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ORIGINAL PAPER

Alternative stable states in host–phage dynamics

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Abstract Bacteriophage are ubiquitous in nature, yet many central aspects of host–phage biology have not been integrated into mathematical models. We propose a novel model of host–phage population dynamics that accounts for the decreased ability of phages to lyse hosts as hosts approach their carrying capacity. In contrast to existing predator–prey-like models, we find a parameter regime in which phages cannot invade a host-only system but, nonetheless, can stably coexist with hosts at lower densities. The finding of alternative stable states suggests clear linkages with observed life history strategies of phages. In addition, we solve a limiting case of the proposed model and show that conservative predator-prey like systems do not inevitably exhibit population cycles. Finally, we discuss possible extensions of the present model and scenarios for experimental testing.

Keywords Bacteriophage · Virus · Evolutionary ecology · Microbial ecology · Bifurcation · Nonlinear dynamics · Population dynamics

Introduction

Bacteriophages are the most abundant organisms on the planet. They modify population dynamics of hosts (Chao et al. 1977; Levin et al. 1977; Lenski 1988), alter nutrient recycling and biogeochemical cycles (Suttle 1994; Fuhrman 1999), and influence the spread of infectious disease (Faruque et al. 2005a,b). The interaction between phage and host is shaped by evolutionary mechanisms and ecological context. For example, recent experiments have shown that phages exploit their hosts (and each other) in a game-theoretic fashion (Turner and Chao 1999; Bull et al. 2006), control ecosystem level process in simple ecological webs (Bohannan and Lenski 1997), and alter selection pressure in ways that depend on the spatial scale (Lythgoe and Chao 2003; Forde et al. 2004). Such findings are not confined to the laboratory. Empirical studies relying on combinations of microbiology and metagenomic techniques have revealed unexpected viral diversity (Edwards and Rohwer 2005; Culley et al. 2006), a central role of phages in shuttling genes (Sano et al. 2004; Silander et al. 2005), and evidence that phages alter and enhance host metabolism (Lindell et al. 2004; Sullivan et al. 2005). This revolution in the study of the ecological and evolutionary impacts of phages provides an opportunity to revisit the mathematical description of host–phage dynamics. Do current models adequately describe the dynamics of microbial–viral interactions and do they make testable predictions?

Bacteriophage are typically classified as either virulent or temperate. Virulent phages kill their hosts without undergoing an extended intracellular phase, whereas temperate phages can also incorporate their genome into that of the host (Weinbauer 2004). In this paper, we restrict ourselves to the case of virulent phages and associated hosts. The dynamics of virulent phages and hosts have been described, for the most part, using extensions of Lotka–Volterra models

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(Levin et al. 1977; Lenski 1988). Innovations include the incorporation of a time delay between infection and lysis (Levin et al. 1977; Beretta and Kuang 2001; Fort and Méndez 2002), the use of ratio models that relate viral-to-host ratio with effectiveness of killing (Bohannan and Lenski 1997), and extensions to evolutionary models that incorporate changes in kinetic parameters (Wang et al. 1996; Weitz et al. 2005).

Here, we revisit the basic description of Lotka–Volterra-type population dynamics in the original model of Levin et al. (1977) by proposing an alternative, though related, model that links phage-induced mortality rate of hosts to host reproduction rate. Reduced lysis arises as a direct consequence of the fact that phages exploit their hosts, which provide energy and materials for phage synthesis. Indeed, early studies of host–phage biology established the dependence of many aspects of phage dynamics, including lysis rate, on the physiological state of the host cell (Cohen 1949). Since then, numerous experimental studies have shown that the lysis of hosts via phages is reduced when hosts are not reproducing (Ricciuti 1972; Haywood 1974; Middleboe 2000; Sillankorva et al. 2004; Abedon and Yin 2006).

There are many biological mechanisms that would account for reduced lysis near stationary phase. A few examples include reduction of phage-adsorption sites, reduced phage progeny per infection, reduced effectiveness of lysis due to cell wall thickening, or increased number of nonviable infections. The frequency with which such biological mechanisms operate in situ is unclear because many factors beside host density can alter phage reproduction, including availability of nutrients, temperature, and life history strategies (Moebus 1996; Sillankorva et al. 2004; De Paepe and Taddei 2006). We therefore propose a model that captures the essential dynamical features in a two-component model representing the population densities of hosts and phages. To our knowledge, such reduced lysis has not been explored previously in mathematical models of phages, nor has the system been examined in the theoretical ecology literature generally.

We begin by defining a model of host–phage population dynamics and classifying its behavior using standard nonlinear dynamics methods. We find that reduced killing at high host densities leads to alternative stable states in that ecological outcomes depend on the initial population densities. As a consequence of these alternative stable states, we predict sensitivity of dynamics to small perturbations so that slightly different densities of phages added to a host-only system may lead to (1) coexistence or (2) phage extinction. Next, we demonstrate that coexistence is generally preceded by oscillations, whereas phage extinction arises by, at most, a single boom–bust event. We explicitly solve the model in the limit where host mortality is due exclusively to phages, which provides additional support for the analysis of the full model. Finally, we discuss ways to test the model under different inoculation conditions.

Dynamics of hosts and phages

Consider the following model of host–phage population dynamics:

$$\frac{dN}{dt} = rN(1 - N/K) - \phi NV\overbrace{(1 - aN/K)}^{\text{new term}} - dN, \tag{1}$$

$$\frac{dV}{dt} = \beta\phi NV\overbrace{(1 - aN/K)}^{\text{new term}} - mV, \tag{2}$$

where N and V are the densities of hosts and phages, respectively; r is the maximal growth rate of hosts; ϕ is the adsorption rate; K is the host carrying capacity; d is the density-independent mortality rate of hosts; β is the burst size; a is the fractional reduction of lysis at carrying capacity; and m is the mortality rate of phages. We construct this model by starting with the standard Lotka–Volterra model with carrying capacity for the hosts (Murray 2002) and modifying phage reproduction to diminish as hosts approach stationary phase. The slowdown of bacterial growth and phage predation under crowded conditions can be interpreted as (1) an overall reduction of growth and susceptibility in all cells, (2) a proportion of cells entering a stationary and refractory stage, or (3) some combination thereof. We nondimensionalize this model by making the following substitutions: $t \to rt/a, \phi \to \phi\beta K/r, m \to am/r$, $d \to (ad/r + (1 - a))$, $N \to aN/K$, and $V \to aV/(\beta K)$. The same model can be written in a dimensionless form as:

$$\frac{dN}{dt} = N(1 - N) - \phi NV(1 - N) - dN, \tag{3}$$

$$\frac{dV}{dt} = \phi NV(1 - N) - mV. \tag{4}$$

Unlike typical Lotka–Volterra models or simple extensions, this model has, at most, four fixed points. First is the trivial fixed point, $(0, 0)$, second is the host-only point, $(1 - d, 0)$. There are two coexistence points, $(N_1^*, 1/\phi - dN_1^*/m)$ and $(N_2^*, 1/\phi - dN_2^*/m)$, where N_1^* and N_2^* are the solutions to the quadratic $N(1 - N) = m/\phi$. The maximum value of $N(1 - N)$ on the interval

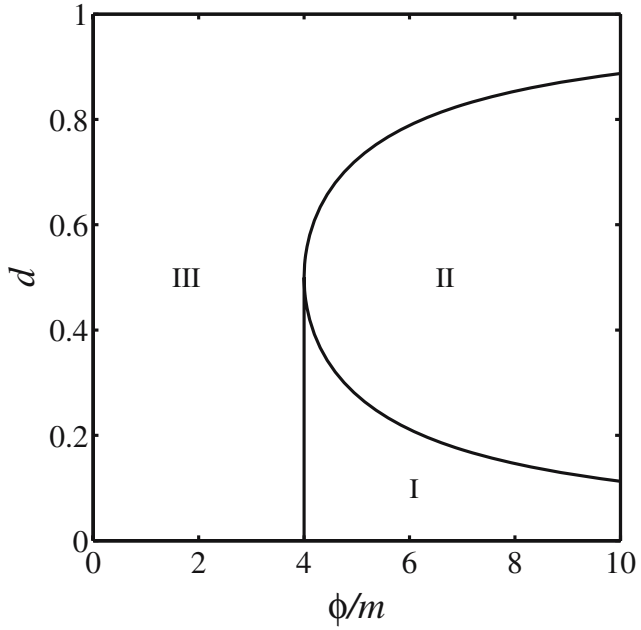

Fig. 1 Bifurcation diagram for the model in Eqs. 3 and 4. The labels *I*, *II*, and *III* denote regions of phase space: *I* initial conditions determine coexistence, *II* coexistence occurs for all nontrivial initial conditions, and *III* phage density approaches zero at equilibrium. The curved phase boundary satisfies the condition, $\phi/m = 1/[d(1-d)]$. Phase space diagrams are depicted in Fig. 2

[0, 1] is 1/4; thus, a necessary condition for host–phage coexistence is $(\phi/m) \geq 4$. As we will soon show, the point (N_2^*, V_2^*), when it exists, lies on a separatrix that separates the basins of attraction for the two alternative stable states.

The local stability of the fixed points can be assessed via the Jacobian,

$$J = \begin{bmatrix} (1-2N^*)(1-\phi V^*) - d & -\phi N^*(1-N^*) \\ (1-2N^*)\phi V^* & \phi N^*(1-N^*) - m \end{bmatrix}. \tag{5}$$

Simple algebraic analysis shows that the host-only equilibrium $(1-d, 0)$ is an unstable saddle whenever $\phi/m > 1/[d(1-d)]$, and in such a case, the unstable internal equilibrium does not exist. The condition determines two curves in the plane and forms the basis for a bifurcation diagram shown in Fig. 1. When the host-only equilibrium is unstable, then all trajectories converge to the stable coexistence fixed point (see Fig. 1). When the host-only fixed point is stable, then two possibilities exist: either initial conditions determine whether coexistence is possible (which is the case when d is small) or all trajectories lead to phage extinction in the system (which is the case when $d \to 1$). The phase space dynamics of these scenarios are shown explicitly in Fig. 2. Note that we do not visualize the case $d > 1$, which leads to the trivial fixed point (0, 0).

The finding of alternative stable states does not depend sensitively on whether lysis is reduced completely as host density increases. The parameter a in Eqs. 1 and 2 denotes the degree to which lysis is reduced at carrying capacity. When $a = 0$, such a model is equivalent to that of Lotka–Volterra dynamics, and when $a = 1$, phages are completely inhibited at carrying capacity. Alternative stable states can occur for some values of ϕ/m so long as $d < 1/2$. However, $d \to (ad/r + (1-a))$; thus, when $a < 1/2$, the rescaled host mortality rate is always greater than 1/2, leading to, at most, one interior equilibrium. When $a > 1/2$, there is a parameter regime where alternative stable states should be expected. The parameter regime grows larger as $a \to 1$.

As a means to understand the alternative stable states in region I of Fig. 1, consider the following thought experiment: First, inoculate a culture with a small density of hosts and then allow the hosts to approach equilibrium. Then, at different points along the logistic growth curve, add a small titer of phage. The model predicts that if phages are added too late,

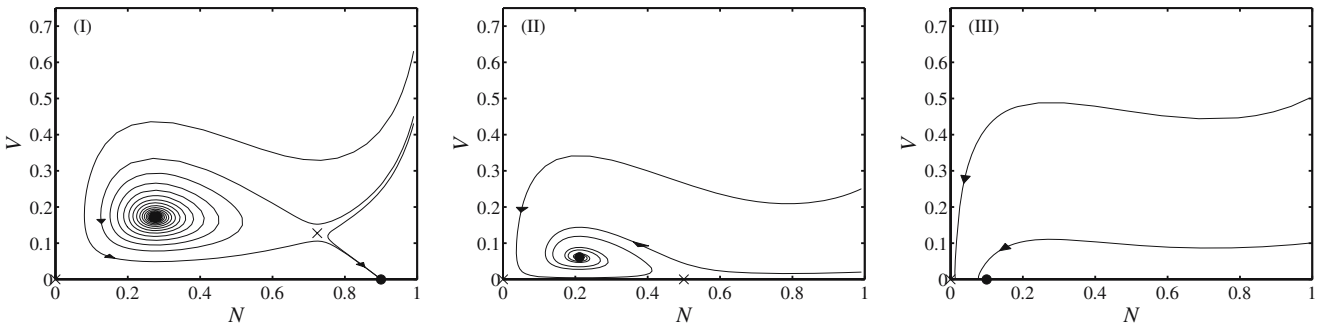

Fig. 2 Phase space dynamics of Eqs. 3 and 4 for the cases $\phi/m = 5$, $d = 0.1$ (*I*); $\phi/m = 6$, $d = 0.5$ (*II*); and $\phi/m = 5$, $d = 0.8$ (*III*). *Solid circles* denote stable fixed points, *multiplication signs* denote unstable fixed points, and *arrowheads* denote the direction of trajectories

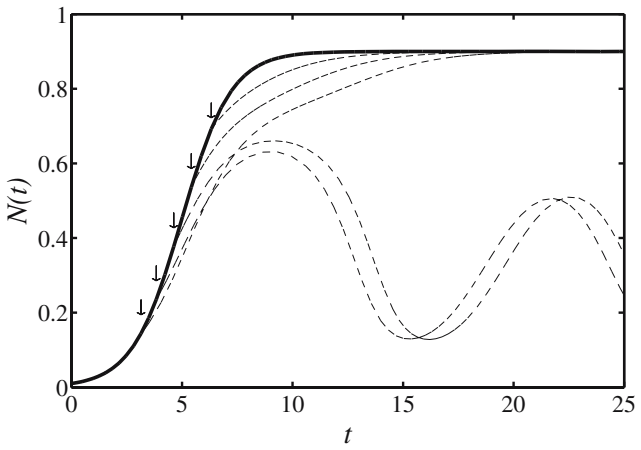

Fig. 3 Dynamics of hosts without phages (*solid line*) and with phages added at different time points of logistic growth (*dashed lines*) under the same parameter conditions as in Fig. 2, I. The *arrows* denote the times of phage addition. In all cases, dynamics obey those of Eqs. 3 and 4, given that $\phi = 5, m = 1, d = 0.1$, initial host density is $N(t = 0) = 0.01$, and initial phage density when added is $V = 0.06$

they will be unable to prevent hosts from approaching stationary phase, and thus, phages will be driven out of the system. Similarly, if phages are added so early that they crash before the host population reaches a density that can support them, they may be unable to control the host, and be driven out. Thus, whether the outcome is coexistence or viral extinction depends on the initial densities of hosts and phages (see Fig. 3 for an example).

Conservation laws in a limiting model

In the limit that $d = 0$, the dimensionless form of the model in the previous section is

$$\frac{dN}{dt} = N(1-N) - \phi NV(1-N), \tag{6}$$

$$\frac{dV}{dt} = \phi NV(1-N) - mV. \tag{7}$$

Though it is unlikely that density-independent mortality of hosts is absent in natural systems, it is generally assumed that death of hosts due to phages is much higher than mortality due to endogenous causes. Studying the $d = 0$ model sheds light on the more general model where d is small but non-zero.

The $d = 0$ model has four equilibria. First is the trivial equilibrium, $(0, 0)$, second is the host-only equilibrium, $(1, 0)$. There are two coexistence equilibria, $(N_1, 1/\phi)$ and $(N_2, 1/\phi)$, where N_1 and N_2 are the solutions to the quadratic $N(1-N) = m/\phi$ and $N_1 \leq N_2$. The condition for existence of these coexistence points is $(\phi/m) \geq 4$.

The local stability of the coexistence fixed points can be assessed using the Jacobian. The Jacobian is:

$$J = \begin{bmatrix} 0 & -m \\ (1-2N^*) & 0 \end{bmatrix} \tag{8}$$

where the two zeros on the diagonal indicate that one of the interior fixed points may be neutrally stable. Solving for the eigenvalues $\lambda_{1,2}$ leads to the following condition: $\lambda = \pm\sqrt{m(2N^* - 1)}$; hence, when $N^* < 1/2$, the eigenvalues are purely imaginary. Ignoring the case where there is a degenerate fixed point at $(1/2, 1/\phi)$, whenever the coexistence equilibria exist, then $N_1 < 1/2$ and $N_2 > 1/2$. Numerical simulations verify the existence of a limit cycle around $(N_1, 1/\phi)$ (see Fig. 4).

The density dependence of host reproduction and mortality indicates the possibility that Eqs. 6 and 7 satisfy the conditions for a conservative system (Murray 2002). Consider the derivative of N with respect to V,

$$\frac{dN}{dV} = \frac{N(1-N)(1-\phi V)}{\phi V\left(N(1-N) - \frac{m}{\phi}\right)}. \tag{9}$$

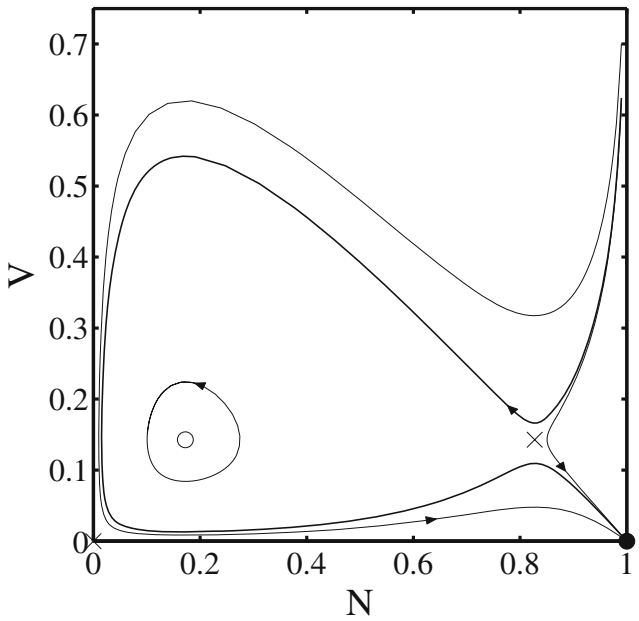

Fig. 4 Numerical simulation of host–phage dynamics for $m = 1$ and $\phi = 7$ for different initial conditions in the conservative system of Eqs. 6 and 7. Note the unusual, whale-like shape of the phase diagram, due to the neutrally stable equilibrium (near the head) and the unstable saddle (near the tail). The *solid circle* denotes stable equilibria, the *open circle* denotes neutrally stable equilibria, *multiplication symbols* denote unstable equilibria, and *arrowheads* denote direction of trajectories

Separating and integrating this equation, we find the following conservation law:

$$N + V - \frac{\log V}{\phi} - \frac{m}{\phi} \log\left(\frac{N}{1-N}\right) = \text{Const.} \tag{10}$$

Interestingly, although a conservation law exists, population dynamics do not lead inevitably to limit cycles. Rather, a limit cycle is possible for certain initial conditions, whereas there is also an attracting point at $(1, 0)$, which we anticipate from the dynamics in region I of the model where $d \neq 0$. Because each trajectory has a conserved parameter associated with it, we can predict the decay of population density as the system approaches the point $(1, 0)$.

Consider $n \equiv 1 - N$ and $v \equiv V$. The conservation law can be rewritten as

$$1 - n + v - \frac{\log v}{\phi} - \frac{m}{\phi} \log\left(\frac{1-n}{n}\right) = \text{Const.} \tag{11}$$

Retaining all terms of order n^0, n^{-1}, n^{-2}, etc., the conservation condition becomes

$$\log\left(\frac{n^{m/\phi}}{v^{1/\phi}}\right) = \text{Const.} \tag{12}$$

For this to be satisfied along the entire approach to the fixed point $(1, 0)$, then $v \propto n^m$. Thus, a power-law relationship should exist between relative host density and phage density. Numerical integration of Eqs. 6 and 7 confirms the existence of such power-law relationships (see Fig. 5).

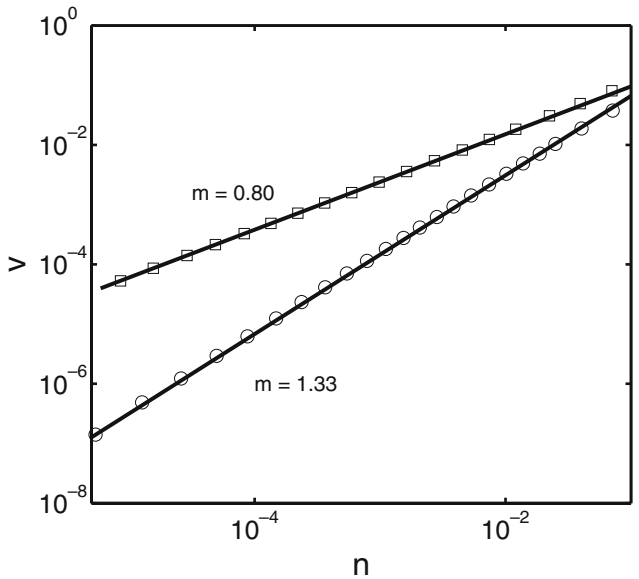

Fig. 5 Numerical results for simulation of host–phage dynamics in Eqs. 6 and 7 near the decay to the host-only equilibrium. Results show the relationship between v and n for the cases of $m = 0.8$ and $\phi = 5$ (*squares*) as well as $m = 1.33$ and $\phi = 9$ (*circles*). *Solid lines* are the power-law functions, $v \propto n^m$, expected from theory

Discussion

The natural world is comprised of organisms with sizes spanning many scales. Yet, the interest in predator–prey dynamics from its origins in the North Atlantic fishing industry to the study of simple carnivore–herbivore systems reflects a decidedly macroecological bias. It is likely that the rules that apply to terrestrial land animals, fish, or even insects, may prove less appropriate in describing the dynamics of the microbial world. The system of host and phage provides an opportunity to develop testable models that incorporate known biological and biophysical principles in the context of simple mathematical descriptions.

Making quantitative predictions of population dynamics requires estimation, via experiment or from first principles, of the kinetic parameters in a model. Just as important, however, is to ensure that model dynamics incorporate key biological interactions. In this paper, we have shown that the limitation of phage predation at high host densities has dramatic consequences for predictions about host–pathogen dynamics. Importantly, such a decline in predation rate as a function of host density has extensive experimental support. Whether grown in liquid culture or on bacterial lawns, the effectiveness of phages in lysing hosts declines as hosts approach stationary phase (Ricciuti 1972; Haywood 1974; Middleboe 2000; Sillankorva et al. 2004; Burch and Chao 2004; Abedon and Yin 2006). Despite being common, this decrease in effectiveness is not universal; indeed, there may be phages that operate in ecological niches specifically targeting stationary-phase hosts (Sullivan, personal communication).

The analysis of the model presented in this paper leads to testable predictions. Consider, for example, the parameter regime described in region I of Fig. 2. Given an initial density of hosts, analysis of the full model, Eqs. 1 and 2, implies that there should be a finite range of phage density, which, when added, results in coexistence. If too few phages are added, they cannot reproduce sufficiently to draw down hosts, whereas if too many are added, they lead to a boom in numbers and a subsequent crash that, in the long term, leads to phage extinction. The model also predicts that, as hosts near saturation, the timing of viral addition will lead to radically different outcomes (see Fig. 3). Finally, we predict that, when phage and host coexist,

they will generally undergo oscillations, whereas when phages are washed out, at most a single boom–bust cycle will take place. The full solution of the model with exclusively phage-dependent mortality of hosts in the previous section supports the findings of oscillations. Furthermore, the convergence of some trajectories to the phage extinction fixed point in this limiting case refutes the commonly held understanding that conservative predator-prey like systems inevitably lead to oscillations (Murray 2002). Importantly, both outcomes, washout and oscillations, have already been observed in liquid culture studies of host–phage dynamics (Bohannan and Lenski 1997).

The equations we propose support the notion that biological distinctions in terms of mechanisms of killing/exploitation may help explain currently observed phenomena in microbial dynamics, as well as predict new phenomena. Clearly, Eqs. 1 and 2 are not comprehensive. First, the time delay between phage adsorption and lysis and its potentially destabilizing effects are not included (Beretta and Kuang 2001). Second, we model resources implicitly, though resources could be made explicit by adding a term of the form dR/dt, via which both hosts and viruses depend for reproduction (Levin et al. 1977; Lenski 1988)—such equations should take into account the recycling of organic material via viral killing of hosts (Fuhrman 1999). Third, the existence of a lysogenic phase is not modeled. Alternative life histories may permit phage to exploit a population approaching stationary phase in ways that a strictly lytic phage could not. The list could go on and on, and which model is the right one depends on the questions we want to ask.

Experiments that include multiple phage and host types suggests that general principles may be within our grasp when considering phage life history (De Paepe and Taddei 2006). Likewise, breakthroughs in sampling viral metagenomes are providing new insights into the diversity, function, and dynamics of environmental phages (Breitbart et al. 2002; Edwards and Rohwer 2005). It will take closer coordination between theory and experiment to determine how much detail is necessary to predict the dynamics of host, phage, nutrients, and evolutionary outcomes. It will take even more work to connect population dynamics to the increasing understanding of the regulatory networks and protein–protein interactions that inform the kinetic parameters in similar models (McAdams and Arkin 1997). In the long term, continued efforts to develop and extend quantitative microbial and viral population biology may well provide the opportunity for clarifying that what works for big organisms does not always fit for the small.

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