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DYNAMICS OF A DELAY DIFFERENTIAL EQUATION MODEL OF PHAGE GROWTH IN TWO-STAGE CHEMOSTAT

By

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Abstract. In this paper, we consider a mathematical model for phage growth in a two-stage chemostat, taking account of the delay from infection to lysis. We give sufficient conditions for the globally asymptotic stability of noninfected equilibrium and obtain sufficient conditions for the local stability of infected equilibrium. We also perform some numerical simulations which illustrate the theoretical results obtained. The formula for $\mathcal{R}_0$ shows that decreasing the delay and/or increasing the burst size will increase $\mathcal{R}_0$.

1. Introduction. In the last decade or so, there has been much interest in the dynamics of the chemostat model (see, for example, [5], [7], [9]–[10]). As we know, phage evolution in a one-stage chemostat represents essentially a simple predator-prey system where populations regulate limiting resources, and phage predation regulates the resources. However phage evolution in a two-stage chemostat system parallels natural systems in which a population thrives on a resource arriving independently of population density. Recently, Bull et al. in [2] presented a delay differential equation model of phage growth in a two-stage chemostat, where the first chamber is used merely to brew a complex resource for the phage chamber. In the two-stage chemostat, the resources are input at the same level and the phage suspension is maintained at a constant volume by

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washout in the second vessel. The model was described as follows:

$$\begin{cases} \frac{dU}{dt} = -wU + Cw - \delta PU, \\ \frac{dP}{dt} = -wP - \delta PU - \delta PI + be^{-w\tau}\delta P(t-\tau)U(t-\tau), \\ \frac{dI}{dt} = -wI + \delta PU - e^{-w\tau}\delta P(t-\tau)U(t-\tau), \end{cases} \tag{1.1}$$

where $U(t)$, $P(t)$ and $I(t)$ represent the densities of uninfected host cells, the free phage (lytic viruses) and the infected host cells, respectively, and C denotes the density of uninfected host cells from the source. The parameter $\tau > 0$ is the time from infection to lysis, w is the washout rate, δ is the adsorption rate of phage to host cells, and b is the burst size, i.e, the number of offspring released by one infected cell at lysis (see [2] for details).

In [2], Bull et al. concluded that phage adaptation impacts host density but has a small effect on equilibrium phage density by analyzing the equilibria for model (1.1); moreover, experiments supported this model with both phenotypic and molecular data.

To the best of our knowledge, no rigorous work has previously been done for the dynamics on system (1.1). The purpose of this paper is to revisit the delay differential equations of phage growth in a two-stage chemostat, theoretically justifying the stability of equilibria on system (1.1) by adopting the lines in [11]–[12].

The remainder of this paper is organized as follows: in Section 2, the positivity and boundedness of solutions of the system (1.1) are presented. The stability analysis for the two equilibria are given in Section 3, and some numerical simulations are shown in Section 4 to support our analytical theory. Finally, in Section 5, conclusions are drawn from the obtained results in previous sections.

2. Positivity and boundedness. Let $X = C([-\tau, 0]; R)$ be the Banach space of continuous mappings from $[-\tau, 0]$ to R equipped with the sup-norm. Using the results in Hale and Verduyn Lunel [6], we can check that there is a unique solution $(U(t), P(t), I(t))$ to system (1.1) with nonnegative initial conditions

$$U(\theta) \geq 0, \;\; P(\theta) \geq 0, \;\; I(\theta) \geq 0, \;\; \theta \in [-\tau, 0] \tag{2.1}$$

and positive initial conditions

$$U(0) > 0, \qquad P(0) > 0, \qquad I(0) > 0. \tag{2.2}$$

Moreover, the compatibility conditions are given for system (1.1):

$$I(0) = \delta \int_{-\tau}^{0} e^{w\xi} U(\xi) P(\xi) d\xi. \tag{2.3}$$

The biological explanation of (2.3) is: $\delta \int_{-\tau}^{0} e^{w\xi} U(\xi) P(\xi) d\xi$ represents the surviving infected cells produced in the interval $[-\tau, 0]$, that is, the density of infected cells at $t = 0$.

2.1. *Positivity.*

THEOREM 2.1. Let $(U(t), P(t), I(t))$ be the solutions of system (1.1) with conditions (2.1), (2.2) and (2.3). Then $U(t), P(t), I(t)$ are positive for $t > 0$. In fact, we have

$$I(t) = \delta \int_{t-\tau}^{t} e^{-w(t-\xi)} U(\xi) P(\xi) d\xi.$$

Proof. We first consider the case of $U(t) > 0$ for $t > 0$.

It follows from the first equation in (1.1) that

$$U(t) = U(0)e^{-\int_0^t (w+\delta P(\xi))d\xi} + \int_0^t wCe^{-\int_s^t (w+\delta P(\xi))d\xi} ds,$$

which indicates that $U(t) > 0$ for all $t > 0$.

We next show the conclusion of $P(t) > 0$ for $t > 0$.

It follows from the second equation in (1.1) that

$$\begin{aligned} P(t) = {} & P(0)e^{-\int_0^t (w+\delta U(\xi)+\delta I(\xi))d\xi} \\ & + \int_0^t b\delta e^{-w\tau} e^{-\int_s^t (w+\delta U(\xi)+\delta I(\xi))d\xi} P(s-\tau)U(s-\tau)ds, \end{aligned}$$

which implies that $P(t) > 0$ for all $t > 0$.

Finally, we prove that $I(t) = \delta \int_{t-\tau}^t e^{-w(t-\xi)} U(\xi)P(\xi)d\xi$.

Observe that the third equation in (1.1) implies that

$$\frac{dI}{dt} + wI(t) = \delta e^{-wt} \frac{d}{dt} \int_{t-\tau}^t e^{w\xi} U(\xi)P(\xi)d\xi,$$

which leads to

$$\frac{d}{dt}(e^{wt} I(t)) = \frac{d}{dt}[\delta \int_{t-\tau}^t e^{w\xi} U(\xi)P(\xi)d\xi].$$

Hence

$$I(t) = \delta \int_{t-\tau}^t e^{-w(t-\xi)} U(\xi)P(\xi)d\xi + e^{-wt}[I(0) - \delta \int_{-\tau}^0 e^{w\xi} U(\xi)P(\xi)d\xi].$$

Noting that

$$I(0) = \delta \int_{-\tau}^0 e^{w\xi} U(\xi)P(\xi)d\xi,$$

we have

$$I(t) = \delta \int_{t-\tau}^t e^{-w(t-\xi)} U(\xi)P(\xi)d\xi.$$

From $U(t) > 0$ and $P(t) > 0$, it follows that $I(t) \geq 0$ for $t \geq 0$.

This completes the proof of Theorem 2.1. □

2.2. *Boundedness.* In this section, we will consider boundedness of the solutions of system (1.1).

THEOREM 2.2. Let $(U(t), P(t), I(t))$ be the solutions of system (1.1) with conditions (2.1), (2.2) and (2.3). Then

(i) $U(t), P(t), I(t)$ are ultimately bounded for $t \geq 0$;

(ii) $\overline{\lim}_{t\to\infty} U(t) \leq C, \overline{\lim}_{t\to\infty} P(t) \leq C(b-1)$ and $\overline{\lim}_{t\to\infty} I(t) \leq C\frac{b-1}{b}$ hold.

Proof. From the first equation of (1.1), it follows that

$$\frac{d[(b-1)U(t)]}{dt} = -w(b-1)U(t) + Cw(b-1) - \delta(b-1)P(t)U(t). \tag{2.4}$$

From the second and third equation of (1.1), this implies that

$$\frac{d}{dt}[bI(t) + P(t)] = -w[bI(t) + P(t)] + (b-1)\delta P(t)U(t) - \delta P(t)I(t). \tag{2.5}$$

Combining (2.4) and (2.5), we have

$$\begin{aligned}\frac{d}{dt}[bI(t)+P(t)+(b-1)U(t)] &= -w[bI(t)+P(t)+(b-1)U(t)] - \delta P(t)I(t) + Cw(b-1)\\ &< -w[bI(t)+P(t)+(b-1)U(t)] + Cw(b-1). \qquad (2.6)\end{aligned}$$

Let

$$G(t) = bI(t) + P(t) + (b-1)U(t).$$

From (2.6), it follows that

$$\frac{dG(t)}{dt} \le -wG(t) + wC(b-1).$$

By the standard comparison theorem [8], this leads to

$$G(t) \le \hat{G}(t),$$

where $\hat{G}(t)$ is the solution of $\dot{\hat{G}}(t) = -w\hat{G}(t) + wC(b-1)$, with $\hat{G}(0) \ge G(0)$. Hence,

$$G(t) \le \hat{G}(t) = C(b-1) + (\hat{G}(0) - C(b-1))e^{-wt}, \ \ t \ge 0.$$

Using the positivity of $U(t), P(t)$ and $I(t)$, it follows that

$$U(t) \le \frac{1}{b-1}G(t), \quad I(t) \le \frac{1}{b}G(t), \quad P(t) \le G(t).$$

Notice that $\lim_{t\to\infty} \hat{G}(t) = C(b-1)$ as $t \to \infty$, which implies that conclusions (i) and (ii) of Theorem 2.2 hold.

This completes the proof of Theorem 2.2. □

3. Stability analysis.

3.1. *Equilibria.* The system (1.1) has a noninfected equilibrium $E_0 = (C, 0, 0)$. The noninfected equilibrium has no infected host cell present. This is the only biologically meaningful equilibrium if

$$\mathcal{R}_0 \triangleq b\delta e^{-\omega\tau}\frac{C}{\omega + \delta C} < 1.$$

However, if $\mathcal{R}_0 > 1$, in addition to E_0, there is another infected equilibrium

$$\begin{aligned}E_1 &= (\bar{U}, \bar{P}, \bar{I})\\ &= \Big(\frac{C(1-e^{-w\tau}) + \frac{w}{\delta}}{(b-1)e^{-w\tau}}, \frac{w[C(be^{-w\tau}-1) - \frac{w}{\delta}]}{\delta[C(1-e^{-w\tau}) + \frac{w}{\delta}]}, \frac{(e^{w\tau}-1)[C(be^{-w\tau}-1) - \frac{w}{\delta}]}{b-1}\Big). \qquad (3.1)\end{aligned}$$

Obviously,

$$\bar{P} > 0 \Leftrightarrow \mathcal{R}_0 > 1,$$

which derives the formula for $\mathcal{R}_0$.

3.2. *Local stability of noninfected equilibrium E_0.* We linearize about the noninfected equilibrium of (1.1) to determine the model's local behavior. For the noninfected equilibrium the linearized equations are

$$\begin{cases} \frac{dU}{dt} = -wU - \delta CP, \\ \frac{dP}{dt} = -(w+\delta C)P + Cb\delta e^{-w\tau}P(t-\tau), \\ \frac{dI}{dt} = -wI + \delta CP - C\delta e^{-w\tau}P(t-\tau). \end{cases} \tag{3.2}$$

The characteristic equation for (3.2) is as follows:

$$(\lambda + w)(\lambda + w + \delta C - Cb\delta e^{-w\tau}e^{-\lambda\tau}) = 0. \tag{3.3}$$

Since $\lambda_1 = -w$ is a negative real root of the above equation, it suffices to solve the following equation:

$$\lambda + w + \delta C - Cb\delta e^{-w\tau}e^{-\lambda\tau} = 0. \tag{3.4}$$

From this first degree exponential polynomial equation (3.4), it is easy to see that if $\mathcal{R}_0 < 1$, then the root for (3.4) is negative; otherwise, it is positive. The results can be explained in Fig. 1 and Fig. 2, where $f(\lambda) = \lambda + w + \delta C, g(\lambda) = \delta Cbe^{-w\tau}e^{-\tau\lambda}$, A denotes $\delta Cbe^{-w\tau}$ and B denotes $w + \delta C$.

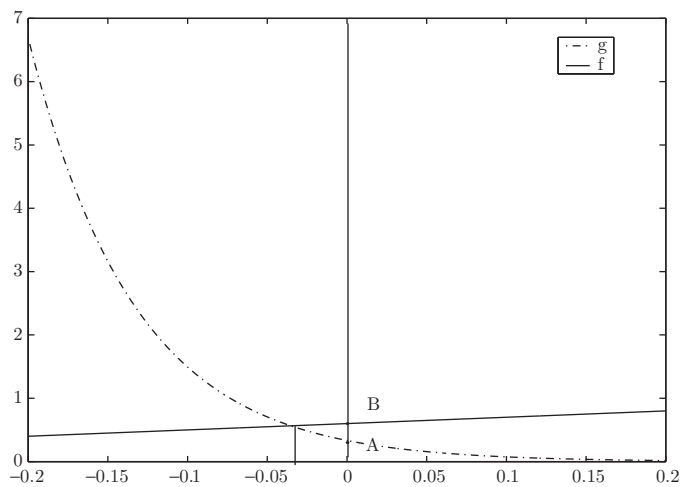

FIG. 1. The graph of the root of Eq. (3.4) for $\mathcal{R}_0 < 1$. Here $w = 0.3, \delta = 3 \times 10^{-9}, C = 10^8, b = 100, \tau = 15$, and the root for (3.4) is negative.

Hence, we have the following conclusions.

LEMMA 3.1. (i) If $\mathcal{R}_0 < 1$, then the equation (3.3) has no positive roots.

(ii) If $\mathcal{R}_0 > 1$, then the equation (3.3) has one positive root.

From Lemma 3.1 , we have the following theorem.

THEOREM 3.2. (i) If $\mathcal{R}_0 < 1$, then the noninfected equilibrium $(\hat{U}, \hat{P}, \hat{I})$ is locally asymptotical stable.

(ii) If $\mathcal{R}_0 > 1$, then the noninfected equilibrium is unstable and the infected equilibrium $(\bar{U}, \bar{P}, \bar{I})$ occurs.

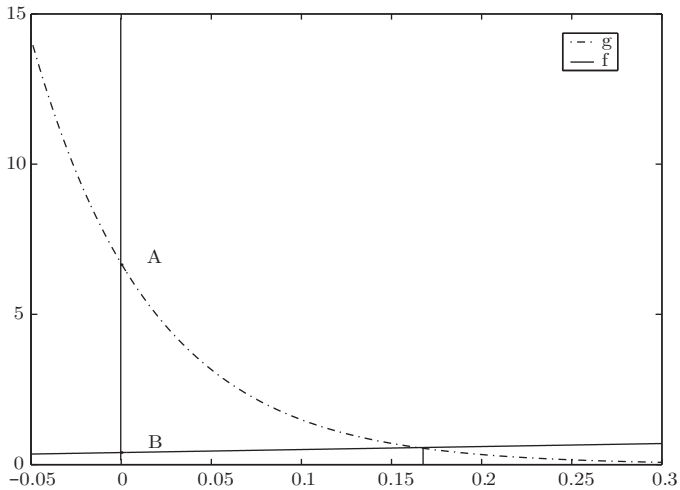

FIG. 2. The graph of the root of Eq. (3.4) for $\mathcal{R}_0 > 1$. Here $w = 0.1, \delta = 3 \times 10^{-9}, C = 10^8, b = 100, \tau = 15$, and the root for (3.4) is positive.

3.3. *Globally asymptotic stability of noninfected equilibrium E_0.* First, we consider the global attractability of a noninfected equilibrium.

LEMMA 3.3. Let $(U(t), P(t), I(t))$ be the solutions of system (1.1) with conditions (2.1), (2.2) and (2.3). If $\mathcal{R}_0 < 1$, then

$$\lim_{t\to\infty} P(t) = 0, \quad \lim_{t\to\infty} I(t) = 0, \quad \lim_{t\to\infty} U(t) = C.$$

Proof. From the second equation of (1.1), it follows that

$$\begin{aligned}\frac{dP(t)}{dt} &= -P(w + \delta U + \delta I) + b\delta e^{-w\tau} U(t-\tau)P(t-\tau) \\ &= -wP(t) - \delta P(t)I(t) + (be^{-w\tau} - 1)\delta U(t)P(t) - b\delta e^{-w\tau} \frac{d}{dt}\int_{t-\tau}^{t} U(\xi)P(\xi)d\xi.\end{aligned}$$

Using Conclusion (ii) of Theorem 2.2 and noticing that $\mathcal{R}_0 < 1$, it follows that there is some $T > 0$ such that

$$\begin{aligned}&\frac{d}{dt}[P(t) + b\delta e^{-w\tau}\int_{t-\tau}^{t} U(\xi)P(\xi)d\xi] \\ &\qquad \le -(w + \delta C - b\delta C e^{-w\tau})P(t) - \delta P(t)I(t)\end{aligned}$$

as $t \ge T$; that is,

$$\begin{aligned}&\frac{d}{dt}[P(t) + b\delta e^{-w\tau}\int_{t-\tau}^{t} U(\xi)P(\xi)d\xi] \\ &\qquad \le -(w + \delta C - b\delta C e^{-w\tau})P(t) \qquad (3.5)\end{aligned}$$

as $t \ge T$.

Then we integrate (3.5) from 0 to $t \geq T$ to obtain

$$P(t) + b\delta e^{-w\tau} \int_{t-\tau}^{t} U(\xi)P(\xi)d\xi \leq M - K \int_0^t P(\xi)d\xi,$$

where $M = P(0) + b\delta e^{-w\tau} \int_{-\tau}^{0} U(\xi)P(\xi)d\xi$ and $K = w + \delta C - b\delta C e^{-w\tau}$.

So, we have

$$P(t) \leq M - K \int_0^t P(\xi)d\xi. \tag{3.6}$$

Letting $g(t) = \int_0^t P(\xi)d\xi$, from (3.6), it follows that

$$\frac{d}{dt}g(t) \leq M - Kg(t),$$

which leads to

$$\frac{d}{dt}[g(t)e^{Kt}] \leq Me^{Kt}. \tag{3.7}$$

Integrating (3.7) from 0 to $t \geq T$, we have

$$\begin{aligned} g(t) &\leq g(0)e^{-Kt} + e^{-Kt} \int_0^t Me^{K\xi}d\xi \\ &= \frac{M}{K}(1 - e^{-Kt}) \leq \frac{M}{K} \end{aligned}$$

as $t \geq T$. Hence, from the above, it follows that $\lim_{t\to\infty} \int_0^t P(\xi)d\xi = \lim_{t\to\infty} g(t)$ exists since $g(t)$ is also a monotonic increasing function. Noting that $\frac{d}{dt}P(t)$ is bounded and $P(t) > 0$, this implies that $\lim_{t\to\infty} P(t) = 0$.

Applying the above and the theory of an asymptotically autonomous system (see [4]) to the third and first equations of system (1.1), we conclude that

$$\lim_{t\to\infty} I(t) = 0, \qquad \lim_{t\to\infty} U(t) = C.$$

This completes the proof of Lemma 3.3. □

From Lemma 3.3 and the conclusion (i) of Theorem 3.2, we have the following theorem on globally asymptotic stability of a noninfected equilibrium E_0.

THEOREM 3.4. If $\mathcal{R}_0 < 1$, then the noninfected equilibrium E_0 is globally asymptotically stable.

3.4. *Local stability of infected equilibrium E_1.* The linearized equations of system (1.1) at the infected equilibrium $E_1 = (\bar{U}, \bar{P}, \bar{I})$ are

$$\begin{cases} \frac{dU}{dt} = -wU - \delta\bar{P}u - \delta\bar{U}P, \\ \frac{dP}{dt} = -\delta\bar{P}U - (w + \delta\bar{U} + \delta\bar{I})P - \delta\bar{P}I + b\delta e^{-w\tau}[\bar{P}U(t-\tau) + \bar{U}P(t-\tau)], \\ \frac{dI}{dt} = -wI + \delta\bar{P}U + \delta\bar{U}P - e^{-w\tau}\delta[\bar{P}U(t-\tau) + \bar{U}P(t-\tau)]. \end{cases} \tag{3.8}$$

Since system (3.7) is linear in U, P and I, it has a solution the form

$$(U(t), P(t), I(t)) = (K_1e^{\lambda t}, K_2e^{\lambda t}, K_3e^{\lambda t}),$$

where K_1, K_2 and K_3 are constants. Substituting it into system (3.7), it follows respectively from the first equation in (3.7), the second and third ones in (3.7), that

$$K_2 = -\frac{\lambda + \delta\bar{P} + w}{\delta\bar{U}} K_1$$

and

$$(\lambda + w + \delta\bar{U} + \delta\bar{I} - b\delta\bar{U})K_2 = (b-1)\delta\bar{P}K_1 - (\delta\bar{P} + b\lambda + bw)K_3.$$

So,

$$\begin{aligned} K_3 &= \frac{(\lambda + w + \delta\bar{U} + \delta\bar{I} - b\delta\bar{U})\frac{\lambda+w+\delta P}{\delta\bar{U}} + (b-1)\delta\bar{P}}{\delta\bar{P} + bw + b\lambda} K_1 \\ &= \{\frac{(\lambda + w + \delta\bar{P})(\lambda + w + \delta\bar{U} + \delta\bar{I})}{[b(\lambda + w) + \delta\bar{P}]\delta\bar{U}} - 1\}K_1. \end{aligned}$$

Substituting K_2 and K_3 into the third equation of system (3.7), and cancelling K_1, we have

$$\begin{aligned} &(\lambda + w)\{\frac{(\lambda + w + \delta\bar{P})(\lambda + w + \delta\bar{U} + \delta\bar{I})}{[b(\lambda + w) + \delta\bar{P}]\delta\bar{U}} - 1\} \\ &= (\delta\bar{P} - \delta e^{-w\tau}\bar{P}e^{-\lambda\tau}) - (\delta\bar{U} - \delta\bar{U}e^{-w\tau}e^{-\lambda\tau})\frac{(\lambda + \delta\bar{P} + w)}{\delta\bar{U}} \\ &= -(\lambda + w) + (\lambda + w)e^{-w\tau}e^{-\lambda\tau}. \end{aligned}$$

Hence, the characteristic equation for (3.7) is

$$(\lambda+w)\{[(\lambda+w+\delta\bar{P})(\lambda+w+\delta\bar{U}+\delta\bar{I})]-[\delta b\bar{U}e^{-w\tau}\lambda+(bw+\delta\bar{P})\delta\bar{U}e^{-w\tau}]e^{-\lambda\tau}\} = 0. \quad (3.9)$$

One of the roots of the characteristic equation (3.8) is $\lambda_1 = -w$. The remaining two roots are obtained by considering

$$(\lambda + w + \delta\bar{P})(\lambda + w + \delta\bar{U} + \delta\bar{I}) - [\delta b\bar{U}e^{-w\tau}\lambda + (bw + \delta\bar{P})\delta\bar{U}e^{-w\tau}]e^{-\lambda\tau} = 0. \quad (3.10)$$

Obviously, the equation (3.9) is equivalent to

$$\lambda^2 + A_1\lambda + A_0 - (B_1\lambda + B_0)e^{-\lambda\tau} = 0, \quad (3.11)$$

where

$$\begin{aligned} &A_1 = 2w + \delta(\bar{P} + \bar{U} + \bar{I}), \\ &A_0 = (w + \delta\bar{P})(w + \delta\bar{U} + \delta\bar{I}) = w^2 + \delta w(\bar{P} + \bar{U} + \bar{I}) + \delta^2(\bar{U} + \bar{I})\bar{P}, \\ &B_1 = \delta b\bar{U}e^{-w\tau}, \\ &B_0 = \delta\bar{U}e^{-w\tau}(bw + \delta\bar{P}). \end{aligned}$$

Note that A_1, A_0, B_1, B_0 all depend on the delay τ.

Clearly, if $\mathcal{R}_0 > 1$, then $\lambda = 0$ is not a root of the equation (3.10), since

$$\begin{aligned}
A_0 - B_0 &= w^2 + \delta w(\bar{P} + \bar{U} + \bar{I}) + \delta^2(\bar{U} + \bar{I})\bar{P} - \delta\bar{U}e^{-w\tau}(bw + \delta\bar{P}) \\
&= w^2 + \delta w[\bar{P} + (C - \frac{1}{1-e^{-w\tau}}\bar{I}) + \bar{I}] + \delta^2(\bar{U} + \bar{I})\bar{P} - \delta\bar{U}e^{-w\tau}(bw + \delta\bar{P}) \\
&= w^2 + \delta w\{C + w[C(be^{-w\tau} - 1) - \frac{w}{\delta}]\frac{[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{(b-1)[\delta C(1 - e^{-w\tau}) + w]}\} \\
&\quad + \ \delta^2\frac{w}{\delta}\frac{[C(be^{-w\tau} - 1) - \frac{w}{\delta}]}{[C(1 - e^{-w\tau}) + \frac{w}{\delta}]}\frac{[bc(1 - e^{-w\tau}) + \frac{w}{\delta}]}{(b-1)} - \delta wC - w^2 \\
&= \delta w\frac{[C(be^{-w\tau} - 1) - \frac{w}{\delta}]}{[C(1 - e^{-w\tau}) + \frac{w}{\delta}]}\{\frac{w[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{\delta(b-1)} + \frac{[bC(1 - e^{-w\tau}) + \frac{w}{\delta}]}{b-1}\} \\
&= \delta w\frac{[C(be^{-w\tau} - 1) - \frac{w}{\delta}]}{[C(1 - e^{-w\tau}) + \frac{w}{\delta}]}[\frac{wb - 2w - \delta C(1 - e^{-w\tau}) + \delta bC(1 - e^{-w\tau}) + w}{\delta(b-1)}] \\
&= \delta w[C(be^{-w\tau} - 1) - \frac{w}{\delta}] > 0. \qquad (3.12)
\end{aligned}$$

If $\tau = 0$, then the equation (3.10) becomes

$$\lambda^2 + (A_1 - B_1)\lambda + A_0 - B_0 = 0. \qquad (3.13)$$

Moreover, if $\mathcal{R}_0 > 1$ and $b > 2 + \frac{\delta C}{w}$, then

$$\begin{aligned}
A_1 - B_1 &= 2w + \delta(\bar{P} + \bar{U} + \bar{I}) - b\delta\bar{U}e^{-w\tau} \\
&= 2w + \delta\{C + w[C(be^{-w\tau} - 1) - \frac{w}{\delta}]\frac{[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{(b-1)[\delta C(1 - e^{-w\tau}) + w]}\} - b\delta e^{-w\tau}\frac{[C(1 - e^{-w\tau}) + \frac{w}{\delta}]}{(b-1)e^{-w\tau}} \\
&= 2w + \delta C - b\delta\frac{[C(1 - e^{-w\tau}) + \frac{w}{\delta}]}{(b-1)} + \delta w[C(be^{-w\tau} - 1) - \frac{w}{\delta}]\frac{[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{(b-1)[\delta C(1 - e^{-w\tau}) + w]} \\
&= w\frac{b-2}{b-1} + \delta C[1 - \frac{b(1 - e^{-w\tau})}{b-1}] + \delta w[C(be^{-w\tau} - 1) - \frac{w}{\delta}]\frac{[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{(b-1)[\delta C(1 - e^{-w\tau}) + w]} \\
&> w\frac{b-2}{b-1} + \frac{w}{b-1} + \delta w[C(be^{-w\tau} - 1) - \frac{w}{\delta}]\frac{[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{(b-1)[\delta C(1 - e^{-w\tau}) + w]} \\
&= w + \delta w[C(be^{-w\tau} - 1) - \frac{w}{\delta}]\frac{[b - 2 - \frac{\delta C}{w}(1 - e^{-w\tau})]}{(b-1)[\delta C(1 - e^{-w\tau}) + w]} > 0. \qquad (3.14)
\end{aligned}$$

From (3.11) and (3.13), it follows that all roots of (3.10) have negative real parts for $\tau = 0$. Note that all roots of (3.10) depend continuously on τ (see [3]). Notice also that the assumption (ii) of [1] holds and this ensures that no root will come in from infinity. That is, $\mathrm{Re}(\lambda) < +\infty$ for any root of (3.10). Therefore, as the delay τ increases, the roots of (3.10) can cross the imaginary axis only through a pair nonzero purely imaginary roots. Let $\lambda = iw$ with $w > 0$ be a purely imaginary root of (3.10). Then,

$$-w^2 + iA_1w + A_0 = (iB_1w + B_0)e^{-iw\tau}.$$

Rewriting the above equation and taking moduli gives

$$|-w^2 + iA_1w + A_0| = |iB_1w + B_0|.$$

Letting $y = w^2$ yields

$$y^2 + (A_1^2 - B_1^2 - 2A_0)y + A_0^2 - B_0^2 = 0. \tag{3.15}$$

A calculation gives

$$\begin{aligned}
A_1^2 - B_1^2 - 2A_0 &= (A_1 + B_1)(A_1 - B_1) - 2A_0 \\
&= [2w + \delta(\bar{P} + \bar{U} + \bar{I}) + \delta b\bar{U}e^{-w\tau}][2w + \delta(\bar{P} + \bar{U} + \bar{I}) - \delta b\bar{U}e^{-w\tau}] \\
&\quad - 2(w + \delta\bar{P})(w + \delta\bar{U} + \delta\bar{I}) \\
&= [2w + \delta(\bar{P} + \bar{U} + \bar{I}) + \delta b\bar{U}e^{-w\tau}][2w + \delta(\bar{P} + \bar{U} + \bar{I}) - \delta b\bar{U}e^{-w\tau} - 2(w + \delta\bar{P})] \\
&\quad + 2(w + \delta\bar{P})(\bar{P}\delta + \delta be^{-w\tau}\bar{U} + w) \\
&= [2w + \delta(\bar{P} + \bar{U} + \bar{I}) + \delta b\bar{U}e^{-w\tau}]\delta[(\bar{U} + \bar{I}) - (b\bar{U}e^{-w\tau} + \bar{P})] \\
&\quad + 2(w + \delta\bar{P})(\bar{P}\delta + \delta be^{-w\tau}\bar{U} + w) \\
&= -[2w + \delta(\bar{P} + \bar{U} + \bar{I}) + \delta b\bar{U}e^{-w\tau}](w + \delta\bar{P}) + 2(w + \delta\bar{P})(\bar{P}\delta + \delta be^{-w\tau}\bar{U} + w) \\
&= (w + \delta\bar{P})\delta[\bar{P} - (\bar{U} + \bar{I} - be^{-w\tau}\bar{U})] \\
&= (w + \delta\bar{P})\delta(\bar{P} + \frac{w}{\delta}) \\
&= (w + \delta\bar{P})^2 > 0.
\end{aligned}$$

This, together with (3.11), implies that (3.14) has no nonnegative real root. Therefore, there is no root $\lambda = iw, w > 0$ for (3.10) and hence all roots of (3.10) have negative real parts for all $\tau \geq 0$ as long as $\mathcal{R}_0 > 1$ and $b > 2 + \frac{\delta C}{w}$. Hence, we have

LEMMA 3.5. If $\mathcal{R}_0 > 1$ and $b > 2 + \frac{\delta C}{w}$, then all roots of (3.10) have negative real parts.

This follows immediately from Lemma 3.5. The following theorem is on the stability of the infected equilibrium E_1.

THEOREM 3.6. If $\mathcal{R}_0 > 1$ and $b > 2 + \frac{\delta C}{w}$, then the infected equilibrium $E_1 = (\bar{U}, \bar{P}, \bar{I})$ is asymptotically stable.

4. Numerical simulations. In this section, we illustrate the validity of the obtained results in Section 3. All numerical simulations are carried out using the software Matlab.

Consider system (1.1). Take $w = 0.1, \delta = 10^{-3}, C = 10, b = 20$ and $\tau = 15$. Straightforward calculations show that the uninfected equilibrium $E_0 = (10, 0, 0)$ and $\mathcal{R}_0 = 0.33 < 1$. Simulation shows that E_0 is asymptotically stable. This is consistent with the result in Theorem 3.4 (see Fig. 3).

Next, we take another set of values for the parameters: $w = 0.1, \delta = 10^{-3}, C = 100, b = 20$ and $\tau = 6.4$. For these values, $\mathcal{R}_0 = 5.3 > 1$ and $b > 2 + \frac{\delta C}{w} = 3$. In addition to the uninfected equilibrium $E_0 = (100, 0, 0)$, there is an infected equilibrium $E_1 = (14.6, 836.2, 40.1)$. Simulation shows that E_1 is asymptotically stable, which is consistent with the result in Theorem 3.6 (see Fig. 4).

5. Conclusions. Based on the assumptions that the resources are input at the same level and the input cell density is not regulated by phage, Bull et al. constructed a delay differential equation model of phage growth in a two-stage chemostat, where the first

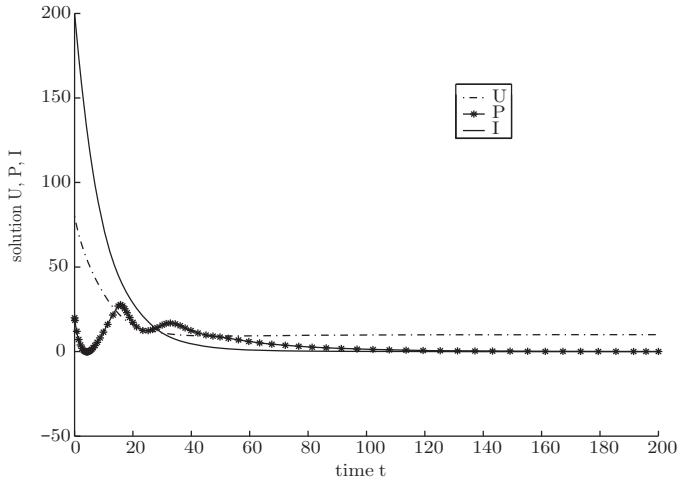

FIG. 3. The stability of the uninfected equilibrium E_0 of system (1.1) with $w = 0.1, \delta = 10^{-3}, C = 10, b = 20$ and $\tau = 15$ giving $\mathcal{R}_0 = 0.33 < 1$. The initial conditions are $U(\theta) = 80, P(\theta) = 20, I(\theta) = 200$ for $\theta \in [-\tau, 0]$.

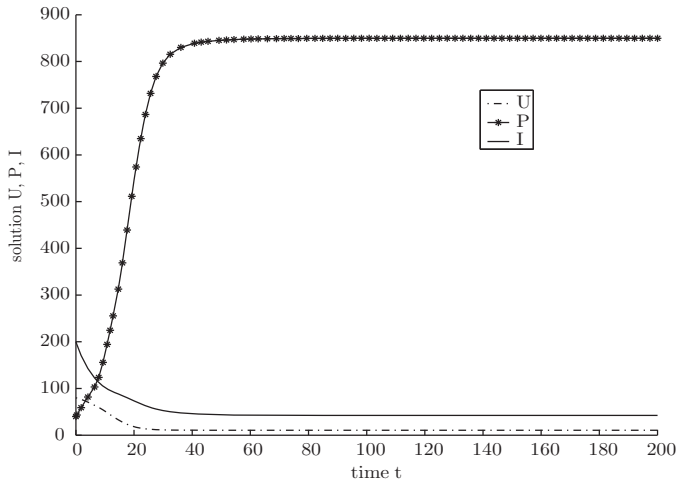

FIG. 4. The stability of the infected equilibrium E_1 of system (1.1) with $w = 0.1, \delta = 10^{-3}, C = 100, b = 20$ and $\tau = 6.4$ giving $\mathcal{R}_0 = 5.3 > 1$ and $2 + \frac{\delta C}{w} = 3$. The initial conditions are $U(\theta) = 80, P(\theta) = 40, I(\theta) = 200$ for $\theta \in [-\tau, 0]$.

chamber contains merely host cells and there are both phage and cells in the second vessel. For this model, we have analyzed theoretically that the uninfected equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$. Moreover, we have proved that when $\mathcal{R}_0 > 1$, the uninfected equilibrium E_0 becomes unstable and there occurs an infected equilibrium E_1, which is asymptotically stable when $b > 2 + \frac{\delta C}{w}$. We have performed some numerical simulations to support the obtained theoretical results.

From the theoretical and numeric results summarized above, we conclude that to raise the concentrations of the phage, a strategy should aim to increase the value of $\mathcal{R}_0$ to the above one. By the explicit formula for $\mathcal{R}_0$, we see that $\mathcal{R}_0$ can be enlarged by decreasing the time from infection to lysis and/or increasing the burst size.

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