma^{-1}$. The i,j matrix elements of Σ^{-1} correspond to the expected duration in state i of a viral genome that begins in state j. For this model,

$$-\Sigma^{-1} = \begin{bmatrix} \frac{1}{\eta+d'} & 0 \\ \frac{\beta}{\phi S^*+m}\left(\frac{\eta}{\eta+d'}\right) & \frac{1}{\phi S^*+m} \end{bmatrix} \tag{A4}$$

As a consequence, the basic reproduction number is:

$$\mathcal{R}_0 = \frac{\beta\phi S^*}{\phi S^*+m}\left(\frac{\eta}{\eta+d'}\right) \tag{A5}$$

2. Temperate-like strategies

Consider the dynamics of susceptible cells, infected cells (which denote lysogens), and virus particles:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \overbrace{bS\left(1-N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}} \\ \frac{\mathrm{d}L}{\mathrm{d}t} &= \overbrace{qb'I\left(1-N/K\right)}^{\text{lysogen growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{p\eta L}^{\text{lysis}} - \overbrace{d'L}^{\text{cell death}} \\ \frac{\mathrm{d}V}{\mathrm{d}t} &= \overbrace{\beta p\eta L}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}} \end{aligned} \tag{A6}$$

where $N = S+I$ is the total cell population density. As before, we linearize the dynamics around the virus-free equilibrium, $(S^*,0,0)$ where $S^* = K(1-d/r)$, and focus on the infected subsystem of $X(t) = [L(t)\ V(t)]^\intercal$. The linearized infected subsystem dynamics can be written as $\dot{X} = (T+\Sigma)X$ where

$$T = \begin{bmatrix} qb'(1-S^*/K) & \phi S^* \\ 0 & 0 \end{bmatrix} \tag{A7}$$

denote transmission events and

$$\Sigma = \begin{bmatrix} -p\eta - d' & 0 \\ \beta p\eta & -\phi S^* - m \end{bmatrix} \tag{A8}$$

denote transition events. For this model,

$$-\Sigma^{-1} = \begin{bmatrix} \frac{1}{d'+p\eta} & 0 \\ \left(\frac{\beta p\eta}{p\eta+d'}\right)\frac{1}{\phi S^*+m} & \frac{1}{\phi S^*+m} \end{bmatrix} \tag{A9}$$

As a consequence, the basic reproduction number is:

$$\mathcal{R}_0 = \frac{qb'(1-S^*/K)}{d'+p\eta} + \frac{\beta\phi S^*}{\phi S^*+m}\left(\frac{p\eta}{p\eta+d'}\right) \tag{A10}$$

3. Chronic strategies

Consider the model of interactions between chronic viruses and microbial hosts:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \overbrace{bS\left(1-N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}} \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \overbrace{b'I\left(1-N/K\right)}^{\text{logistic growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{d'I}^{\text{cell death}} \\ \frac{\mathrm{d}V}{\mathrm{d}t} &= \overbrace{\alpha I}^{\text{virion production}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}} \end{aligned} \tag{A11}$$

where $N = S+I$ is the total population density of cells. We recognize that the previous temperate model and the current chronic strategy model can be re-scaled to be equivalent. Nonetheless, the trade-off mechanisms are different and we note that in chronic infections, release of new virions need not be associated with lysis.

As before, we linearize the dynamics around the virus-free equilibrium, $(S^*,0,0)$ where $S^* = K(1-d/b)$, and focus on the infected subsystem of $X(t) = [I(t)\ V(t)]^\intercal$. The linearized infected subsystem dynamics can be written as $\dot{X} = (T+\Sigma)X$ where

$$T = \begin{bmatrix} b'(1-S^*/K) & \phi S^* \\ 0 & 0 \end{bmatrix} \tag{A12}$$

denote transmission events and

$$\Sigma = \begin{bmatrix} -d' & 0 \\ \alpha & -\phi S^* - m \end{bmatrix} \tag{A13}$$

denote transition events. For this model,

$$-\Sigma^{-1} = \begin{bmatrix} \frac{1}{d'} & 0 \\ \left(\frac{\alpha}{d'}\right)\frac{1}{\phi S^*+m} & \frac{1}{\phi S^*+m} \end{bmatrix} \tag{A14}$$

As a consequence, the basic reproduction number is:

$$\mathcal{R}_0 = \frac{b'(1-S^*/K)}{d'} + \frac{\phi S^*}{\phi S^*+m}\left(\frac{\alpha}{d'}\right) \tag{A15}$$