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DYNAMICS OF EVOLUTIONARY COMPETITION BETWEEN BUDDING AND LYTIC VIRAL RELEASE STRATEGIES

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Abstract. In this paper, we consider the evolutionary competition between budding and lytic viral release strategies, using a delay differential equation model with distributed delay. When antibody is not established, the dynamics of competition depends on the respective basic reproductive ratios of the two viruses. If the basic reproductive ratio of budding virus is greater than that of lytic virus and one, budding virus can survive. When antibody is established for both strains but the neutralization capacities are the same for both strains, consequence of the competition also depends only on the basic reproductive ratios of the budding and lytic viruses. Using two concrete forms of the viral production functions, we are also able to conclude that budding virus will outcompete if the rates of viral production, death rates of infected cells and neutralizing capacities of the antibodies are the same for budding and lytic viruses. In this case, budding strategy would have an evolutionary advantage. However, if the antibody neutralization capacity for the budding virus is larger than that for the lytic virus, the lytic virus can outcompete the budding virus provided that its reproductive ratio is very high. An explicit threshold is derived.

1. **Introduction.** In the real world, there are mainly two types of viral release strategies: lytic and budding. Viruses can be released from the host cell by lysis, a process that kills the cell by bursting its membrane, after a period of accumulation of new virions inside the host cell. This is a feature of many bacterial and animal naked viruses, such as many types of phages, rhinoviruses and picornaviruses [2]. Many viruses do not lyse their host cells; instead, progeny virions are released from the cells over a period of time by gradually budding. Enveloped viruses, such as HIV and influenza, are typically released from host cells by this strategy (see [5, 9]). During this process a virus acquires its envelope from cell surface membrane.

A typical viral production process consists of viral attachment (to the host cells), penetration, uncoating, replication and release. However, lytic and budding viral strains have different life cycles. A lytic virus has a lytic cycle during which the new virions are produced and accumulated inside the host cell, and released by a burst (lysis) when the number of viruses inside becomes too large for the cell to

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hold. A budding virus reproduces inside and escapes the host cell by constantly budding throughout the lifespan of the infected cell.

There is some research on the kinetics of viral production. Coombs [4] examined the optimal virus production schedules by considering the trade-off between viral replication and cell death rate. Burst size, defined as the expected number of virions produced over the lifetime of an infected cell, was considered as viral reproductive fitness. It was found that if viral production rate and cell mortality rate are linked, replicating at the maximal rate so that the burst size is maximized, may not be the optimal strategy for virus, even if natural selection favors viral strains whose virion production rate maximizes viral burst size. The optimal viral production rate may be lower than the maximum viral production rate, or may not be a constant, meaning that it may vary with the time or the age of the infected cell, depending on the trade-off between cell mortality and viral production. In a subsequent work, Gilchrist *et al.* [6] used an age-structured model of virus dynamics to study the optimal viral fitness. It was shown that trade-offs between virion production and immune system clearance of infected cells could lead natural selection to favor production rates lower than the one that maximizes burst size. Nelson *et al.* [10] also used an age structured model to study the influence of different profiles of nonconstant viral production rate and nonconstant infected cell death rate on HIV infection dynamics. As for lytic virus, Wang *et al.* (see [13, 14]) studied the optimal lysis time and phage fitness. It was found that a delay in lysis time can lead to production of more progeny per infected host. Therefore, there is a trade-off between a present immediate linear gain by extending the vegetative cycle of phage and a future uncertain exponential gain derived from lysing the current host and releasing the progeny virion.

Komarova [8] studied the evolutionary competition between budding and lytic strategies. It was concluded that if all the parameters, such as the rate of viral production, cell lifespan and neutralizing capacity of antibodies, were the same for the lytic and budding viruses, the budding life-strategy would have a large evolutionary advantage because it is advantageous for an organism to reproduce earlier in life rather than later, given that the offspring is the same in both cases. However when the antibody effect is considered, the difference in removal capacity of the antibodies against budding and lytic virions could make lytic virus evolutionarily more competitive. Newly produced virions of a budding virus exit the host cell gradually and are immediately attacked by antibodies, while that of a lytic strain exit all at once, in a burst, and if there are sufficiently many of them, they can "flood" the immune system making it less effective.

Komarova [8] used the Euler-Lotka equation for the host cell population and reaction diffusion equations for antibody flooding effect. The disadvantage of the Euler-Lotka model is that it only models a steady state of viral spread, when the uninfected host cells are freely available. In this paper, we aim at providing an alternative perspective by focusing on the infection age and release strategy. More specifically, we propose a mathematical model described by ordinary differential equations with distributed delay accounting for infection age. By analyzing this structured model system, we study the evolutionary competition between these two viral productive strategies.

The rest of this paper is organized as follows. In Section 2, we present an age structured model and its simplified form with distributed delay. In Section 3, we prove that all the solutions of our model are positive and bounded. In Section 4, the

equilibria of the model and their stability are discussed. In Section 5, we give two explicit forms of the viral production function and investigate the effect of antibody on evolutionary competition of budding and lytic strategies. The paper is ended by Section 6, where in addition to conclusion, some discussion is also presented.

2. **Model formulation.** Age structured models have been used to study the within-host dynamics for HIV (see [6, 10, 11]). We use an age structured model for the infected cell population. The infection age, a, is the time lapsed since a cell was infected by a virus. Suppose that $T(t)$ is the concentration of uninfected target cells at time t; $V_B(t)$ is the concentration of virus produced by the budding strategy at time t (we call it budding virus); $V_L(t)$ is the concentration of virus produced by the lytic strategy at time t (we call it lytic virus); $T_B^*(t,a)$ is the concentration of infected cells at infection age a at time t, which are infected by budding virus; $T_L^*(t,a)$ is the concentration of infected cells at infection age a and at time t, which are infected by lytic virus; $A(t)$ is the concentration of antibody at time t. By infection, budding virus and lytic virus compete for uninfected target cells. Assuming mass action infection mechanism, we propose the following system of differential equations to describe the competition dynamics of budding and lytic viruses:

$$\begin{cases} \dfrac{dT(t)}{dt} = H - d_T T(t) - \beta_B T(t) V_B(t) - \beta_L T(t) V_L(t), \\ \dfrac{\partial T_B^*(t,a)}{\partial t} + \dfrac{\partial T_B^*(t,a)}{\partial a} = -d_{T_B^*}(a) T_B^*(t,a), \\ \dfrac{\partial T_L^*(t,a)}{\partial t} + \dfrac{\partial T_L^*(t,a)}{\partial a} = -d_{T_L^*}(a) T_L^*(t,a), \\ \dfrac{dV_B(t)}{dt} = \displaystyle\int_{\tau_B}^{\tau^*} \gamma_B(a) T_B^*(t,a) da - d_V V_B(t) - \eta_B V_B(t) A(t), \\ \dfrac{dV_L(t)}{dt} = \displaystyle\int_{\tau_L}^{\tau^*} \gamma_L(a) T_L^*(t,a) da - d_V V_L(t) - \eta_L V_L(t) A(t), \\ \dfrac{dA(t)}{dt} = p(V_B(t) + V_L(t)) A(t) - d_A A(t) - \eta_B V_B(t) A(t) - \eta_L V_L(t) A(t). \end{cases} \tag{1}$$

Here, β_B and β_L represent the infection rates of budding virus and lytic virus respectively. $\gamma_B(a)$ and $\gamma_L(a)$ are the virion production rates from infected cells with an infection age a by budding strategy and by lytic strategy respectively. τ_B and τ_L denote the ages when the infected cells begin to release new virions by budding and lysis respectively. p is the activation rate of antibodies. η_B and η_L are the neutralization rates of antibodies for budding virus and lytic virus respectively. Although the model (1) looks symmetric in its form for the two viruses, it is the particular forms of the two functions $\gamma_B(a)$ and $\gamma_L(a)$ that will actually characterize the nature of the production/release strategies of the two viruses, and thereby, make the model (1) asymmetric. This will be discussed in Section 5, particularly demonstrated in Fig. 4 and Fig. 5.

We assume that viruses are introduced at time $t = 0$, meaning that there is neither virus nor infection for $t \in [-\tau^*, 0)$, and infection occurs at $t = 0$ immediately after introduction of viruses. Accordingly

$$T_B^*(0,a) = 0, \quad T_L^*(0,a) = 0, \ \text{ for all } \ a > 0.$$

The infected cells of age zero come from the new infections, that is

$$T_B^*(t,0) = \beta_B T(t) V_B(t), \ \ T_L^*(t,0) = \beta_L T(t) V_L(t).$$

Now, for the budding virus, the dynamics are determined by the following initial-boundary value problem:

$$\begin{cases} \dfrac{\partial T_B^*(t,a)}{\partial t} + \dfrac{\partial T_B^*(t,a)}{\partial a} = -d_{T_B^*}(a) T_B^*(t,a), \\ T_B^*(t,0) = \beta_B T(t) V_B(t), \\ T_B^*(0,a) = 0, \quad \forall a > 0. \end{cases} \tag{2}$$

Solving this problem by the method of characteristics, we obtain

$$T_B^*(t,a) = \begin{cases} \beta_B T(t-a) V_B(t-a) e^{-\int_0^a d_{T_B^*}(\xi) d\xi} & t \geq a, \\ 0 & t < a. \end{cases}$$

Similarly, we have

$$T_L^*(t,a) = \begin{cases} \beta_L T(t-a) V_L(t-a) e^{-\int_0^a d_{T_L^*}(\xi) d\xi} & t \geq a, \\ 0 & t < a. \end{cases}$$

Substituting the above formulas for $T_B^*(t,a)$ and $T_L^*(t,a)$ into V_B and V_L equations in (1), and by our assumptions that $V_B(\theta) = 0$, $V_L(\theta) = 0$, for all $\theta \in [-\tau^*, 0)$, we obtain the following model system:

$$\begin{cases} \dfrac{dT(t)}{dt} = H - d_T T(t) - \beta_B T(t) V_B(t) - \beta_L T(t) V_L(t), \\ \dfrac{dV_B(t)}{dt} = \displaystyle\int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi) d\xi} \beta_B T(t-a) V_B(t-a) da \\ \qquad\qquad - d_V V_B(t) - \eta_B V_B(t) A(t), \\ \dfrac{dV_L(t)}{dt} = \displaystyle\int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi) d\xi} \beta_L T(t-a) V_L(t-a) da \\ \qquad\qquad - d_V V_L(t) - \eta_L V_L(t) A(t), \\ \dfrac{dA(t)}{dt} = p(V_B(t) + V_L(t)) A(t) - d_A A(t) - \eta_B V_B(t) A(t) - \eta_L V_L(t) A(t). \end{cases} \tag{3}$$

In the rest of the paper, we shall investigate the dynamics of this system.

TABLE 1. The descriptions of the parameters in the model (3)

Varibles/Parameters	Descriptions
T	Density of target cells
V_B	Viral load of budding virus
V_L	Viral load of lytic virus
A	Density of antibody
H	Recruitment rate of target cells
$d_T, d_{T_B^*}, d_{T_L^*}$	Death rates of target cells/budding-virus-infected cells/ lytic-virus-infected cells
d_V, d_A	Clearance rates of virus/antibodies
β_B, β_L	Infection rates of budding virus/lytic virus
γ_B, γ_L	Viral production rates of infected cells by budding/lytic strategy
η_B, η_L	Neutralization rates of antibodies induced by budding/lytic virus
p	Activation rate of antibodies

3. **Positivity and boundedness of solutions.** Let $\mathbb{X} = C([-\tau^*, 0], \mathbb{R}^4)$ be the Banach space of continuous functions with supremum norm. By the fundamental theory of FDEs [7], we know that there is a unique solution $(T(t), V_B(t), V_L(t), A(t))$ to the system with given initial conditions $(T(\theta), V_B(\theta), V_L(\theta), A(\theta)) \in \mathbb{X}$. Due to the biological meanings of the unknown functions, we need to further assume that the initial functions $T(\theta)$, $V_B(\theta)$, $V_L(\theta)$, and $A(\theta)$ satisfy

$$\begin{cases} T(\theta) \geq 0,\ V_B(\theta) = 0,\ V_L(\theta) = 0,\ A(\theta) \geq 0, \text{ for all } \theta \in [-\tau^*, 0)\,, \\ T(0) > 0,\ V_B(0) > 0,\ V_L(0) > 0,\ A(0) > 0. \end{cases} \tag{4}$$

The following theorem addresses the well-posedness of the model (3).

Theorem 3.1. *Let $(T(t), V_B(t), V_L(t), A(t))$ be a solution of the system (3) satisfying (4). Then $T(t)$, $V_B(t)$, $V_L(t)$ and $A(t)$ are non-negative and bounded for all $t \geq 0$.*

Proof. From the first and last equations of the system (3), we have

$$T(t) = T(0)e^{-\int_0^t (d_T + \beta_B V_B(\xi) + \beta_L V_L(\xi))d\xi} + \int_0^t H e^{-\int_\eta^t (d_T + \beta_B V_B(\xi) + \beta_L V_L(\xi))d\xi} d\eta > 0,$$

$$A(t) = A(0)e^{\int_0^t [pV_B(\xi) + pV_L(\xi) - d_A - \eta_B V_B(\xi) - \eta_L V_L(\xi)]d\xi} > 0.$$

Next, we show that $V_B(t) > 0$ for all $t \in (0, \infty)$. Otherwise, there exists a first time $t_1 > 0$ such that $V_B(t_1) = 0$ and $V_B(t) > 0$ for $t \in [0, t_1)$. This would lead to

$$\frac{dV_B(t_1)}{dt} = \int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} \beta_B T(t_1 - a) V_B(t_1 - a) da > 0.$$

This implies $V_B(t)$ is negative in a small left neighborhood of t_1, a contradiction. Therefore, $V_B(t) > 0$ for all $t > 0$. Similarly, we can prove $V_L(t) > 0$ for all $t > 0$.

To prove the boundedness, let $\bar{\gamma}_B = \max_{a \in [\tau_B, \tau^*]} \gamma_B(a)$, $\bar{\gamma}_L = \max_{a \in [\tau_L, \tau^*]} \gamma_L(a)$, $\bar{\gamma} = \max\{\bar{\gamma}_B, \bar{\gamma}_L\}$, $d_{T^*} = \min\{\min_{\tau_B \leq a \leq \tau^*}, d_{T_B^*}(a), \min_{\tau_L \leq a \leq \tau^*} d_{T_L^*}(a)\}$ and $\eta = \min\{\eta_B, \eta_L\}$. Define

$$G(t) = \bar{\gamma} \int_{\tau_B}^{\tau^*} e^{-d_{T^*} a} T(t - a) da + V_B(t) + V_L(t) + \frac{\eta}{p} A(t).$$

By the nonnegativity of solutions, it follows that

$$\begin{aligned} \frac{dG(t)}{dt} =& H\bar{\gamma} \int_{\tau_B}^{\tau^*} e^{-d_{T^*} a} da - d_T \bar{\gamma} \int_{\tau_B}^{\tau^*} e^{-d_{T^*} a} T(t - a) da \\ & - \bar{\gamma} \int_{\tau_B}^{\tau^*} e^{-d_{T^*} a} [\beta_B T(t - a) V_B(t - a) + \beta_L T(t - a) V_L(t - a)] da \\ & + \int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} \beta_B T(t - a) V_B(t - a) da - d_V V_B(t) \\ & + \int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} \beta_L T(t - a) V_L(t - a) da - d_V V_L(t) \\ & - \eta_B V_B(t) A(t) - \eta_L V_L(t) A(t) \\ & + \eta(V_B(t) + V_L(t)) A(t) - \frac{d_A \eta}{p} A(t) - \frac{\eta \eta_B}{p} V_B(t) A(t) - \frac{\eta \eta_L}{p} V_L(t) A(t) \end{aligned}$$

$$\begin{aligned}
&\leq H\bar{\gamma}\int_{\tau_B}^{\tau^*} e^{-d_{T^*}a}da - d_T\bar{\gamma}\int_{\tau_B}^{\tau^*} e^{-d_{T^*}a}T(t-a)da \\
&\quad - d_V V_B(t) - d_V V_L(t) - d_A\frac{\eta}{p}A(t) \\
&\leq Q - dG(t),
\end{aligned}$$

where $Q = H\bar{\gamma}\int_{\tau_B}^{\tau^*} e^{-d_{T^*}a}da > 0$ and $d = \min\{d_T, d_V, d_A\} > 0$. Therefore, $\limsup_{t\to\infty} G(t) \leq Q/d$, implying that $G(t)$ is bounded, and so are $T(t)$, $V_B(t)$, $V_L(t)$ and $A(t)$. □

4. **Equilibria and their stability.** Let

$$R_B^{(0)} = \frac{\beta_B H K_B}{d_V d_T},\ R_L^{(0)} = \frac{\beta_L H K_L}{d_V d_T},$$

$$R_B^{(1)} = R_B^{(0)} - \sigma_B,\ R_L^{(1)} = R_L^{(0)} - \sigma_L,$$

where

$$K_B = \int_{\tau_B}^{\tau^*} \gamma_B(a)e^{-\int_0^a d_{T_B^*}(\xi)d\xi}da,\ K_L = \int_{\tau_L}^{\tau^*} \gamma_L(a)e^{-\int_0^a d_{T_L^*}(\xi)d\xi}da,$$

$$\sigma_B = \frac{\beta_B d_A}{d_T(p-\eta_B)},\ \sigma_L = \frac{\beta_L d_A}{d_T(p-\eta_L)}.$$

Here, $e^{-\int_0^a d_{T_B^*}\xi d\xi}$ denotes the age-specific survival probability of an infected cell infected by budding virus, i.e., the probability of an infected cell remaining alive at infection age a. Thus, K_B is the total number of new virions produced by one infected cell, infected by budding virus, over its whole lifespan. We call K_B the burst size of budding virus. Similarly, K_L is the burst size of lytic virus. Notice that $1/d_V$ is the life span of budding virus in the absence of antibody, H/d_T is the cell concentration without infection, and β_B is the infection rate. Hence, one budding virus, once inoculated into an environment containing H/d_T uninfected cells, can lead to $\beta_B H/(d_T d_V)$ infected cells. These infected cells then produce the amount $\beta_B H K_B/(d_T d_V)$ of new virions. Therefore, $R_B^{(0)}$ gives the reproductive ratio of the budding virus in the absence of antibody (also referred to as the basic reproductive number). In parallel, $R_L^{(0)}$ is the reproductive ratio of the lytic virus in the absence of antibody. Note that σ_B accounts for the clearance rate of antibody for budding virus. Thus, $R_B^{(1)}$ is the reproductive ratio of budding virus when the antibody for budding virus is established. Similarly, $R_L^{(1)}$ is the reproductive ratio of lytic virus when the antibody for lytic virus is established.

For the system (3), there always exists an infection-free equilibrium $E_0 = (T^{(0)}, 0, 0, 0)$, where $T^{(0)} = H/d_T$. Other possible equilibria are summarized below:

(I) If $R_B^{(0)} > 1$, there exists an equilibrium $E_{10} = \left(T^{(10)}, V_B^{(10)}, 0, 0\right)$, where

$$T^{(10)} = \frac{d_V}{K_B\beta_B},\ V_B^{(10)} = \frac{d_T}{\beta_B}\left(R_B^{(0)} - 1\right).$$

(II) If $R_L^{(0)} > 1$, there exists an equilibrium $E_{01} = \left(T^{(01)}, 0, V_L^{(01)}, 0\right)$, where

$$T^{(01)} = \frac{d_V}{K_L\beta_L},\ V_L^{(01)} = \frac{d_T}{\beta_L}\left(R_L^{(0)} - 1\right).$$

(III) If $R_B^{(0)} = R_L^{(0)} > 1$, there are infinitely many equilibria of the form $\hat{E} = \left(\hat{T}, \hat{V}_B, \hat{V}_L, 0\right)$, where

$$\hat{T} = \frac{d_V}{K_B \beta_B},\ \beta_B \hat{V}_B + \beta_L \hat{V}_L = d_T(R_B^{(0)} - 1).$$

(IV) If $p > \eta_B$ and $R_B^{(1)} > 1$, there exists an equilibrium $E_{20} = \left(T^{(20)}, V_B^{(20)}, 0, A^{(20)}\right)$, where

$$T^{(20)} = \frac{H}{d_T(1+\sigma_B)},\ V_B^{(20)} = \frac{d_A}{p-\eta_B},\ A^{(20)} = \frac{d_V}{\eta_B(1+\sigma_B)}\left(R_B^{(1)} - 1\right).$$

(V) If $p > \eta_L$ and $R_L^{(1)} > 1$, there exists an equilibrium $E_{02} = \left(T^{(02)}, 0, V_L^{(02)}, A^{(02)}\right)$, where

$$T^{(02)} = \frac{H}{d_T(1+\sigma_L)},\ V_L^{(02)} = \frac{d_A}{p-\eta_L},\ A^{(02)} = \frac{d_V}{\eta_L(1+\sigma_L)}\left(R_L^{(1)} - 1\right).$$

(VI) The positive equilibrium $E_{22} = \left(T^{(22)}, V_B^{(22)}, V_L^{(22)}, A^{(22)}\right)$, where

$$\begin{aligned} T^{(22)} &= \frac{H(\eta_L - \eta_B)}{d_T\left(R_B^{(0)}\eta_L - R_L^{(0)}\eta_B\right)},\ A^{(22)} = \frac{d_V\left(R_L^{(0)} - R_B^{(0)}\right)}{R_B^{(0)}\eta_L - R_L^{(0)}\eta_B}, \\ V_B^{(22)} &= \frac{d_T(\frac{H}{T^{(22)}d_T} - 1 - \sigma_L)\sigma_B}{\beta_B(\sigma_B - \sigma_L)},\ V_L^{(22)} = \frac{d_T(\frac{H}{T^{(22)}d_T} - 1 - \sigma_B)\sigma_L}{\beta_L(\sigma_L - \sigma_B)}, \end{aligned}$$

exists in any of the following cases:

(VI-1) $\sigma_B > \sigma_L$, $\eta_L > \eta_B$, $R_L^{(0)} > R_B^{(0)}$, and

$$R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_L)(1 - \frac{\eta_L}{\eta_B}) > R_L^{(0)} > R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_B)(1 - \frac{\eta_L}{\eta_B}).$$

(VI-2) $\sigma_B > \sigma_L$, $\eta_L < \eta_B$, $R_L^{(0)} < R_B^{(0)}$, and

$$R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_B)(1 - \frac{\eta_L}{\eta_B}) > R_L^{(0)} > R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_L)(1 - \frac{\eta_L}{\eta_B}).$$

(VI-3) $\sigma_B < \sigma_L$, $\eta_L > \eta_B$, $R_L^{(0)} > R_B^{(0)}$, and

$$R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_B)(1 - \frac{\eta_L}{\eta_B}) > R_L^{(0)} > R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_L)(1 - \frac{\eta_L}{\eta_B}).$$

(VI-4) $\sigma_B < \sigma_L$, $\eta_L < \eta_B$, $R_L^{(0)} < R_B^{(0)}$, and

$$R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_L)(1 - \frac{\eta_L}{\eta_B}) > R_L^{(0)} > R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_B)(1 - \frac{\eta_L}{\eta_B}).$$

We now consider the stability of some equilibria. The following result suggests that if the basic reproductive ratios of both budding virus and lytic virus are less than one, then the population sizes of both budding virus and lytic virus will approach zero as $t \to \infty$ and the antibody cannot be established.

Theorem 4.1. *The equilibrium $E_0 = (H/d_T, 0, 0, 0)$ is globally asymptotically stable if $R_B^{(0)} < 1$ and $R_L^{(0)} < 1$.*

Proof. First we consider local stability of the equilibrium E_0. Linearizing the system (3) at equilibrium E_0 leads to

$$\begin{cases} \dfrac{du_1(t)}{dt} = -d_T u_1(t) - \beta_B \dfrac{H}{d_T} u_2(t) - \beta_L \dfrac{H}{d_T} u_3(t), \\ \dfrac{du_2(t)}{\partial t} = \displaystyle\int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} \beta_B \frac{H}{d_T} u_2(t-a)da - d_V u_2(t), \\ \dfrac{du_3(t)}{dt} = \displaystyle\int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} \beta_L \frac{H}{d_T} u_3(t-a)da - d_V u_3(t), \\ \dfrac{du_4(t)}{dt} = -d_A u_4(t). \end{cases} \tag{5}$$

The characteristic equation of this linear system is

$$J_0(\lambda) = \begin{vmatrix} \lambda + d_T & \beta_B \frac{H}{d_T} & \beta_L \frac{H}{d_T} & 0 \\ 0 & \lambda + d_V - \beta_B \frac{H}{d_T} \bar{K}_B(\lambda) & 0 & 0 \\ 0 & 0 & \lambda + d_V - \beta_L \frac{H}{d_T} \bar{K}_L(\lambda) & 0 \\ 0 & 0 & 0 & \lambda + d_A \end{vmatrix} = 0,$$

where

$$\bar{K}_B(\lambda) = \int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\left(\int_0^a d_{T_B^*}(\xi)d\xi + \lambda a\right)} da, \bar{K}_L(\lambda) = \int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\left(\int_0^a d_{T_L^*}(\xi)d\xi + \lambda a\right)} da.$$

It is obvious that $\lambda_1 = -d_T < 0$ and $\lambda_2 = -d_A < 0$ are two eigenvalues and the other eigenvalues are determined by

$$\lambda + d_V = \beta_B \frac{H}{d_T} \bar{K}_B(\lambda),$$

and

$$\lambda + d_V = \beta_L \frac{H}{d_T} \bar{K}_L(\lambda),$$

which are equivalent respectively to

$$\frac{\lambda}{d_V} + 1 = R_B^{(0)} \frac{\bar{K}_B(\lambda)}{K_B}, \tag{6}$$

and

$$\frac{\lambda}{d_V} + 1 = R_L^{(0)} \frac{\bar{K}_L(\lambda)}{K_L}. \tag{7}$$

We need to show that under the conditions of the theorem, all roots of (6) and (7) have negative real parts. Let $\lambda = x + iy$ be a root of (6). We show that $x < 0$. Otherwise, $x \geq 0$ implies

$$\left|\bar{K}_B(\lambda)\right| \leq \int_{\tau_B}^{\tau^*} \gamma_B(a) \left| e^{-\left(\int_0^a d_{T_B^*}(\xi)d\xi + \lambda a\right)} \right| da \leq \int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} da = K_B.$$

Thus, if $R_B^{(0)} < 1$, then

$$\left| \frac{\lambda}{d_V} + 1 \right| \geq 1, \left| R_B^{(0)} \frac{\bar{K}_B(\lambda)}{K_B} \right| < 1,$$

a contradiction to (6). Therefore, $x < 0$ under $R_B^{(0)} < 1$, implying that all roots of (6) have negative real parts if $R_B^{(0)} < 1$. Similarly, if $R_L^{(0)} < 1$, then all roots of (7)

also have negative real parts. It follows from [7], that the equilibrium E_0 is locally asymptotically stable if $R_B^{(0)} < 1$ and $R_L^{(0)} < 1$.

To show that E_0 is globally asymptotically stable, it is sufficient to show that E_0 is globally attractive. By the positivity of solutions, we have

$$\begin{aligned} \frac{dT(t)}{dt} &= H - d_T T(t) - \beta_B T(t) V_B(t) - \beta_L T(t) V_L(t), \\ &\leq H - d_T T(t). \end{aligned}$$

This implies

$$\limsup_{t\to\infty} T(t) \leq \frac{H}{d_T}. \tag{8}$$

Denote

$$R_B^{(0)}(\varepsilon) = \frac{\beta_B (H+\varepsilon) K_B}{d_V d_T}, \quad R_L^{(0)}(\varepsilon) = \frac{\beta_L (H+\varepsilon) K_L}{d_V d_T}.$$

Let $\varepsilon > 0$ be sufficiently small such that $R_B^{(0)}(\varepsilon) < 1$ and $R_L^{(0)}(\varepsilon) < 1$. For such an $\varepsilon > 0$, by (8), there exists a $t^* > 0$ such that

$$T(t) \leq \frac{H+\varepsilon}{d_T}, \quad \text{for } t \geq t^*.$$

Thus,

$$\begin{aligned} \frac{dV_B(t)}{\partial t} &\leq \frac{H+\varepsilon}{d_T} \int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} \beta_B V_B(t-a)da - d_V V_B(t), \\ \frac{dV_L(t)}{dt} &\leq \frac{H+\varepsilon}{d_T} \int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} \beta_L V_L(t-a)da - d_V V_L(t). \end{aligned}$$

We consider the following auxiliary linear system

$$\begin{cases} \dfrac{dw_2(t)}{\partial t} = \dfrac{H+\varepsilon}{d_T} \displaystyle\int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} \beta_B w_2(t-a)da - d_V w_2(t), \\ \dfrac{dw_3(t)}{dt} = \dfrac{H+\varepsilon}{d_T} \displaystyle\int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} \beta_L w_3(t-a)da - d_V w_3(t). \end{cases} \tag{9}$$

Notice that the two equations in (9) are the same as the second and third equations in (5) except that H is replaced by $H+\varepsilon$. Thus, the characteristic equation of (9) is the product of two equations of the form (6) and (7) with H replaced by $H+\varepsilon$. Thus, $R_B^{(0)}(\varepsilon) < 1$ and $R_L^{(0)}(\varepsilon) < 1$ ensure that all eigenvalues of (9) have negative real parts, and hence, the trivial solution of (9) is globally (since (9) is linear) asymptotically stable, meaning that every solution $(w_2(t), w_3(t)) \to (0,0)$ as $t \to \infty$. Notice that (9) is a co-operative delay system. By the comparison theorem [12], we conclude that $\lim_{t\to\infty} (V_B(t), V_L(t))^T = (0,0)$.

Finally, the first and the last equations of (3) form a system which has the following autonomous system as the limit system.

$$\begin{cases} \dfrac{dw_1(t)}{dt} = H - d_T w_1(t), \\ \dfrac{dw_4(t)}{dt} = -d_A w_4(t). \end{cases}$$

Obviously, every solution of this system approaches $(H/d_T, 0)$. By the theory of asymptotically autonomous systems (see, e.g., [3]), for any positive solution

$(T(t), V_B(t), V_L(t), A(t))$ of (3), $T(t) \to H/d_T$ and $A(t) \to 0$ as $t \to \infty$, and therefore, $(T(t), V_B(t), V_L(t), A(t)) \to (H/d_T, 0, 0, 0)$ as $t \to \infty$. That is, E_0 is globally attractive, completing the proof. □

The following result indicates that if the basic reproductive ratio for the budding virus is greater than one and exceeds the basic reproductive ratio for the lytic virus, then the budding virus can survive when the antibody effect is not established.

Theorem 4.2. *Assume that $R_B^{(0)} > 1$ and $R_B^{(0)} > R_L^{(0)}$. If either* (**i**) $p \le \eta_B$; *or* (**ii**) $p > \eta_B$ *and* $R_B^{(1)} < 1$, *then the equilibrium E_{10} is locally asymptotically stable. If $R_B^{(0)} < R_L^{(0)}$, or $p > \eta_B$ and $R_B^{(1)} > 1$, then this equilibrium is unstable.*

Proof. Linearizing system (3) at equilibrium E_{10} gives

$$\begin{cases} \dfrac{du_1(t)}{dt} = -d_T u_1(t) - \beta_B V_B^{(10)} u_1(t) - \beta_B T^{(10)} u_2(t) - \beta_L T^{(10)} u_3(t), \\ \dfrac{du_2(t)}{dt} = \displaystyle\int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} [\beta_B V_B^{(10)} u_1(t-a) + \beta_B T^{(10)} u_2(t-a)]da \\ \qquad\qquad - d_V u_2(t) - \eta_B V_B^{(10)} u_4(t), \\ \dfrac{du_3(t)}{dt} = \displaystyle\int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} \beta_L T^{(10)} u_3(t-a)da - d_V u_3(t), \\ \dfrac{du_4(t)}{dt} = (p-\eta_B) V_B^{(10)} u_4(t) - d_A u_4(t). \end{cases}$$

The characteristic equation of this linear system is

$$\begin{vmatrix} \lambda + d_T' & \beta_B T^{(10)} & \beta_L T^{(10)} & 0 \\ -\beta_B V_B^{(10)} \bar{K}_B(\lambda) & \lambda + d_V - \beta_B T^{(10)} \bar{K}_B(\lambda) & 0 & \eta_B V_B^{(10)} \\ 0 & 0 & \lambda + d_V - \beta_L T^{(10)} \bar{K}_L(\lambda) & 0 \\ 0 & 0 & 0 & \lambda + d_A' \end{vmatrix}$$

$= 0$, where $d_T' = d_T + \beta_B V_B^{(10)}$, $d_A' = d_A - (p - \eta_B) V_B^{(10)}$. One eigenvalue is

$$\lambda_1 = -d_A + (p - \eta_B) V_B^{(10)} = \frac{d_A}{\sigma_B} \left(R_B^{(1)} - 1 \right).$$

It is clear that if $p \le \eta_B$, then $\lambda_1 < 0$. If $p > \eta_B$ but $R_B^{(1)} < 1$, we also have $\lambda_1 < 0$; and if $R_B^{(1)} > 1$, then $\lambda_1 > 0$.

The other eigenvalues are determined by

$$\lambda + d_V = \beta_L T^{(10)} \bar{K}_L(\lambda), \tag{10}$$

and

$$(\lambda + d_T)(\lambda + d_V) + (\lambda + d_V)\beta_B V_B^{(10)} - (\lambda + d_T)\beta_B T^{(10)} \bar{K}_B(\lambda) = 0. \tag{11}$$

Equation (10) is equivalent to

$$\frac{\lambda}{d_V} + 1 = \frac{R_L^{(0)}}{R_B^{(0)}} \frac{\bar{K}_L(\lambda)}{K_L}. \tag{12}$$

By a similar argument to that in analyzing (6), we conclude that all roots of (10) have negative real parts if $R_B^{(0)} > R_L^{(0)}$. Equation (11) is equivalent to

$$(\lambda + d_T)(\lambda + d_V) + (\lambda + d_V) d_T (R_B^{(0)} - 1) - (\lambda + d_T) d_V \frac{\bar{K}_B(\lambda)}{K_B} = 0,$$

which can be further rewritten as

$$(\lambda + d_T R_B^{(0)}) \left(\frac{\lambda}{d_V} + 1 \right) = (\lambda + d_T) \frac{\bar{K}_B(\lambda)}{K_B}. \tag{13}$$

Let $\lambda = x + iy$ be a root of (13). If $x \geq 0$, then by $R_B^{(0)} > 1$, we have

$$\left| \lambda + d_T R_B^{(0)} \right| > |\lambda + d_T|, \ \left| \frac{\lambda}{d_V} + 1 \right| \geq 1, \ \left| \frac{\bar{K}_B(\lambda)}{K_B} \right| \leq 1.$$

Therefore,

$$\left| (\lambda + d_T R_B^{(0)}) \left(\frac{\lambda}{d_V} + 1 \right) \right| > \left| (\lambda + d_T) \frac{\bar{K}_B(\lambda)}{K_B} \right|.$$

This is a contradiction to equation (13). Therefore, if $R_B^{(0)} > 1$, then $x < 0$ for equation (13), implying that all roots of (13) have negative real parts.

In summary, we have shown that under the assumption that $R_B^{(0)} > 1$ and $R_B^{(0)} > R_L^{(0)}$, if either (**i**) $p < \eta_B$, or (**ii**) $p > \eta_B$ and $R_B^{(1)} < 1$, then all roots of the characteristic equation have negative real parts and hence equilibrium E_{10} is locally asymptotically stable.

If $p > \eta_B$ and $R_B^{(1)} > 1$, then $\lambda_1 > 0$ implying that E_{10} is unstable. For case that $R_B^{(0)} < R_L^{(0)}$, let

$$\psi(\lambda) = \frac{\lambda}{d_V} + 1 - \frac{R_L^{(0)}}{R_B^{(0)}} \frac{\bar{K}_L(\lambda)}{K_L}.$$

Then

$$\psi(0) = 1 - \frac{R_L^{(0)}}{R_B^{(0)}} < 0.$$

On the other hand, $\psi(\lambda) \to +\infty, \text{as } \lambda \to +\infty$. Thus, there exists a $\lambda^* > 0$ such that $\psi(\lambda^*) = 0$, that is, (12) has a positive root, implying that E_{10} is unstable. The proof is completed. □

Parallel to Theorem 4.2, we have the following conclusion about the lytic virus when the antibody effect against lytic virus is not established.

Theorem 4.3. *Assume that $R_L^{(0)} > 1$ and $R_L^{(0)} > R_B^{(0)}$. If (i) $p < \eta_L$; or (ii) $p > \eta_L$ and $R_L^{(1)} < 1$, then the equilibrium E_{01} is locally asymptotically stable. If $R_L^{(0)} < R_B^{(0)}$ or $p > \eta_L$ and $R_L^{(1)} > 1$, then this equilibrium is unstable.*

Assume that $R_B^{(0)} > 1$ and $p > \eta_B$. Then when $R_B^{(1)}$ passes the value 1, E_{10} loses its stability, giving rise to the equilibrium E_{20}. The following theorem describes the stability of E_{20}, characterizing the conditions under which the budding virus will persist in the presence of established andibody.

Theorem 4.4. *Assume that $p > \eta_B$ and $R_B^{(1)} > 1$. If*

$$R_L^{(0)} < 1 + \sigma_B + \frac{\eta_L}{\eta_B} \left(R_B^{(1)} - 1 \right), \tag{14}$$

the equilibrium E_{20} is locally asymptotically stable; if

$$R_L^{(0)} > 1 + \sigma_B + \frac{\eta_L}{\eta_B} \left(R_B^{(1)} - 1 \right), \tag{15}$$

this equilibrium is unstable.

Proof. Firstly, note that $p > \eta_B$ and $R_B^{(1)} > 1$ imply $R_B^{(0)} > 1$. Linearizing the system (3) at E_{20} leads to

$$\begin{cases} \dfrac{du_1(t)}{dt} = -d_T u_1(t) - \beta_B V_B^{(20)} u_1(t) - \beta_B T^{(20)} u_2(t) - \beta_L T^{(20)} u_3(t), \\ \dfrac{du_2(t)}{dt} = \displaystyle\int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} [\beta_B V_B^{(20)} u_1(t-a) + \beta_B T^{(20)} u_2(t-a)]da \\ \qquad\qquad - d_V u_2(t) - \eta_B A^{(20)} u_2(t) - \eta_B V_B^{(20)} u_4(t), \\ \dfrac{du_3(t)}{dt} = \displaystyle\int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} \beta_L T^{(20)} u_3(t-a)da - d_V u_3(t) - \eta_L A^{(20)} u_3(t), \\ \dfrac{du_4(t)}{dt} = (p-\eta_B) A^{(20)} u_2(t) + (p-\eta_L) A^{(20)} u_3(t) + (p-\eta_B) V_B^{(20)} u_4(t) - d_A u_4(t). \end{cases}$$

The characteristic equation of this linear system is

$$J_{20}(\lambda) = \begin{vmatrix} \lambda + d_T + \beta_B V_B^{(20)} & \beta_B T^{(20)} & \beta_L T^{(20)} & 0 \\ -\beta_B V_B^{(20)} \bar{K}_B(\lambda) & \lambda + d_V + \eta_B A^{(20)} - \beta_B T^{(20)} \bar{K}_B(\lambda) & 0 & \eta_B V_B^{(20)} \\ 0 & 0 & \lambda + d_V + \eta_L A^{(20)} - \beta_L T^{(20)} \bar{K}_L(\lambda) & 0 \\ 0 & -(p-\eta_B) A^{(20)} & -(p-\eta_L) A^{(20)} & \lambda + d_A - (p-\eta_B) V_B^{(20)} \end{vmatrix} = 0.$$

The roots of this equation are determined by

$$\lambda + d_V + \eta_L A^{(20)} - \beta_L T^{(20)} \bar{K}_L(\lambda) = 0, \tag{16}$$

and

$$\begin{vmatrix} \lambda + d_1 & \beta_B T^{(20)} & 0 \\ -\beta_B V_B^{(20)} \bar{K}_B(\lambda) & \lambda + d_2 - \beta_B T^{(20)} \bar{K}_B(\lambda) & \eta_B V_B^{(20)} \\ 0 & -(p-\eta_B) A^{(20)} & \lambda + d_3 \end{vmatrix} = 0, \tag{17}$$

where $d_1 = d_T + \beta_B V_B^{(20)}$, $d_2 = d_V + \eta_B A^{(20)}$, $d_3 = d_A - (p-\eta_B) V_B^{(20)}$.

Equation (16) is equivalent to

$$\lambda + d_V + \frac{\eta_L}{\eta_B} \frac{d_V}{1+\sigma_B} \left(R_B^{(1)} - 1 \right) = R_L^{(0)} \frac{d_V}{1+\sigma_B} \frac{\bar{K}_L(\lambda)}{K_L},$$

which can be further rewritten as

$$\frac{1+\sigma_B}{d_V} \lambda + 1 + \sigma_B + \frac{\eta_L}{\eta_B} \left(R_B^{(1)} - 1 \right) = R_L^{(0)} \frac{\bar{K}_L(\lambda)}{K_L}. \tag{18}$$

Let $\lambda = x + iy$ be a root of (18). If $x \geq 0$, then the left hand side of the equation (18) satisfies

$$\left| \frac{1+\sigma_B}{d_V} \lambda + 1 + \sigma_B + \frac{\eta_L}{\eta_B} \left(R_B^{(1)} - 1 \right) \right| \geq 1 + \sigma_B + \frac{\eta_L}{\eta_B} \left(R_B^{(1)} - 1 \right),$$

and the right hand side of the equation satisfies

$$\left| R_L^{(0)} \frac{\bar{K}_L(\lambda)}{K_L} \right| \leq R_L^{(0)}.$$

Therefore, if (14) holds, then the above two inequalities contradict to each other. Thus $x < 0$ if (14) holds, implying that all roots of (18) have negative real parts.

Equation (17) is equivalent to

$$\lambda\left[(\lambda+d_T)\left(\lambda+d_V+\eta_B A^{(20)}\right)+\beta_B V_B^{(20)}\left(\lambda+d_V+\eta_B A^{(20)}\right)\right.$$
$$\left.-\beta_B T^{(20)}\bar{K}_B(\lambda)(\lambda+d_T)\right]+\eta_B V_B^{(20)}(p-\eta_B)A^{(20)}\left(\lambda+d_T+\beta_B V_B^{(20)}\right)=0,$$

which is further equivalent to

$$\left(1+\frac{\sigma_B}{\frac{\lambda}{d_T}+1}\right)\left(\frac{1+\sigma_B}{d_V R_B^{(0)}}\lambda+1\right)+\frac{d_A}{\lambda}\left(1-\frac{1}{R_B^{(0)}}\right)\left(1+\frac{\sigma_B}{\frac{\lambda}{d_T}+1}\right)=\frac{\bar{K}_B(\lambda)}{K_B}. \quad (19)$$

Let $\lambda = x + iy$ be a root of (19). If $x \geq 0$, by $R_B^{(0)} > 1$, the right hand side of the equation (19) satisfies

$$\left|\frac{\bar{K}_B(\lambda)}{K_B}\right| \leq 1,$$

and the left hand side of the equation satisfies

$$\begin{aligned}
&\left|\left(1+\frac{\sigma_B}{\frac{\lambda}{d_T}+1}\right)\left(\frac{1+\sigma_B}{d_V R_B^{(0)}}\lambda+1\right)+\frac{d_E}{\lambda}\left(1-\frac{1}{R_B^{(0)}}\right)\left(1+\frac{\sigma_B}{\frac{\lambda}{d_T}+1}\right)\right| \\
>\ &\left|\left(1+\frac{\sigma_B}{\frac{\lambda}{d_T}+1}\right)\left(\frac{1+\sigma_B}{d_V R_B^{(0)}}\lambda+1\right)\right| \\
>\ &1,
\end{aligned}$$

leading to a contradiction to (19). Thus $x < 0$, implying that all roots of (19) have negative real parts.

In summary, we conclude that if (14) holds, then the equilibrium E_{20} is locally asymptotically stable.

Let

$$\psi(\lambda) = \frac{1+\sigma_B}{d_V}\lambda + 1 + \sigma_B + \frac{\eta_L}{\eta_B}\left(R_B^{(1)}-1\right) - R_L^{(0)}\frac{\bar{K}_L(\lambda)}{K_L}.$$

Then $\psi(\lambda) \to \infty$ as $\lambda \to \infty$. On the other hand

$$\psi(0) = 1 + \sigma_B + \frac{\eta_L}{\eta_B}\left(R_B^{(1)}-1\right) - R_L^{(0)} < 0,$$

provided that (15) holds. Therefore, there exists a $\lambda^* > 0$, such that $\psi(\lambda^*) = 0$. This means the equation (18) has at least one positive eigenvalue, implying that the equilibrium E_{20} is unstable. The proof of the theorem is completed. □

Similarly, for lytic virus we have the following result when the antibody effect is established.

Theorem 4.5. *Assume that $p > \eta_L$ and $R_L^{(1)} > 1$. If*

$$R_B^{(0)} < 1 + \sigma_L + \frac{\eta_B}{\eta_L}\left(R_L^{(1)}-1\right), \quad (20)$$

the equilibrium E_{02} is locally asymptotically stable; if

$$R_B^{(0)} > 1 + \sigma_L + \frac{\eta_B}{\eta_L}\left(R_L^{(1)}-1\right), \quad (21)$$

this equilibrium is unstable.

The conditions for the existence and stability of some equilibria are summarized in Table 2. We see that if $p < \eta_B$ and $p < \eta_L$, there may only be three equilibria E_0, E_{01}, and E_{10} (except the equilibrium line $\hat{E}$), whose stability are determined by basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$. If $R_B^{(0)} > 1$ and $R_B^{(0)} > R_L^{(0)}$, E_{10} is locally asymptotically stable. If $R_L^{(0)} > 1$ and $R_L^{(0)} > R_B^{(0)}$, E_{01} is locally asymptotically stable. In this case, the antibody does not play a role in the long-term virus dynamics, this is because when p is too small ($p < \eta_B$ and $p < \eta_L$), activation of new antibodies cannot satisfy the demand on antibodies involved in neutralization of the virus for both strains. In the following discussion, we always assume that $p > \eta_B$ or $p > \eta_L$.

TABLE 2. The conditions for the existence and stability of the equilibria

	Existence	L.A.S.	Outcompetes
E_0	Always	$R_B^{(0)} < 1$ and $R_L^{(0)} < 1$	No virus
E_{10}	$R_B^{(0)} > 1$	$R_B^{(0)} > R_L^{(0)}$ and $\{p < \eta_B$, or $p > \eta_B$ & $R_B^{(1)} < 1\}$	Budding Virus
E_{01}	$R_L^{(0)} > 1$	$R_L^{(0)} > R_B^{(0)}$ and $\{p < \eta_L$, or $p > \eta_L$ & $R_L^{(1)} < 1\}$	Lytic Virus
E_{20}	$p > \eta_B$, $R_B^{(1)} > 1$	$R_L^{(0)} < R_B^{(0)} \frac{\eta_L}{\eta_B} + (1+\sigma_B)(1 - \frac{\eta_L}{\eta_B})$	Budding Virus
E_{02}	$p > \eta_L$, $R_L^{(1)} > 1$	$R_L^{(0)} > R_B^{(0)} \frac{\eta_L}{\eta_B} + (1+\sigma_L)(1 - \frac{\eta_L}{\eta_B})$	Lytic Virus

The bifurcation diagrams in different cases are given by figures in Fig. 1 to Fig. 3, representing the three cases $\eta_B > \eta_L$, $\eta_B = \eta_L$, $\eta_B < \eta_L$ respectively.

For the case $\eta_B > \eta_L$, the bifurcation diagram is shown in Fig. 1, in which, the first quadrant of $R_B^{(0)} - R_L^{(0)}$ plane is divided into sub-regions with appropriate shadings, representing the stability of the different equilibria. The shadings are given in such a way that regions with the same shading pattern share the same stable equilibrium. For example, in Fig. 1-(a) where $\sigma_B > \sigma_L$, the stability regions of equilibria E_{ij} $(i, j = 0, 1, 2)$ with respect to $R_B^{(0)}$ and $R_L^{(0)}$ are denoted by S_i; $i = 1, ..., 13$. Here the *solid diagonal line* is $R_L^{(0)} = R_B^{(0)}$; the *dash-dot line* is $R_L^{(0)} = R_B^{(0)} \frac{\eta_L}{\eta_B} + (1+\sigma_B)(1 - \frac{\eta_L}{\eta_B})$; and the *dashed line* is $R_L^{(0)} = R_B^{(0)} \frac{\eta_L}{\eta_B} + (1+\sigma_L)(1 - \frac{\eta_L}{\eta_B})$. In the regions shaded with *vertical* lines (S_1, S_3 and S_5), E_{10} is locally asymptotically; in regions shaded with *southwest-northeast* lines (S_6, S_7 and S_8), E_{20} is locally asymptotically stable. In these six regions, budding virus outcompetes. Similarly, in the regions shaded with *horizontal* lines (i.e., S_2 and S_4), E_{01} is locally asymptotically stable; in the regions shaded with *northwest-southeast* lines (i.e., S_9, S_{10} and S_{11}), E_{02} is locally asymptotically stable. In these five regions, lytic virus outcompetes. In the regions with overlap shadings, there are two locally asymptotically stable equilibria. For instance, in S_{13} both E_{20} and E_{02} are locally asymptotically stable; and in S_{12}, both E_{10} and E_{01} are locally asymptotically stable. In these two regions with overlap shadings (S_{12} and S_{13}), in addition to the two locally stable boundary equilibria (E_{10} and E_{01}, or E_{20} and E_{02}) there is also a positive equilibrium E_{22} whose stability is undetermined. In the region S_0, the disease-free equilibrium E_0 is locally asymptotically stable. Table 3 summarizes the situations in these regions.

In Fig. 1-(b), $\sigma_B < \sigma_L$. As is shown in this figure, existence and stability of equilibria are the same as Fig. 1-(a) in all regions other than S_5, S_{12} and S_{13}, the situation of which is shown in Table 4: in both regions S_{12} and S_{13} there is no stable equilibrium except the positive equilibrium E_{22} whose stability is undetermined.

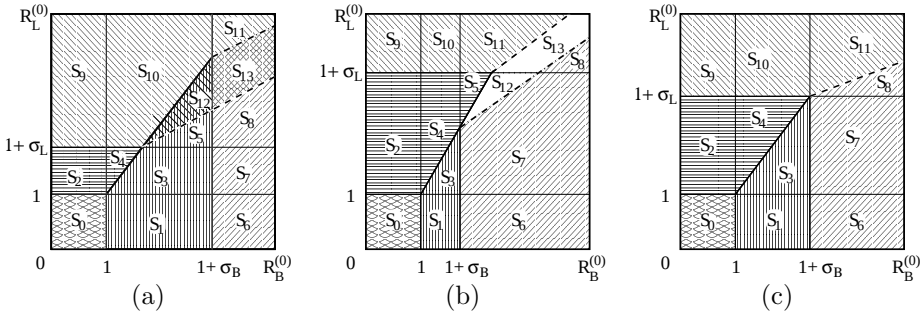


FIGURE 1. The stability regions $(S_i;\ i = 1, ..., 13)$ of equilibria $(E_{ij};\ i, j = 0, 1, 2)$ with respect to $R_B^{(0)}$ and $R_L^{(0)}$, when $\eta_B > \eta_L$: (a) $\sigma_B > \sigma_L$, (b) $\sigma_B < \sigma_L$, (c) $\sigma_B = \sigma_L$.

TABLE 3. Stability regions of the equilibria corresponding to Fig. 1-(a)

Region	Existence	L.A.S.	Possibly S.
S_0	E_0	E_0	–
S_1	E_0, E_{10}	E_{10}	–
S_2	E_0, E_{01}	E_{01}	–
S_3	E_0, E_{10}, E_{01}	E_{10}	–
S_4	E_0, E_{01}, E_{10}	E_{01}	–
S_5	E_0, E_{01}, E_{10}, E_{02}	E_{10}	–
S_6	E_0, E_{10}, E_{20}	E_{20}	–
S_7	E_0, E_{10}, E_{01}, E_{20}	E_{20}	–
S_8	E_0, E_{10}, E_{01}, E_{20}, E_{02}	E_{20}	–
S_9	E_0, E_{01}, E_{02}	E_{02}	–
S_{10}	E_0, E_{01}, E_{10}, E_{02}	E_{02}	–
S_{11}	E_0, E_{01}, E_{10}, E_{02},E_{20}	E_{02}	–
S_{12}	E_0, E_{01}, E_{10}, E_{02}, E_{22}	E_{10}, E_{02}	E_{22}
S_{13}	E_0, E_{10}, E_{01}, E_{20}, E_{02}, E_{22}	E_{20}, E_{02}	E_{22}

TABLE 4. Stability regions of the equilibria corresponding to Fig. 1-(b)

Region	Existence	L.A.S.	Possibly S.
S_5	E_0, E_{01}, E_{10}, E_{20}	E_{01}	–
S_{12}	E_0, E_{01}, E_{10}, E_{20}, E_{22}	–	E_{22}
S_{13}	E_0, E_{10}, E_{01}, E_{20}, E_{02}, E_{22}	–	E_{22}

Fig. 1-(c) covers the case $\sigma_B = \sigma_L$. Comparing Fig. 1-(c) with Fig. 1-(a) and Fig. 1-(b), there is no region S_5, S_{12} and S_{13}. The existence and stability of equilibria in all other regions remain the same as Fig. 1-(a) and Fig. 1-(b).

By symmetry, we have Fig. 2 for the case $\eta_B < \eta_L$ which is parallel to Fig. 1. Tables parallel to Table 3 and Table 4 can be drawn but are omitted here.

If $\eta_B = \eta_L$ (see Fig. 3), the positive equilibrium E_{22} does not exist. Furthermore, there are no regions S_{12} and S_{13}. The properties of equilibria in all other regions are same as Fig. 1-(a) for Fig. 3-(a), Fig 1-(b) for Fig. 3-(b), Fig. 1-(c) for Fig. 3-(c).

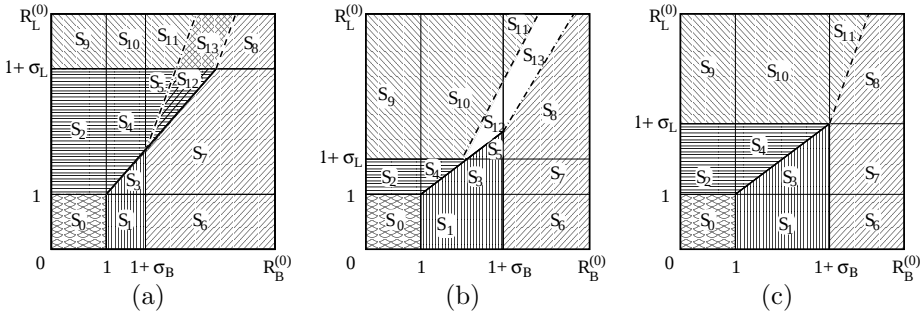


FIGURE 2. The stability regions of equilibria with respect to $R_B^{(0)}$ and $R_L^{(0)}$, when $\eta_B < \eta_L$: (a) $\sigma_B < \sigma_L$, (b) $\sigma_B > \sigma_L$, (c) $\sigma_B = \sigma_L$.

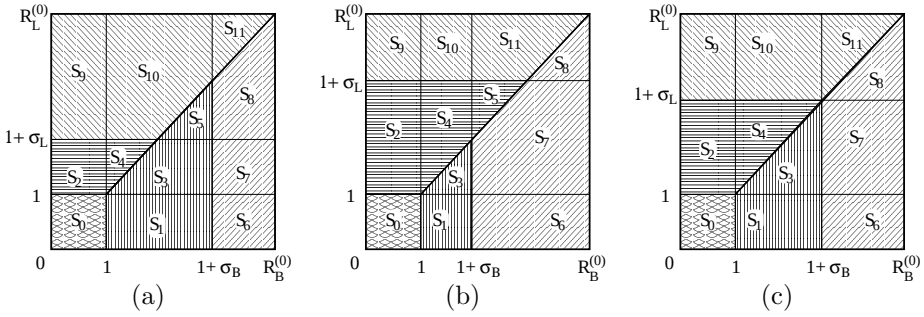


FIGURE 3. The stability regions of equilibria with respect to $R_B^{(0)}$ and $R_L^{(0)}$, when $\eta_B = \eta_L$: (a) $\sigma_B > \sigma_L$, (b) $\sigma_B < \sigma_L$, (c) $\sigma_B = \sigma_L$.

From the above analysis, we know that if $p < \min\{\eta_B, \eta_L\}$, the antibody cannot establish and the dynamics of the model (3) are determined by basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$. If $R_B^{(0)} > \max\{1, R_L^{(0)}\}$, the budding strategy is advantageous over the lytic strategy; if $R_L^{(0)} > \max\{1, R_B^{(0)}\}$, the lytic strategy is advantageous. If $\max\{R_B^{(0)}, R_L^{(0)}\} < 1$, neither strategy will succeed since both strains will eventually go to extinction.

If $p > \eta_B$ or $p > \eta_L$, antibody may have effect on the dynamics, depending on the antibody mediated reproductive ratios $R_B^{(1)}$ and $R_L^{(1)}$. If $p > \max\{\eta_B, \eta_L\}$ and $\max\{R_B^{(1)}, R_L^{(1)}\} < 1$, the dynamical behavior of the model also only depends on the basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$. If $R_B^{(1)} > 1$ or $R_B^{(1)} > 1$, antibody will affect the dynamics, since there exists the stable equilibrium E_{20} or E_{02} or E_{22}.

We also see from Fig. 3 that if the neutralizing capacities of the antibodies for budding and lytic viruses are the same (i.e., $\eta_B = \eta_L$), the evolutionary dominance of budding or lytic virus is also determined by the basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$, regardless of $p < \min\{\eta_B, \eta_L\}$ or $p > \min\{\eta_B, \eta_L\}$, in the sense that when $R_B^{(0)} > \max\{1, R_L^{(0)}\}$, then E_{10} or E_{20} is locally asymptotically stable, implying that

budding virus can survive. Similarly, if $R_L^{(0)} > \max\{1, R_B^{(0)}\}$, then E_{01} or E_{02} is locally asymptotically stable.

5. **Influence of antibody effect on the evolutionary competition between budding and lytic strategies.** From the above results on the dynamics of the model (3), we see that the impact of the production/release strategies for new virions is reflected by the dependence of the reproductive ratios on K_B and K_L, the burst sizes of budding virus and lysis virus under the respective production/release strategies represented by $\gamma_B(a)$ and $\gamma_L(a)$ and the initial releasing time τ_B and τ_L. In this section, we consider two particular forms for the release strategy functions $\gamma_B(a)$ and $\gamma_B(a)$, by which we hope to obtain more information on the impact of antibody and the release strategy. To this end, we assume that the total number of virions replicated from an infected cell without considering cell death is the same for all strategies, that is,

$$\int_{\tau_B}^{\tau^*} \gamma_B(a)da = \int_{\tau_L}^{\tau^*} \gamma_L(a)da = N \ \text{(a constant)}. \tag{22}$$

The first possible candidate for the viral production kernel function is the one used in [10] which has the form

$$\gamma(a) = \begin{cases} m_1\left(1 - e^{-m_2(a-\tau)}\right) & \text{if } a \geq \tau, \\ 0 & \text{if } a < \tau. \end{cases} \tag{23}$$

Here m_2 controls how rapidly the saturation level m_1 is reached, while $\tau \geq 0$ is the initial releasing time. For this production kernel, the constraint equation

$$\int_{\tau}^{\tau^*} \gamma(a)da \equiv N, \tag{24}$$

defines a trade-off relation of τ, m_1 and m_2, which is

$$m_1\left(\tau^* - \tau + \frac{1}{m_2}\left(e^{-m_2(\tau^*-\tau)} - 1\right)\right) = N, \tag{25}$$

or equivalently,

$$m_1 = \frac{Nm_2}{m_2(\tau^* - \tau) + \left(e^{-m_2(\tau^*-\tau)} - 1\right)}. \tag{26}$$

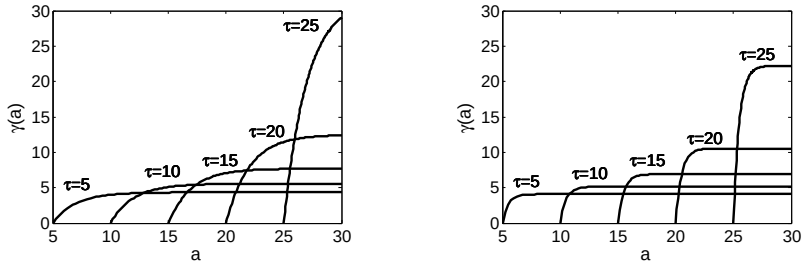
Fig. 4 demonstrates the strategy function $\gamma(a)$ with $N = 100$ and $\tau = 30$ fixed and m_1 determined by the trade-off equation (26) for some values of m_2 and τ. As is shown in Fig. 4, larger m_2 will make $\gamma(a)$ to approach the saturation level m_1 faster. Smaller τ represents the budding strategy and larger τ accounts for lytic strategy.

Another candidate for $\gamma(a)$ has the following form which was used in [1]:

$$\gamma(a) = \begin{cases} \dfrac{k_1(a-\tau)}{k_2 + (a-\tau)^2} & \text{if } a \geq \tau, \\ 0 & \text{if } a \leq \tau. \end{cases} \tag{27}$$

This function is not monotone, and it has the maximum $k_1/(2\sqrt{k_2})$ at $a = \tau + \sqrt{k_2}$. Here k_2 determines how rapidly the maximum is reached. For this function, the calculation gives

$$\int_{\tau}^{\tau^*} \gamma(a)da = \frac{k_1}{2}\ln\left(1 + \frac{(\tau^* - \tau)^2}{k_2}\right),$$



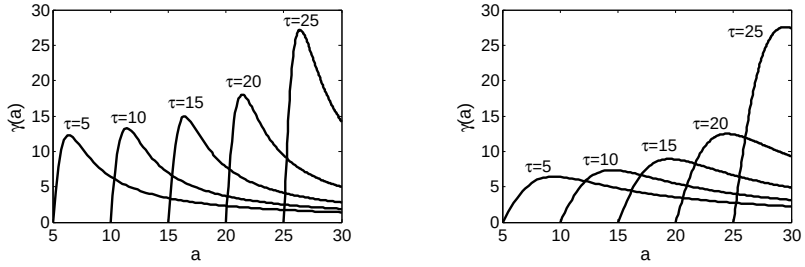
(a) (b)

FIGURE 4. $\gamma(a)$ function given by (23) under the constraint (26), with $N = 100$, $\tau^* = 30$. $m_2 = 0.5$ in (a) and $m_2 = 2$ in (b); different curves correspond to different values of τ: $\tau = 5, 10, 15, 20, 25$. Smaller τ represents the budding virus and large τ accounts for lytic virus.

thus, the constraint (24) reads

$$k_1 = \frac{2N}{\ln\left(1 + \frac{(\tau^* - \tau)^2}{k_2}\right)}. \tag{28}$$

Similarly, Fig. 5 shows the behavior of $\gamma(a)$ given by (27) for some values of the parameters. As is in Fig. 4, we also fix $N = 100$ and $\tau = 30$. k_2 is fixed at $k_2 = 2$ in Fig. 5-(a) and at $k_2 = 20$ in Fig. 5-(b), the plots are for $\tau = 5, 10, 15, 20, 25$ respectively with k_1 determined by (28). We can see from Fig. 5 that with small k_2, $\gamma(a)$ reaches the maximum rapidly. Furthermore, for small τ, there is a small surge in viral production with a subsequent long period of low level viral production; in contrast, for large τ, there is a big surge in viral production. Again, small τ accounts for the scenario of budding strategy while large τ explains lytic strategy.



(a) (b)

FIGURE 5. $\gamma(a)$ function given by (27) under the constraint (28) with $N = 100$ and $\tau^* = 30$ fixed. $k_2 = 2$ in (a) and $k_2 = 20$ in (b); different curves correspond to values of $\tau = 5, 10, 15, 20, 25$ respectively. Small τ accounts for budding strategy and large τ explains lytic strategy.

For the above two concrete forms of $\gamma(a)$, if we further assume that the death rate of infected cells is constant: $d_{T^*}(a) = d_{T^*}$, we can calculate the total number of new virions produced/released by an infected cell under the strategy $\gamma(a)$ as

$$K(\tau) = \frac{Nm_2\left[m_2\left(e^{-d_{T^*}\tau} - e^{-d_{T^*}\tau^*}\right) - d_{T^*}e^{-d_{T^*}\tau^*} + d_{T^*}e^{-m_2(\tau^*-\tau)-d_{T^*}\tau^*}\right]}{d_{T^*}(m_2+d_{T^*})\left[m_2(\tau^*-\tau) + e^{-m_2(\tau^*-\tau)} - 1\right]}, \quad (29)$$

for $\gamma(a)$ given by (23), and

$$K(\tau) = \frac{2Ne^{-d_{T^*}\tau}\int_0^{\tau^*-\tau}\frac{a}{k_2+a^2}e^{-d_{T^*}a}da}{\ln\left(1+\frac{(\tau^*-\tau)^2}{k_2}\right)}, \quad (30)$$

for $\gamma(a)$ given by (27). One can explore the dependence of $K(\tau)$ on τ, as well as on m_2 and k_2, to obtain more information. For example, numeric plots show that these two functions are both decreasing in τ (see Fig. 6).

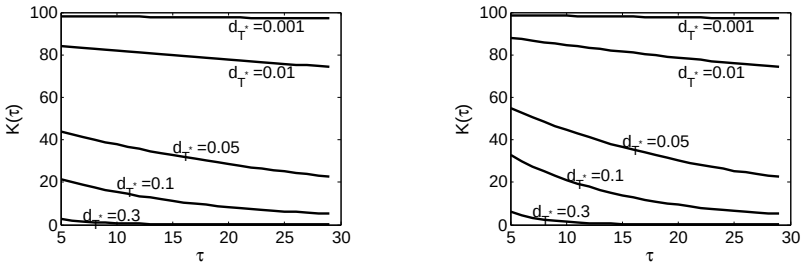


FIGURE 6. Burst size $K(\tau)$, with viral production kernel $\gamma(a)$ given by (23) in (a) and $\gamma(a)$ given by (27) in (b). $N = 100$, $\tau^* = 30$, $k_2 = 2$ and $m_2 = 2$ are fixed and d_{T^*} taking different values.

When $d_{T^*}(a)$ is not constant, it is generally difficult to obtain an explicit formula for K, but numerical calculation can give some information. To illustrate this, we consider the following death rate function proposed in [10]:

$$d_{T*}(a) = \begin{cases} \delta_0 & a < \tau_0, \\ \delta_0 + \delta_1\left(1 - e^{-\delta_2(a-\tau_0)}\right) & a \geq \tau_0, \end{cases} \quad (31)$$

where δ_0 is the background death rate, τ_0 is the delay between infection and the onset of cell-mediated killing or the beginning of cell death due to the viral cytopathic effects, $\delta_0 + \delta_1$ is the maximal death rate and δ_2 controls how quickly it approaches the saturation level. Fig. 7 shows some plots of this function for some parameter values.

For this death function, if $\tau_0 \leq \tau$, the burst size reads

$$K(\tau) := \int_\tau^{\tau^*}\gamma(a)e^{-\int_0^a d_{T^*}(\xi)d\xi}da = e^{\delta_1\tau_0+\frac{\delta_1}{\delta_2}}\int_\tau^{\tau^*}\gamma(a)e^{-\left[(\delta_0+\delta_1)a+\frac{\delta_1}{\delta_2}e^{-\delta_2(a-\tau_0)}\right]}da; \quad (32)$$

if $\tau_0 > \tau$,

$$K(\tau) = \int_\tau^{\tau_0}\gamma(a)e^{-\delta_0 a}da + e^{\delta_1\tau_0+\frac{\delta_1}{\delta_2}}\int_{\tau_0}^{\tau^*}\gamma(a)e^{-\left[(\delta_0+\delta_1)a+\frac{\delta_1}{\delta_2}e^{-\delta_2(a-\tau_0)}\right]}da. \quad (33)$$

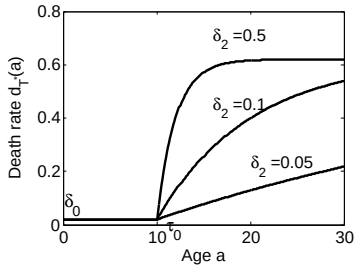


FIGURE 7. The death rate function $d_{T^*}(a)$ of infected cells when $\delta_0 = 0.02$, $\delta_1 = 0.6$, and $\tau_0 = 5$ are fixed and δ_2 taking 0.05, 0.1 and 0.5 respectively.

Numeric plots in Fig. 8 and Fig. 9 also show how the values of τ and δ_2 affect $K(\tau)$, e.g., $K(\tau)$ is indeed decreasing in both τ and δ_2.

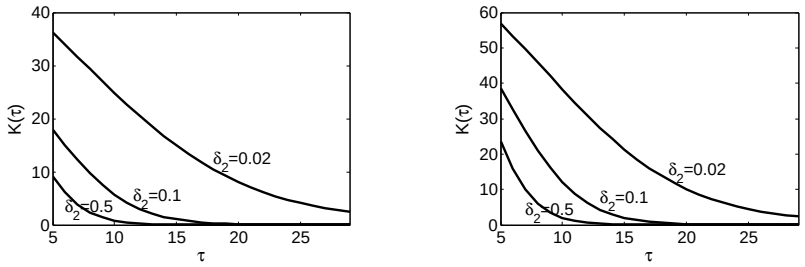


FIGURE 8. The burst size $K(\tau)$ when death rate function is given by (31): (a) with viral production kernel (23); (b) with viral production kernel (27). $N = 100$, $\tau^* = 30$, $k_2 = 2$ and $\tau_0 = 5$.

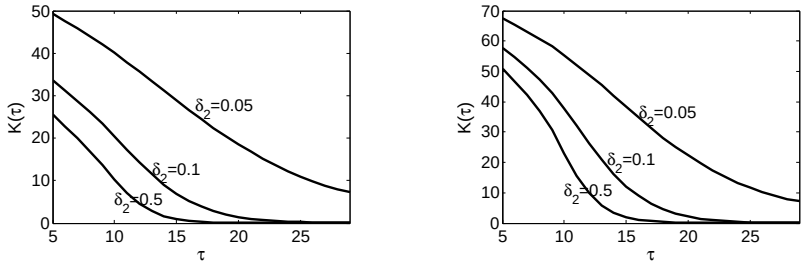
The above framework enables us to compare the burst sizes K_B and K_L when the strategies $\gamma_B(a)$ and $\gamma_L(a)$ have the same form of either (23) or (27). For example, suppose

$$\begin{aligned} \gamma_B(a) &= \begin{cases} m_1\left(1-e^{-m_2(a-\tau_B)}\right) & \text{if } a \geq \tau_B, \\ 0 & \text{if } a < \tau_B; \end{cases} \\ \gamma_L(a) &= \begin{cases} m_1\left(1-e^{-m_2(a-\tau_L)}\right) & \text{if } a \geq \tau_L, \\ 0 & \text{if } a < \tau_L, \end{cases} \end{aligned} \tag{34}$$

where $\tau_B < \tau_L$. If the infected cells have the same death rate for both virus, i.e., $d_{T_B^*}(a) = d_{T_L^*}(a)$, then

$$\int_{\tau_B}^{\tau^*} \gamma_B(a) e^{-\int_0^a d_{T_B^*}(\xi)d\xi} da > \int_{\tau_L}^{\tau^*} \gamma_L(a) e^{-\int_0^a d_{T_L^*}(\xi)d\xi} da, \tag{35}$$

that is, $K_B > K_L$. If we further assume that the budding virus and lytic virus have the same infection rate, $\beta_B = \beta_L$, then $R_B^{(0)} > R_L^{(0)}$ holds, implying that the



(a) (b)

FIGURE 9. The burst sizes, $K(\tau)$, with (a) viral production kernel (23), (b) viral production kernel (27), are decreasing functions of τ. When $N = 100$, $\tau^* = 30$, $k_2 = 2$, $\tau_0 = 10$, and death rate function (31).

budding strategy would have evolutionary advantage and would be favored. If the neutralization capacity of the antibodies against budding virus is larger than that of lytic virus, $\eta_B > \eta_L$, then $\sigma_B > \sigma_L$ assuming also that $\beta_B = \beta_L$.

From the bifurcation diagram Fig. 1 and Table 3, we see that lytic virus can survive if the basic reproductive ratio satisfies

$$R_L^{(0)} > \max\left\{1, \min\left\{R_B^{(0)}, R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_B)\left(1-\frac{\eta_L}{\eta_B}\right)\right\}\right\}.$$

Similarly, budding virus can survive if

$$R_B^{(0)} > \max\left\{1, \min\left\{R_L^{(0)}, R_L^{(0)}\frac{\eta_B}{\eta_L} + (1+\sigma_L)\left(1-\frac{\eta_B}{\eta_L}\right)\right\}\right\}.$$

Both viruses can survive, if $R_L^{(0)} < R_B^{(0)}$ and

$$R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_L)\left(1-\frac{\eta_L}{\eta_B}\right) < R_L^{(0)} < R_B^{(0)}\frac{\eta_L}{\eta_B} + (1+\sigma_B)\left(1-\frac{\eta_L}{\eta_B}\right).$$

With the assumption that $d_{T_B^*} = d_{T_L^*}$ and (22), we also have (35) and further, $R_B^{(0)} > R_L^{(0)}$ if $\beta_B = \beta_L$. Moreover, from Fig. 1, we see that lytic virus should have very high basic reproductive ratio in order to survive, say $R_L^{(0)} > (1+\sigma_B)(1-\frac{\eta_L}{\eta_B}) + \frac{\eta_L}{\eta_B}R_B^{(0)}$ (the equilibrium E_{02} is stable, in region S_{11} where $R_B^{(0)} > R_L^{(0)}$). From Fig. 2, we know that if $\eta_L > \eta_B$, the lytic virus cannot survive, since $R_B^{(0)} > R_L^{(0)}$ (both E_{10} and E_{20} are unstable).

We see that if the neutralization capacities of antibodies against budding and lytic virus are different, the dynamical behavior is not only determined by the basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$, but also by other parameters measuring antibody effects, such as η_B, η_L, σ_B and σ_L.

6. **Discussion and conclusion.** In this paper, proposed and analyzed is a mathematical model with distributed delays that describe the competition of budding and lytic virus within a host. Budding virus is featured by a longer release period of new virions, while lytic virus is characterized by a long accumulation period but

a shorter release period of new virions. These motivate us to use the infection age a and an age structured model to govern the populations of the target cell and virus. Two viral release strategies are distinguished by two beginning ages of viral release, τ_B for budding and τ_L for lytic, as well as by two viral production functions, γ_B and γ_L.

We have analyzed the dynamical behavior of the model (3). More specifically, we studied the global asymptotical stability of the infection-free equilibrium E_0; and we have also established local asymptotical stability of E_{01}, E_{10}, E_{02} and E_{20} which accounts for a scenario that among the two viruses, only one can survive within the host. The local stability depends on $R_B^{(0)}$ and $R_L^{(0)}$, the respective basic reproductive ratios in the absence of antibody, and on $R_B^{(1)}$ and $R_L^{(1)}$, the respective reproductive ratios in the presence of antibody. If $p < \eta_B$ and $p < \eta_L$, there are only three equilibrium E_0, E_{01}, and E_{10} (except the equilibrium line $\hat{E}$), whose stability are determined by basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$. If $R_B^{(0)} < 1$ and $R_L^{(0)} < 1$, E_0 is locally asymptotically stable; if $R_B^{(0)} > 1$ and $R_B^{(0)} > R_L^{(0)}$, E_{10} is locally asymptotically stable; if $R_L^{(0)} > 1$ and $R_L^{(0)} > R_B^{(0)}$, E_{01} is locally asymptotically stable. In this case, the antibody does not have any effect on the long-term dynamics. However, when $p > \eta_B$ and/or $p > \eta_L$, the antibody will have effect on the dynamical behavior of the model. If $\eta_B = \eta_L$, that is, the neutralization capacity of antibody is the same for both budding and lytic viruses, then, whether the budding virus or the lytic virus can survive depends on the basic reproductive ratios $R_B^{(0)}$ and $R_L^{(0)}$ (see Fig. 3). Yet, if $\eta_B > \eta_L$ or $\eta_B < \eta_L$, the positive equilibrium occurs in some regions in the $R_B^{(0)}$-$R_L^{(0)}$ plane. Bistability may arise in these regions. For example, in Fig. 1, in region S_{12}, both E_{10} and E_{02} are locally stable; and in region S_{13}, both E_{02} and E_{20} are locally stable.

We have considered two concrete forms of functions for the viral production kernel, as a function of the infection age. To study the evolutionary competition of budding and lysis strategies, we assume that the total amount of virions replicated during the lifespan of an infected cell is the same for both strains, without considering the release procedure and cell death. Under such a circumstance, the burst size of the budding virus is greater than that of the lytic virus (i.e., $K_B > K_L$) provided that $d_{T_B^*} = d_{T_L^*}$. If the budding virus and lytic virus have a same infection rate, $\beta_B = \beta_L$, then $R_B^{(0)} > R_L^{(0)}$ always holds. This means that if the rate of viral production, the infected cell lifespan and the neutralizing capacity of the antibodies were the same for the budding and lytic viruses, the budding virus would outcompete the lytic virus. In this case, budding strategy would have an evolutionary advantage. If the neutralization capacities of the antibodies against the budding virus and lytic virus are different, then the lytic virus can survive as long as the reproductive ratio $R_L^{(0)}$ is very high.

Using a diffusion model for virus and antibody, Komarova [8] observed that if the production rate of the virions and the efficacy of the antibodies were the *same* for a budding and a lytic virus, the lytic virus would always be significantly less efficient in spreading, and thus the lytic strategy would be evolutionary disadvantageous. Lytic virus can be competitive against budding virus if the antibodies are less effective against lytic virions than they are against budding virions. This is because the effect of *antibody flooding* increases the rate of spread of lytic virions. In this work, we do not consider the diffusion effect of antibodies; instead, we use

an ordinary differential equation model with distributed delays accounting for the release strategies. Our model can also predict a possibility that lytic virus may have an evolutionary advantage when the efficacies of antibodies are different for the two viruses. Thus this work offers an alternative view point for the scenario that a lytic virus can also outcompete budding virus under certain circumstances.

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