COMPARATIVE MODELING OF LYTIC AND LYSOGENIC PHAGE-HOST SYSTEMS

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Abstract

Bacteriophages are the most abundant organisms on the planet and play crucial roles in bacterial population dynamics, microbial food webs, and nutrient cycling. Understanding models of bacteriophage population dynamics is necessary to fully understand these ecological processes, but to do so we must mathematically distinguish between the different virus life cycles. Here, we build on two three-dimensional systems of differential equations, similar to Beretta and Kuang (1998) and Reluga et al. (2009) to model lytic and lysogenic virus life cycles. We used these models to generate hypotheses about the ecological costs and benefits of the two life cycles. The models suggest viral abundance and frequency of infected cells increase with habitat productivity. The lytic system is more prone to sustained oscillations, especially with slow-growing cells and more virulent viruses, whereas the lysogenic system only has sustained oscillations when rates of lysis are high relative to cell growth rates, making lysogenic phages qualitatively resemble lytic phages. The models also suggest that lysogenic viruses are capable of infecting all the cells in a population for realistic parameter regimes, and the evolutionary consequences of this prophage fixation are discussed here. Further research can yield new insights into viral population dynamics, test these models and help us better understand the roles of viruses in ecology.

Introduction

Bacteriophages are the most abundant organisms on the planet (Bergh et al, 1989). They play crucial roles in bacterial population dynamics (Chao et al., 1977; Levin et al., 1977; Lenski 1988; Bossi et al., 2003), microbial food webs (Proctor et al., 1988; Proctor & Fuhrman, 1990; Suttle et al., 1990; Suttle, 2000; Paul, 2000) and nutrient cycling (Fuhrman, 1999; Suttle, 2000; see Weinbauer, 2004 for a comprehensive review of bacteriophage ecology). A better understanding of viral population dynamics and viral ecology is necessary for a more complete understanding of ecology as a whole.

To date, most virus models have focused on viruses that infect cells and immediately lyse, but virus life cycles can be much more complex. Phages (another name for viruses infecting bacteria) exhibit several distinct life cycles: lytic, lysogenic, pseudolysogenic, and chronic infections (Ackermann and DuBow, 1987; Weinbauer, 2004), yet most modeling efforts have

focused exclusively on lytic viruses (Levin et al., 1977; Lenski, 1988; Beretta and Kuang, 1998; Nowak and May, 2000; Weitz and Dushoff, 2008), with one Hepatitis-C model by Reluga et al. (2009) resembling a lysogenic infection. A better understanding of how virus life cycles differ from one another in their dynamical behavior can yield a broader understanding of viral ecology.

In this paper, we build on pre-existing models with the aim of describing two of the major viral life cycles: lytic and lysogenic (also referred to as virulent and temperate, respectively). We investigate what the models suggest about host thresholds for viral persistence, viral abundance, frequency of infected cells, conditions for sustained oscillations, and a novel fixed point in the lysogenic system in which every cell becomes infected yet both the cells and viruses persist. We then use these findings to provide directions for future research in both theoretical and experimental efforts in viral ecology.

The Models

Figure 1 illustrates the key life cycle differences between lytic and lysogenic phages. Lytic phages that successfully infect a cell are assumed to instantaneously begin lysis, whereas lysogenic phages that successfully infect a cell can induce lysis or go dormant. The infected cells containing dormant prophages (the genetic material of lysogenic phages that has been inserted into the host's genome) can either divide to produce daughter infected cells, or be lysed by an induced phage. In both cases, we assume cells cannot be superinfected by analogous phage (Durlington & Levine, 1971; Ackermann & DuBow, 1987; Marsh & Wellington, 1994).

We constructed two three-dimensional systems of ordinary differential equations describing the rates of change of V (viruses), U (uninfected cells), and I (infected cells). The structural similarity of the VUI models makes possible a direct comparison of the dynamics of these two phage systems.

In our models, the phage systems are in a well-mixed environment yielding random encounters between cells and viruses with encounter coefficient a. Not all viruses that encounter a cell successfully infect it, so we define the infection coefficient b, where $b < a$. Free-floating viruses decay exponentially at a rate d. A fixed percentage of the infected cell population is lysing, resulting in exponential decay of infected cell populations at a rate l. From each lysis event, a constant number of viruses, r_V, is produced. Finally, cells grow logistically with an intrinsic growth rate r_c, and both uninfected and infected cells tap into the same limiting resource, producing a modified logistic growth term:

(1) $$\frac{d\mathrm{U}}{dt} = r_c \mathrm{U}\left(1 - \frac{\mathrm{U}+\mathrm{I}}{K}\right)$$

If only uninfected cells divide and that their divisions produce only daughter uninfected cells, we arrive at the lytic phage system.

(2)

$$\frac{d\mathrm{V}}{dt} = r_V l\mathrm{I} - a\mathrm{UV} - d\mathrm{V}$$

$$\frac{d\mathrm{U}}{dt} = r_c\mathrm{U}\left(1 - \frac{\mathrm{U}+\mathrm{I}}{K}\right) - b\mathrm{UV}$$

$$\frac{d\mathrm{I}}{dt} = b\mathrm{UV} - l\mathrm{I}$$

(2) is an expansion of the virus model well-studied in Nowak and May (2000), incorporating density-dependent growth of uninfected cells in place of constant growth. It is also nearly identical to the model extensively analyzed by Beretta and Kuang (1998), with the major difference being the inclusion of a distinct virus infection coefficient, $b < a$.

To account for the division of lysogenic bacteria into daughter cells that are also infected, we added a similar density-dependent growth term for infected cells, assumed that the cost of a dormant prophage for the infected cells is negligible, and modified the third differential equation to arrive at the lysogenic phage system:

(3)

$$\frac{d\mathrm{V}}{dt} = r_V l\mathrm{I} - a\mathrm{UV} - d\mathrm{V}$$

$$\frac{d\mathrm{U}}{dt} = r_c\mathrm{U}\left(1 - \frac{\mathrm{U}+\mathrm{I}}{K}\right) - b\mathrm{UV}$$

$$\frac{d\mathrm{I}}{dt} = r_c\mathrm{I}\left(1 - \frac{\mathrm{U}+\mathrm{I}}{K}\right) + b\mathrm{UV} - l\mathrm{I}$$

Reluga et al. (2009) covered a model similar to (3), except they had a constant growth of uninfected cells in addition to the logistic growth term, and they did not differentiate between encounters and successful infections. For a list of the dimensional parameters of both systems and their estimated values, see table 1 and the appendix.

We then non-dimensionalized time with respect to the virus decay rate and made substitutions listed in table 2 to arrive at the following dimensionless systems:

Lytic

(4)

$$\frac{dV}{d\tau} = \gamma I - \alpha UV - V$$

$$\frac{dU}{d\tau} = \rho U(1 - U - I) - UV$$

$$\frac{dI}{d\tau} = UV - \sigma I$$

Lysogenic

(5)

$$\frac{dV}{d\tau} = \gamma I - \alpha UV - V$$

$$\frac{dU}{d\tau} = \rho U(1 - U - I) - UV$$

$$\frac{dI}{d\tau} = \rho I(1 - U - I) + UV - \sigma I$$

Where it should be noted that γ can also be written as $\gamma' \sigma = \frac{r_V bK}{d}\sigma$, and γ' corresponds to Beretta and Kuang's (1998) "virus multiplication factor". We focused our analytical and numerical investigations on the dimensionless systems, with special emphasis on the virulence and cell-growth parameters γ and ρ, respectively. We occasionally revert back to dimensional parameters for more tangible biological interpretations of our results. Table 3 contains a list of the fixed points and their analytical stability.

Coexistence Steady State, x_{VUI}*, and K-threshold

In both systems, realistic parameter values can fall within the range of stability for the coexistence steady state, **x_{VUI}***, in which viruses, uninfected and infected cells persist. See the appendix for the values of (V,U,I) in the coexistence steady state of each system. The conditions for viral persistence can be used to infer a host carrying capacity threshold below which viruses cannot persist.

In the lytic system, **x_{VUI}*** becomes stable when

(6) $$\gamma > \sigma(\alpha + 1)$$

In the lysogenic system, **x_{VUI}*** becomes stable when

(7) $$\gamma > \sigma(\alpha + 1), \quad \text{and} \quad \rho < {}^{\sigma\gamma}/_{\gamma - \sigma}, \quad \gamma > \sigma$$

See (figure 2).

Reverting back to dimensional parameters, (6), the condition beyond which both systems are stable, suggests a host carrying capacity threshold, K', for phage persistence:

$$K' = \frac{{}^{d}/_{a}}{r_v \, {}^{b}/_{a} - 1}$$

An interesting observation is that the threshold for virus persistence here is independent of cell growth rate and rate of lysis.

In addition to persistence when (6) holds, it's also possible for lysogenic viruses to persist when $\gamma > {}^{\sigma\,\rho}/_{\rho - \sigma}$, the criterion for stability of the prophage fixation fixed point, **x_{VI}***. When there is overlap between stability of **x_{VI}*** and (6), we get bistability. This happens when

(8) $$\sigma(\alpha + 1) > \gamma > {}^{\sigma\,\rho}/_{\rho - \sigma}$$

For these parameter values, the lysogenic system is bistable with both **x_U*** **x_{VI}***, allowing lysogenic viruses to potentially persist despite (6) not holding (see figure 2). This leads to a

conditional carrying capacity threshold in which the lysogenic viruses must have high enough titers in order for viral persistence to occur (see figure 3)

Viral Abundance and Frequency of Infected Cells

Empirical studies suggest that both viral abundance (Boehme et al. 1993; Cochlan et al. 1993; Maranger & Bird, 1995; Paul, 2000) and the frequency of infected cells (Steward et al., 1992; Weinbauer et al., 1993; Steward et al., 1996; Noble & Fuhrman, 2000; Almeida et al., 2001; Guixa-Boixereu et al. 2001; Middleboe et al., 2002; Weinbauer et al., 2003) increase with the productivity of ecosystems. If we consider that cell growth rate and virus burst size both increase with the productivity of the environment (Weinbauer et al., 1993; Weinbauer & Suttle, 1999), then we can use the models presented here to understand how productivity affects viral abundance.

In both systems, viral abundance increases with both ρ and γ, with lysogenic viruses being more abundant than lytic viruses for regions of high productivity. The positive relationship between productivity and overall viral abundance is consistent with empirical data (figure 4).

Similarly, the frequency of infected cells shows a positive relationship with productivity, with lysogenic infected cells reaching higher frequencies than lytic infected cells, primarily through prophage fixation (see below). The exact relationship between lysogeny and habitat productivity is empirically unknown (Weinbauer, 2004) but these models suggest that, all else being constant, the frequency of lysogenic cells should increase with increasing productivity.

Limit Cycles

Both systems undergo supercritical Hopf bifurcations around the fixed point $\mathbf{x_{VUI}}^*$ as γ (virulence) is increased, but the parameter regime for limit cycles in the lytic system is more feasible. Numerical simulations reveal that the Hopf bifurcation in the lytic system occurs for a fixed ratio of ρ and γ, and in the lysogenic system along a curve in ρ=f(γ) bounded above by ρ=σ (see figure 5). When $\rho <$ σ, a necessary condition for oscillations in the lysogenic system, $r_c < l$, and it has been shown that this condition is unrealistic in at least one phage-host system (Lubitz et al., 1984).

In both systems, the magnitude of oscillations increase with increasing γ, but when γ is large the lysogenic system becomes very sensitive to slight changes in ρ near the location of the Hopf bifurcation. The periods of these oscillations are more sensitive to changes in ρ, where decreasing ρ increases the period.

These results suggest that the lytic viruses are more prone to oscillatory behavior, where increasing virulence (burst size r_V, or infectivity b) results in larger oscillations and the

oscillations of phages infecting slow-growing cells will have a longer period than oscillations of phages infecting fast-growing cells.

Prophage Fixation, x_{VI}*

By incorporating density-dependent growth of infected cells, the lysogenic system gives rise to an alternative stable state not found in the lytic system, $\mathbf{x_{VI}}$*, in which every cell becomes infected yet both the viruses and the (infected) population of cells persist. This "prophage fixation" fixed point is stable if and only if:

(9) $$\sigma < \frac{\gamma\rho}{\gamma+\rho} \quad \text{or} \quad 1 < \frac{\gamma'(\frac{\rho}{\sigma})}{\gamma'+(\frac{\rho}{\sigma})}, \quad \gamma' = \frac{r_V bK}{d}$$

(9) is only possible when $\rho > \sigma$ and $\gamma' > \frac{\rho}{\rho-\sigma}$. $\rho > \sigma$, which translates to $r_c > l$, and is a realistic scenario for many phage-host systems. When $r_c \cong l$, which tends to occur only in rich media (Lubitz et al. 1984), prophage fixation is not likely to occur as γ' must become very large. However, for $r_c \gg l$, a realistic condition for sub-optimal media, prophage fixation becomes a feasible steady-state for lysogenic viruses. If prophage fixation does occur, it is most likely to occur in sub-optimal environments, and it could explain the evidence for highest prevalence of lysogeny in environments with low bacterial and primary production (Williamson et al., 2002).

Discussion

The models presented here provide a unique theoretical comparison of lytic and lysogenic virus life cycles. By incorporating density-dependent growth of uninfected cells (lytic) or both uninfected and infected cells (lysogenic), and by distinguishing between virus encounters and successful virus infections of cells, we have built on pre-existing models (Nowak & May, 2000; Reluga et al. 2009) with the aim of producing more mechanistically correct models of virus population dynamics. The behaviors of these models offer a few hypotheses and lead to further questions about the costs and benefits of the two virus life cycles.

The models are consistent with empirical data showing a positive relationship between productivity and both virus particle abundance and frequency of infected cells. The models predict that, if the lytic and lysogenic phages do not compete for the same host, there will be a higher percentage of lysogenic viruses and lysogenic-infected bacteria. However, these patterns could change if the models were modified to capture a reduction of fitness in lysogenic bacteria (Marintcheva et al., 2007), a time-delay for latent periods (Beretta & Kuang, 2001), or competitive interactions between lytic and lysogenic phage (Weigle & Delbrük, 1951; Korona & Levin, 1993; Turner et al., 1999).

These models suggest that populations of lytic phages are more prone to limit cycles, a dynamical regime not present in the standard virus model of Nowak and May (Tuckwell & Wan, 2004). These limit cycles occur when virulence is high relative to host growth rate. Lytic oscillations increase in magnitude and decrease in frequency with increasing virulence of the phage, but the frequency is more sensitive to changes in cell growth rates than phage virulence. The feasibility of these oscillations may be a coincidence of the phage life-cycle, but it's possible it could allow for evolutionary entrainment of lytic phage oscillations with oscillations in the cell populations independent of phage. Further studies looking at lytic phage dynamics in steady-state and periodic cell cultures could test these models or similar models where host population size or growth rates change periodically with time.

In contrast, the lysogenic system is only capable of oscillations in the unlikely parameter regime when the host intrinsic growth rate is less than the rate of lysis. With these constraints, oscillations of lysogenic phage are only likely to happen in the presence of high concentrations of inducing agents that decrease cell growth rates and/or increase rates of lysis, making lysogenic phage behave as lytic phage. In general, though, these models predict that under constant cell growth rates and rates of lysis, lysogenic phage populations are not likely to oscillate. However, the rates of lysis of lysogenic phage may not be constant, since inducing agents such as intensity of sunlight, H_2O_2, temperature or concentrations of environmental pollutants can be periodic (Cochran et al., 1998; Weinbauer & Suttle, 1999). Further research is needed to determine how periodicity in the rate of lysis affects the population dynamics of lysogenic phage and the overall dynamical behavior of the lysogenic model.

Finally, the incorporation of a density-dependent growth term for lysogenic cells yielded a "prophage fixation" steady state in which lysogenic phages infect every cell in the population. The conditions for stability of prophage fixation overlaps comfortably with the range of realistic parameter values obtained from the literature, but whether or not it occurs in nature is unclear. Empiricists have found percent lysogeny values high and even near 100% (Cochran et al. 1998; Williamson et al, 2002; Weinbauer et al. 2003, Ghosh et al. 2008), with the highest occurrence found in habitats with lowest bacterial primary productivity (Williamson et al., 2002), consistent with our models. Also, genomic studies find a large percentage of bacterial genomes containing prophages (Ohnishi et al. 2001; Perna et al. 2001; Ohnishi et al. 2002; Paul, 2008), but the presence of phages in genomes could be due to a defective phage infecting one cell and becoming fixed through binary fission and horizontal gene transfer.

If prophage fixation occurs in nature, it would have large effects on the evolution of novel gene functions. With every cell infected, and without the possibility of superinfection with analogous phage, there would be no more evolutionary benefit for a lysogenic phage to lyse the cell, effectively coupling the virus fitness with host fitness. The feasibility of prophage

fixation in these models warrants further investigation. However, the evolutionary pressure to not lyse, due to high frequencies of "immune" infected cells, may be large enough long before prophage fixation occurs, preventing fixation entirely. To address whether prophage fixation occurs, a model accounting for this trade-off, similar to Weitz and Dushoff (2007), but having density dependent growth of infected cells could be analyzed to see if prophage fixation is still possible. Experimentally, it would be necessary to develop more accurate ways of quantifying percent lysogeny, as exposure to mitomycin-C and other inducing agents underestimates the true percent lysogeny (Weinbauer, 2004). A more accurate method for determining percent lysogeny could then be employed in chemostat studies to see if and when prophage fixation occurs.

Further theoretical and experimental research can yield new insights into viral population dynamics, test these models and help us better understand the roles of viruses in ecology.

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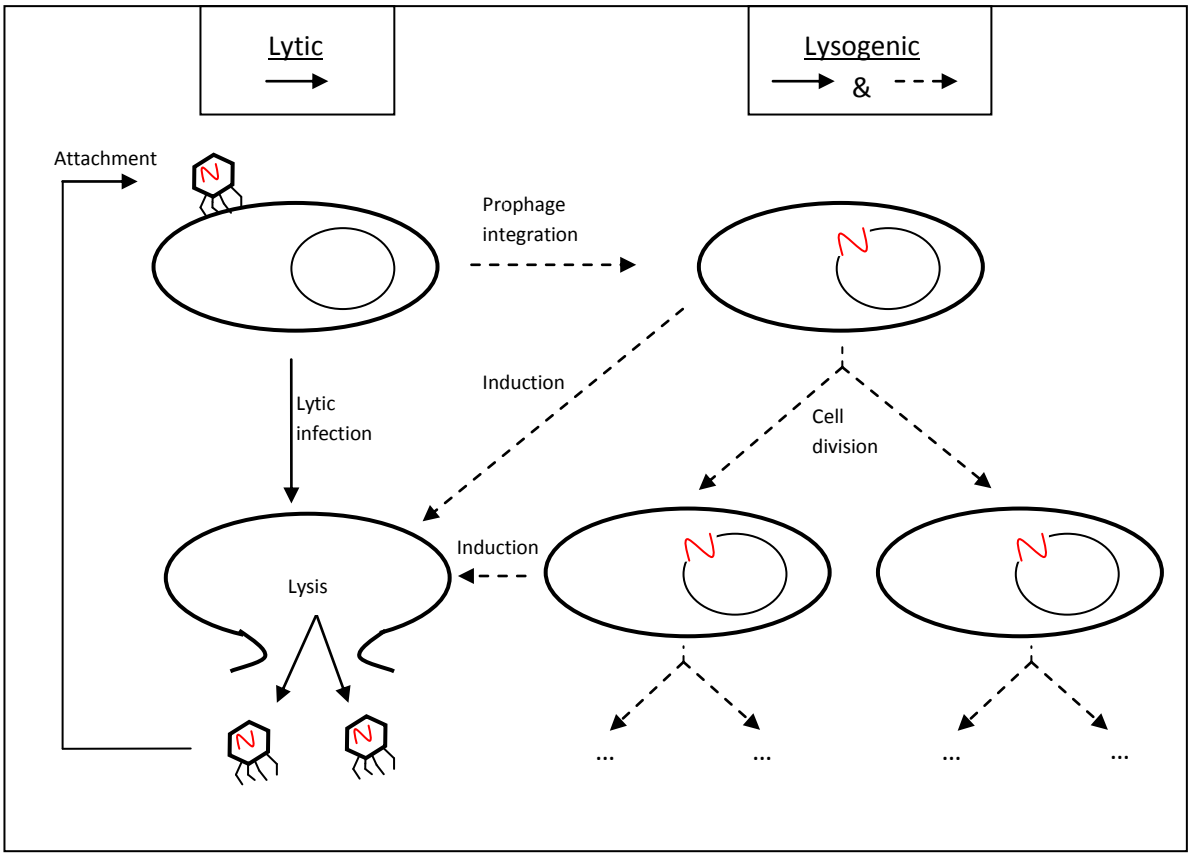

Figure 1: Diagram of lytic and lysogenic virus life cycles as they are modeled in this paper. Lytic viruses immediately induce lysis of the infected cells, whereas lysogenic viruses can either induce lysis of infected cell or be replicated during cell division to produce daughter infected cells.

Parameter	Definition	Values
r_c	Cell growth rate	0.2-2.4 day^{-1}
r_V	burst size	24-64 $ml \cdot Virus^{-1} \cdot Cell^{-1}$
a	Adsorption constant.	$2.4 \cdot 10^{-7}$-1.02 $ml \cdot Cell^{-1} \cdot day^{-1}$
b	Infection constant	10^{-8}-0.34 $ml \cdot Virus^{-1} \cdot day^{-1}$
d	Virus decay rate	0.019-0.30 day^{-1}
l	Lysis rate constant	0.012-12 day^{-1}
K	Carrying Capacity	10^5 - 10^6 $Cell \cdot ml^{-1}$

Table 1: List of parameters for the dimensional systems. See Appendix for comments and citations for parameter values.

Parameter	Substitution	Definition	Range
α	$\frac{aK}{d}$	Encounter Coefficient	0.046 - 1.275
γ	$\frac{r_V lbK}{d^2}$	Virulence coefficient	1.8- $4 \cdot 10^5$
ρ	$\frac{r_c}{d}$	Growth coefficient	0.18 - 18.75
σ	$\frac{l}{d}$	Lysis coefficient	$4.5 \cdot 10^{-5}$-1.9

Table 2: list of parameters for the non-dimensionalized systems. Note that γ can be re-written as $\gamma' \sigma$, where $\gamma' = \frac{r_V bK}{d}$.

Fixed Point	Stability Conditions (Lytic)	Stability Conditions (Lysogenic)
$\mathbf{x_0}^*$=(0,0,0)	$\rho < 0$	$\rho < 0$
$\mathbf{x_u}^*$=(0,1,0)	$\gamma < \sigma(\alpha + 1)$	$\gamma < \sigma(\alpha + 1)$
$\mathbf{x_{VUI}}^*$=(V,U,I) †	$\sigma(\alpha + 1) < \gamma <$?††	$\sigma(\alpha + 1) < \gamma <$?‡
$\mathbf{x_{VI}}^*$=$(\gamma(1 - {}^{\sigma}/_{\rho}), 0, (1 - {}^{\sigma}/_{\rho}))$	N/A	$\sigma < \frac{\gamma\rho}{\gamma + \rho}$

Table 3: Fixed points and their conditions of stability.

†See "balanced steady state" section for the expressions for $\mathbf{x_{VUI}}^*$ in both systems.

††Numerical simulations indicate a linear function of γ and ρ at which a Hopf bifurcation occurs and $\mathbf{x_{VUI}}^*$ becomes unstable for the lytic system (figure 3).

‡For $\rho > \sigma$, $\mathbf{x_{VUI}}^*$ is stable when $\gamma < {}^{\sigma\rho}/_{\rho - \sigma}$, as it undergoes a transcritical bifurcation with $\mathbf{x_{VI}}^*$. For $\rho < \sigma$, there is a curve at which a Hopf bifurcation occurs and $\mathbf{x_{VUI}}^*$ becomes unstable for the lysogenic system (figure 3).

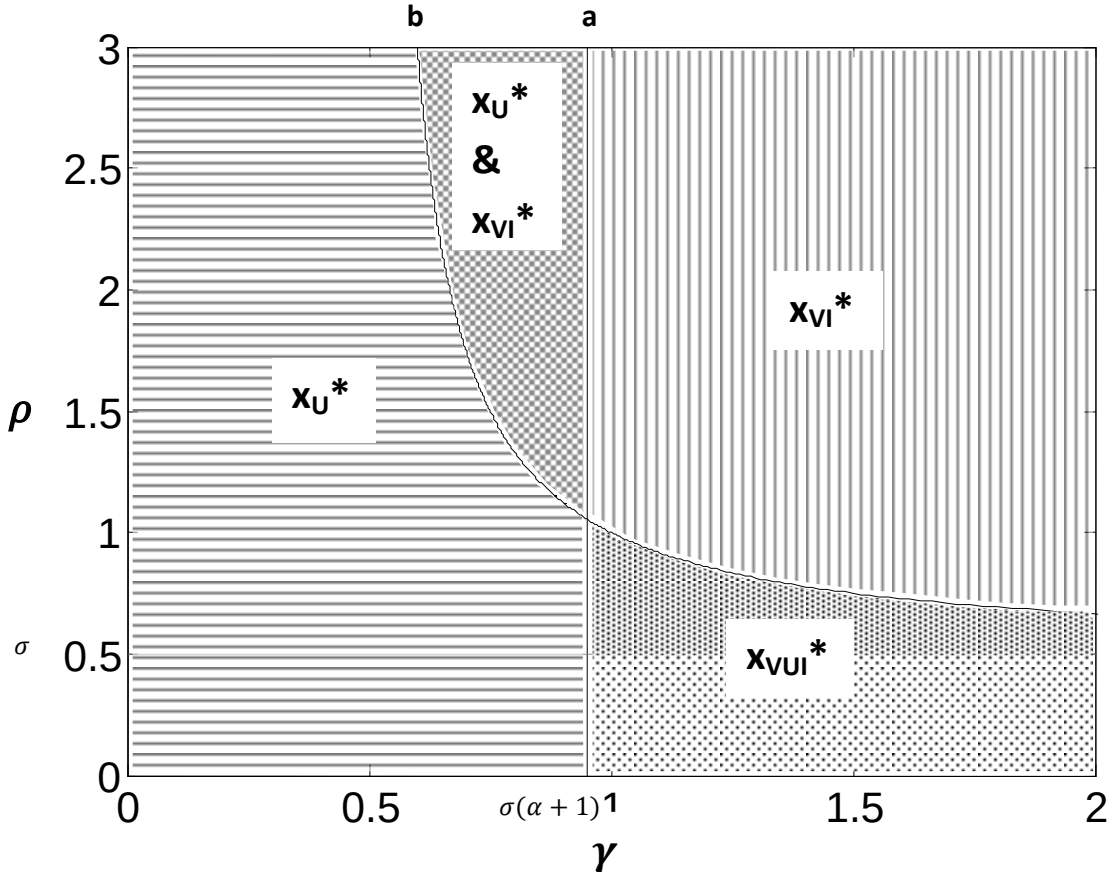

Figure 2: Stability diagram for lysogenic system. α=0.9, σ=0.5. The vertical line, **a**, is where $\gamma = \sigma(\alpha + 1)$ the curved line, **b**, is where $\gamma = {}^{\sigma\,\rho}/_{\rho\,-\,\sigma}$, above which the 'prophage fixation' fixed point $\mathbf{x_{VI}}$* is stable. In both systems, viral persistence is guaranteed when $\gamma >$ **a,** but lysogenic viral persistence can also occur in the bistable region, **a**>γ>**b** where both $\mathbf{x_{VI}}$* and $\mathbf{x_U}$* are stable. Also, since it has been shown for at least one phage-host system that $r_c \geq l$ (Lubitz et al., 1984), it may be that $\mathbf{x_{VUI}}$* is only stable in darker-shaded of the two regions it covers, where **b** $> \rho > \sigma$.

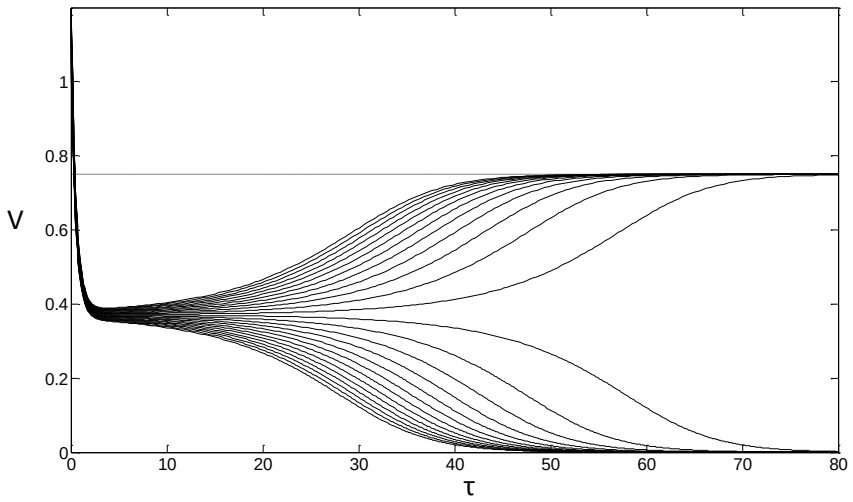

Figure 3: Bistability of lysogenic system. ρ=21, γ=5,σ=3, α=1. Initial values of viruses were increased from 1 to 5. The bistability of the lysogenic system allows for lysogenic viruses to persist even if inequality (6) is not satisfied, provided initial virus titers are large enough. Viruses in this regime, if they do persist, infect every cell and approach the prophage-fixation fixed point (dashed line).

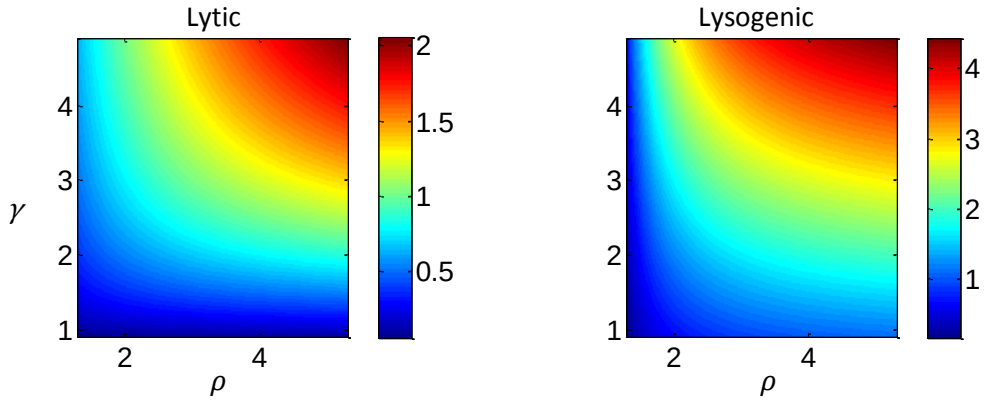

Figure 4: Viral abundance as a function of productivity. σ=0.8, α=0.5. Productivity affects both cell growth rates and virus burst size (Weinbauer et al., 1993; Weinbauer & Suttle, 1999), which corresponds to increases in ρ and γ, respectively. These models are consistent with empirical data showing increasing viral abundance with increasing productivity of the environment. However, the models fail to show a greater relative abundance of lytic phage in more productive environments, and a greater relative abundance of lysogenic phage in less productive environments. Such patterns could be explained by expanding on these systems to model competition between virus types and adding costs for cells infected with lysogenic phage.

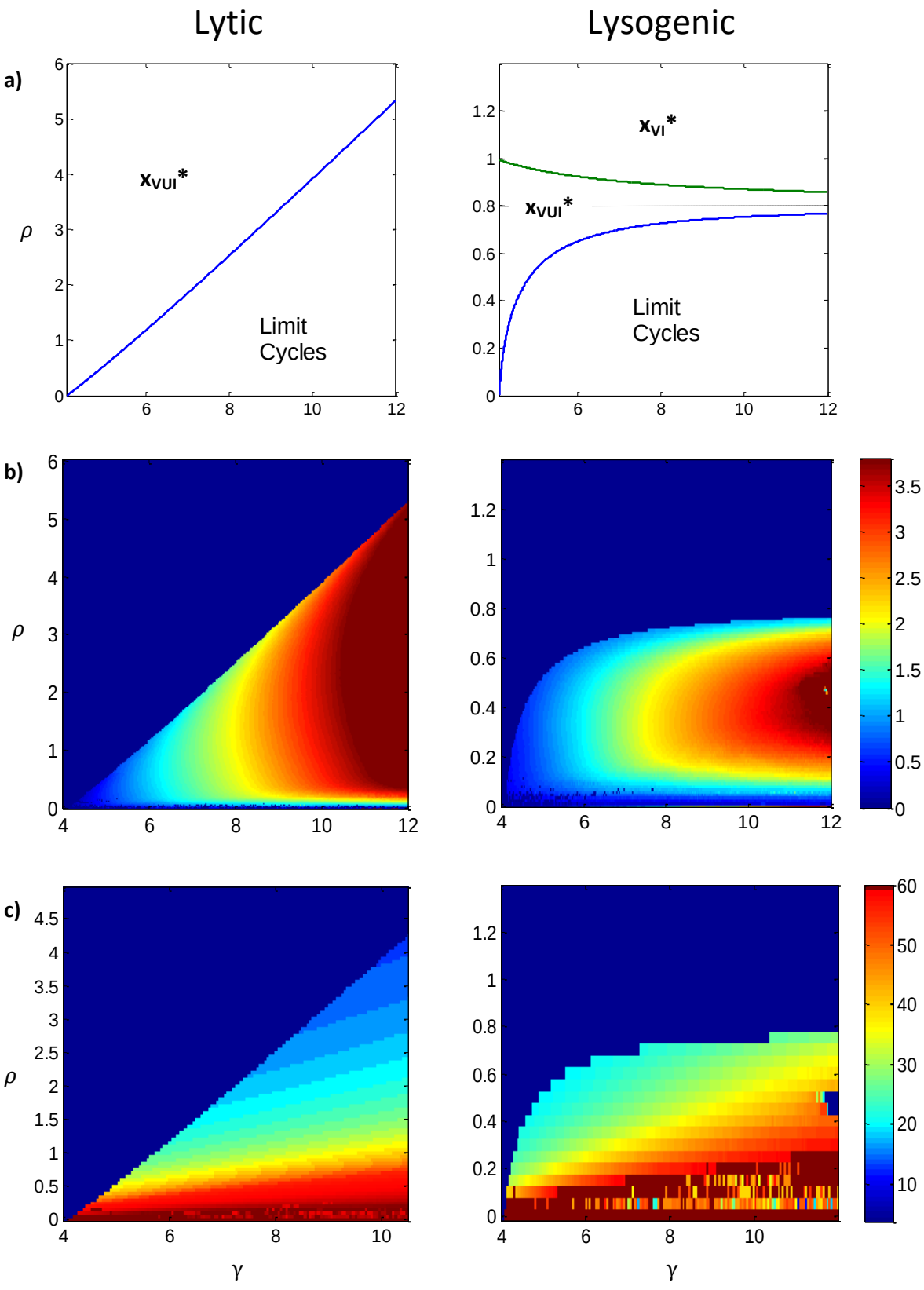
Lytic
Lysogenic
a)
b)
c)
ρ
γ
x_{VUI}*
x_{VI}*
Limit
Cycles

Figure 5: Characteristics of Oscillations around x_{VUI}*. σ=0.8, α=0.5 **a)** Location of Hopf bifurcation for lytic and lysogenic systems, where the dashed line of the lysogenic system is where ρ=σ. Notice that oscillations in the lysogenic system are only possible for ρ<σ, which translates to $r_c < l$. These may be an unrealistic parameter condition, as it has been shown for one phage-host system that $r_c \geq l$ (Lubitz et al., 1984). **b)** Magnitude of oscillations. Increasing γ has the greatest effect on the magnitude of oscillations. **c)** Period of oscillations. Unlike the magnitude, here changing ρ has the greatest effect on the frequency. For very small values of ρ, the lysogenic system becomes very stiff and numerical instability leads to problems in measuring cycle amplitude and period. Altogether, these figures suggest that lytic viruses are more prone to oscillations and that changes in virulence (burst size, infection rate) will have a greater impact on the magnitude of oscillations and that cell growth rate will have the greatest impact on the frequency of oscillations.

Appendix

$\mathbf{x_{VUI}}^*$ = $(\boldsymbol{V}, \boldsymbol{U}, \boldsymbol{I})$ = $(\rho(1-\boldsymbol{U}-\boldsymbol{I})\ ,\ \boldsymbol{U}\ ,\ \frac{(1-\boldsymbol{U})(\alpha\boldsymbol{U}+1)}{\left(\frac{\gamma}{\rho}+\alpha\boldsymbol{U}+1\right)})$,

where $\boldsymbol{U} = \frac{\sigma}{\gamma-\alpha\sigma}$

For the lysogenic system,

$\mathbf{x_{VUI}}^*$ = $(\boldsymbol{V}, \boldsymbol{U}, \boldsymbol{I})$ = $\left(\boldsymbol{V}\ ,\frac{1-\left({}^{\gamma+\rho}/_{\gamma\rho}\right)\boldsymbol{V}}{1+\left({}^{\alpha}/_{\gamma}\right)\boldsymbol{V}}\ ,\ \frac{\boldsymbol{V}(\alpha\boldsymbol{U}+1)}{\gamma}\right)$

where $\boldsymbol{V} = \left(\frac{1}{2}\right)\left((\rho+\sigma-{}^{\gamma}/_{\alpha}) + \sqrt{(\rho+\sigma-{}^{\gamma}/_{\alpha})^2 - 4({}^{\rho}/_{\alpha})(\sigma(\alpha+1)-\gamma)}\right)$

Parameter	**Comments**	**Reference**
r_c	Max values hold for *E. coli in vitro* and are unlikely *in situ*. *In situ* growth rates are more likely in the 0.2-2 day^{-1} range	Ducklow (1983), Stewart et al. (1991), & Middleboe (2000)
r_V	Increases with productivity of environment (presumably through increased sizes of cells in more productive environments)	Wommack & Colwell (2000), Weinbauer et al. (1993), and Weinbauer & Suttle (1999)
a	Adsorption constant.	Nowak & May (2000); Bocharov & Romanyukha (1994)
b	$b<a$	Dahari et al. (2005), Marchuk et al. (1991) Reluga et al. (2009)
d	Measured from half-lives of λ phage at 20-42°C	Jepson and March (2004)
l	In rich medium, $l \cong r_c$, whereas in minimal medium $l \ll r_c$ for phage ΦX174	Lubitz et al. (1984), Middleboe (2000)
K		Hanson et al. (1983)