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Analysis of an age-structured HIV in-host model with proliferation and two infection modes†

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We propose and analyse an age-structured model for within-host HIV virus dynamics which is incorporated with both virus-to-cell and cell-to-cell infection routes, and proliferations of both uninfected and infected cells in the form of logistic growth. The model turns out to be a hybrid system with two differential-integral equations and one first-order partial differential equation. We perform some rigorous analyses for the considered model. Among the interesting dynamical behaviours of the model is the occurrence of backward bifurcation in terms of the basic reproduction number R_0 at $R_0 = 1$, which raises new challenges for effective infection control. We also discuss the cause of such a backward bifurcation, based on our analytical results.

Key words: HIV in-host model, infection age, proliferation, stability, backward bifurcation

Mathematics Subject Classification: 92D25; 34D20; 35F30

1 Introduction

Over the past few decades, extensive studies have been conducted on HIV dynamics within host using different mathematical models. Such studies have resulted in some important insights into the pathogenesis of HIV. Early models of viral infections were usually composed of ordinary differential equations (ODEs) (see, e.g., [15, 17] and the references therein).

When considering virus-to-cell infection only, a typical ODE HIV infection model can be described by the following differential equations:

$$\begin{cases} T' = s - \alpha T - kVT + f(T, T_*), \\ T'_* = kVT - \beta T_* + g(T, T_*), \\ V' = N\beta T_* - \epsilon V. \end{cases} \tag{1.1}$$

Here T and T_* denote the concentration of uninfected and infected target T cells, respectively, at time t, $V(t)$ presents the concentration of free HIV viruses at time t. In the model, uninfected target T cells are assumed to be produced from precursors at a constant rate s, parameters α, β and

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ϵ are the death rates of the uninfected T cells, the infected T cells and the virus particles, respectively. The incidence of infection through contact between viruses and uninfected target cells is assumed to follow a simple mass action term kVT, where constant $k > 0$ is the transmission coefficient. Infected T cells are assumed to produce on average N mature viruses during its lifetime, and the functions f and g describe the cell turnover and proliferation through mitosis. The dynamics of target T cells governed by (1.1) are influenced (determined indeed) by f and g and there have been many works that have used various forms of f and g. For example, when the mitotic proliferation is ignored, then $f = 0$ and $g = 0$, then (1.1) reduces to the simplest ODE model in [15], the dynamics of which is fully determined by basic reproduction number. Leenheer and Smith [5] incorporated proliferation only in uninfected target cells with a *simplified* logistic form $f = rT\left(1 - \frac{T}{T_m}\right)$ (but took $g = 0$); and by employing the theory of monotone dynamical systems, they analysed the global dynamics of the model system. Furthermore, Wang and Li in [25] considered a *full* logistic proliferation term for uninfected target cells with $f = rT\left(1 - \frac{T+T_*}{T_m}\right)$ and $g = 0$. Wang and Ellermeyer [23] discussed a system with a *full* logistic form in *both* uninfected and infected cell populations by taking $f = g = rT\left(1 - \frac{T+T_*}{T_m}\right)$. Moreover, Li and Wang [13] considered a scenario that uninfected and productively infected T cells proliferate at different rates by taking $f = r_1 T\left(1 - \frac{T+T_*}{T_m}\right)$ and $g = r_2 T\left(1 - \frac{T+T_*}{T_m}\right)$ with $r_1 \geq r_2$, and carried out mathematical analysis of the global dynamics and bifurcations for the resulting model in different parameter regimes.

In addition to the virus-to-cell infection mode, HIV spread within a host can also be partially attributed to via cell-to-cell transmission mode, including cell-to-cell contact (horizontal) or mitotic division of infected $CD4^+$ T cells (vertical). For the horizontal transmission of HIV is through cell-to-cell contact between infected and uninfected cells, see, e.g., [11, 12, 15] and the references therein. It has been known that cell-to-cell spread may sometimes be more effective than cell-to-free virus spread in transmitting HIV-1 (see, e.g., [8, 18, 21]). Recently, Gomez-Acevedo and Li [7] investigated the following system with cell-to-cell transmission and cell proliferation of both uninfected and infected cells

$$\begin{cases} x' = \lambda + v_1 x\left(1 - \dfrac{x+y}{K}\right) - d_1 x - \beta xy, \\ y' = \sigma\beta xy + v_2 y\left(1 - \dfrac{x+y}{K}\right) - d_2 y, \end{cases} \tag{1.2}$$

where $x(t)$, $y(t)$ denote the number of uninfected and infected cells at time t, respectively. Here it is assumed that the proliferation of T cells due to mitotic division obeys a logistic growth, meaning that the mitotic proliferation of uninfected and infected cells is described by $v_1 x(t)\left(1 - \frac{x(t)+y(t)}{K}\right)$ and $v_2 y(t)\left(1 - \frac{x(t)+y(t)}{K}\right)$, respectively, where v_1 and v_2 are the proliferation constants and K is the capacity of T cells. The term $\beta x(t)y(t)$ describes the horizontal transmission through cell-to-cell contact between infected and uninfected cells with β being the transmission coefficient. The authors of [7] discussed the existence of a backward bifurcation which raises many new challenges to effective infection control.

Note that death rate and virus production rate of infected cells are both assumed to be constant in the models ([5, 7, 11, 12, 13, 25]). However, biological plausibility and recent observations suggest that the death rate of infected cells should vary over their lifespan. With this scenario,

Nelson *et. al.* [14] proposed and studied an age-structured model for within-host viral dynamics, where the infected cell population is structured by the infection age, i.e., the time that has passed since the moment of infection of the cell by a virion. There have been many other works using models with infection age to address various aspects of the virus replications, see, e.g., [4, 10, 20, 22] and the references therein. Very recently, Wang *et. al.* [24] proposed and discussed the following age-structured HIV infection model:

$$\begin{cases} \dfrac{dT(t)}{dt} = h - dT(t) - \beta_1 T(t)V(t) - \beta_2 T(t)\displaystyle\int_0^{+\infty} q(a)i(t,a)da, \\ \dfrac{\partial i(t,a)}{\partial t} + \dfrac{\partial i(t,a)}{\partial a} = -\theta(a)i(t,a), \quad t \geq 0,\ a \geq 0, \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^{+\infty} p(a)i(t,a)da - cV(t), \quad t \geq 0, \\ i(t,0) = \beta_1 T(t)V(t) + \beta_2 T(t)\displaystyle\int_0^{+\infty} q(a)i(t,a)da, \quad t \geq 0. \end{cases} \tag{1.3}$$

System (1.3) captures the main features of the models extensively studied in the literature, such as those in [11, 12, 14, 20]. More specifically, this model system contains the two modes of infection (virus-to-cell and cell-to-cell), and allows age-dependent death rate and age-dependent production rate. Moreover, it allows the variance in the infectivity with respect to infection age of infected cells in the cell-to-cell mode. The authors of [24] carried out a global analysis for the model (1.3) and successfully established the global stability results both for infection-free equilibrium (when the basic reproduction number is less than 1) and infection equilibrium (when the basic reproduction number is larger than 1) by subtly constructing appropriate Lyapunov function/functional.

Observe that the mitotic proliferations for target cells (both uninfected and infected) are neglected in (1.3), and yet, it has been shown in previous works that the proliferations can make substantial difference in virus dynamics. This observation, together with the existing works on models with proliferations (e.g., [5, 12, 13, 23]), motivate us to incorporate terms for the mitotic proliferations into the model (1.3), leading to the following system of differential equations with age structure:

$$\begin{cases} \dfrac{dT(t)}{dt} = h - d_1 T(t) - kT(t)V(t) - mT(t)\displaystyle\int_0^{+\infty} n(a)i(t,a)da + r_1 T(t)\left[1 - \dfrac{T(t) + q\int_0^{+\infty} i(t,a)da}{K}\right], \\ \dfrac{\partial i(t,a)}{\partial t} + \dfrac{\partial i(t,a)}{\partial a} = -d_2 i(t,a) + r_2 i(t,a)\left[1 - \dfrac{T(t) + q\int_0^{+\infty} i(t,a)da}{K}\right], \quad t \geq 0,\ a \geq 0, \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^{+\infty} p(a)i(t,a)da - d_3 V(t), \quad t \geq 0, \\ i(t,0) = kT(t)V(t) + mT(t)\displaystyle\int_0^{+\infty} n(a)i(t,a)da, \quad t \geq 0. \end{cases} \tag{1.4}$$

Here as in [24] for (1.3), the $CD4^+$ T cell population is partitioned into two subclasses: uninfected T cells and infected T cells, with $T(t)$ denoting the concentration of uninfected target T cells at time t and $i(t,a)$ denoting the density of infected target cells of infection age a at time t.

The variable $V(t)$ represents the concentration of infectious virus at time t, h is the constant recruitment rate, d_1 is the natural death rate of uninfected cells, d_2 is the death rate of infected cells and d_3 is the clearance rate of infectious virion. $n(a)$ measures variance of the infectivity of infected cell with respect to the infection age and $p(a)$ is the viral production rate of an infected cell with infection age a. Here, following previous works, we use the logistic-type growth terms $r_1T[1-(T+qI)/K$ and $r_2i(a)[1-I(T+qI)/K]$ with $r_1>0$ and $r_2>0$ being constants and $I(t)=\int_0^\infty i(t,a)\,da$ being the total number of infected cells, to account for the proliferation rates (due to cell divisions) for uninfected and infected cells. We point out that the proliferation term $r_2i(a)[1-I(T+qI)/K]$ for the infected cells is based on the cell division mechanism of metosis in which all characteristics of mother cells are passed on to their daughter cells, including infections and infection age. Based on the background of (1.4), it should be associated with the following initial condition:

$$T(0)=T_0\geq 0,\quad i(0,a)=i_0(a)\in L^1_+(0,+\infty),\quad V(0)=V_0\geq 0. \tag{1.5}$$

In addition to generalising (1.3), the System (1.4) also extends (1.2) by incorporating infection age. Indeed, the model system (1.4) contains three important factors: (i) infection age; (ii) two infection modes; (iii) logistic-type proliferation terms for both uninfected and infected cells. Thus, it is very interesting and important to investigate the joint effects of (i)–(iii) on the virus dynamics described by (1.4), and this constitutes the purpose of this paper.

Let $\mu=d_2-r_2$, then (1.4) can be rewritten as

$$\begin{cases}\dfrac{dT(t)}{dt}=h-d_1T(t)-kT(t)V(t)-mT(t)\displaystyle\int_0^{+\infty}n(a)i(t,a)da+r_1T(t)\left[1-\frac{T(t)+q\int_0^{+\infty}i(t,a)da}{K}\right],\\ \dfrac{\partial i(t,a)}{\partial t}+\dfrac{\partial i(t,a)}{\partial a}=-\mu i(t,a)-r_2i(t,a)\dfrac{T(t)+q\int_0^{+\infty}i(t,a)da}{K},\quad t\geq 0,\ a\geq 0,\\ \dfrac{dV(t)}{dt}=\displaystyle\int_0^{+\infty}p(a)i(t,a)da-d_3V(t),\quad t\geq 0,\\ i(t,0)=kT(t)V(t)+mT(t)\displaystyle\int_0^{+\infty}n(a)i(t,a)da,\quad t\geq 0.\end{cases} \tag{1.6}$$

We only consider the case $d_2>r_2$ (i.e., $\mu>0$) meaning that the death rate of the infected cells is larger than the proliferation rate of these cells, which represents a scenario that if there is no new recruitment of infected cells at age $a=0$, the infected cells will not be able to persist ($i(t,a)\to 0$ as $t\to\infty$, see Section 3.). The condition $d_2>r_2$ also ensures that $i(t,a)\to 0$ as $a\to\infty$. In the rest of the paper, we always assume $\mu>0$.

The rest of the paper is organised as follows. In Section 2, we introduce some preliminaries and prove the well-posedness of the model (1.6). Then, in Section 3, we derive the basic reproduction number and analyse the local asymptotic stability of the infection-free equilibrium. However, the existence of the positive steady state seems difficult for the general kernel $p(a)$ and $n(a)$. Therefore, in Section 4, we focus on a special form of these two functions and the existence of the unique positive equilibrium is obtained if the basic reproduction number is greater than 1. Moreover, backward bifurcation is possible where two positive equilibria coexist when the basic reproduction number is less than 1. In Section 5, we study the stability of the infection equilibrium. Section 6 contains a summary and brief discussion of our results.

2 Preliminaries and well-posedness

In this section, we will rewrite System (1.6) into an abstract equation on a suitable Banach lattice through which we then establish the well-posedness for System (1.6). To this end, we first collect some preliminaries on linear operators and C_0-semigroup theory and some notations to be used in our discussion.

Let $L : D(L) \subset X \to X$ be a linear operator on a Banach space X. Denote by $\rho(L)$ the resolvent set of L. The spectrum of L is $\sigma(L) = \mathbb{C} \setminus \rho(L)$. The point spectrum of L is the set

$$\sigma_p(L) := \{\lambda \in \mathbb{C} : N(\lambda I - L) \neq \{0\}\}.$$

Definition 2.1 Let $L : D(L) \subseteq X \to X$ be a linear operator. Then, $(L, D(L))$ is called a Hille–Yosida operator if there exist real constants $M \geq 1$, and $\omega \in \mathbb{R}$, such that $(\omega, +\infty) \subseteq \rho(L)$, and

$$\|(\lambda - L)^{-n}\| \leq \frac{M}{(\lambda - \omega)^n}, \ \textit{for } n \in \mathbb{N}_+, \ \textit{and all } \lambda > \omega.$$

For a Hille–Yosida operator, one has the following perturbation result.

Lemma 2.1 (see [6, 16]) *Let $(A, D(A))$ be a Hille–Yosida operator on a Banach space X and $B \in \mathscr{L}(X)$, where $\mathscr{L}(X)$ denotes the set of all bounded linear operators on X, then the sum $C = A + B$ is a Hille–Yosida operator as well.*

If $(L, D(L))$ is a Hille–Yosida operator on Banach space X and

$$\begin{aligned} X_0 &:= (\overline{D(L)}, \|\cdot\|), \\ D(L_0) &:= \{x \in D(L) : Lx \in X_0\}, \\ L_0 x &:= Lx, \quad \text{for } x \in D(L_0), \end{aligned}$$

then the operator $(L_0, D(L_0))$ is called the part of L in X_0 and we have that

Lemma 2.2 (see [6, 16]) *If $(L, D(L))$ is a Hille–Yosida operator, then its part $(L_0, D(L_0))$ generates a C_0-semigroup $(T_0(t))_{t \geqslant 0}$ on X_0.*

Consider

$$X = \mathbb{R} \times L^1((0, +\infty), \mathbb{R}) \times \mathbb{R} \times \mathbb{R}$$

with the norm $\|\cdot\|_X$ defined by

$$\| x \|_X := | x_1 | + \int_0^\infty | x_2(a) | \, da + | x_3 | + | x_4 |, \quad \text{for } x = (x_1, x_2, x_3, x_4) \in X.$$

Let $D(\mathcal{A}) = \mathbb{R} \times W^{1,1}((0, +\infty), \mathbb{R}) \times \mathbb{R} \times \{0\}$ and define the linear operator $\mathcal{A} : D(\mathcal{A}) \subseteq X \longrightarrow X$ by

$$\mathcal{A} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ 0 \end{pmatrix} = \begin{pmatrix} -d_1 x \\ -x_2' - \mu x_2 \\ -d_3 x_3 \\ -x_2(0) \end{pmatrix}.$$

Then $\overline{D(\mathcal{A})} = \mathbb{R} \times L^1((0,+\infty),\mathbb{R}) \times \mathbb{R} \times \{0\}$ which is not dense in X. We also introduce a nonlinear map $\mathcal{F} : \overline{D(\mathcal{A})} \to X$ given by

$$\mathcal{F}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ 0 \end{pmatrix} = \begin{pmatrix} h - kx_1x_3 - mx_1\int_0^{+\infty} n(a)x_2(a)da + r_1x_1(1 - \frac{x_1+q\int_0^{+\infty} x_2(a)da}{K}) \\ -r_2x_2\frac{x_1+q\int_0^{+\infty} x_2(a)da}{K} \\ \int_0^{+\infty} p(a)x_2(a)da \\ kx_1x_3 + mx_1\int_0^{+\infty} n(a)x_2(a)da \end{pmatrix},$$

and let

$$u(t) = (T(t), i(t,\cdot), V(t), 0)^\top \in X.$$

Then we can reformulate System (1.6) as the following abstract Cauchy problem:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}(u(t)) = \mathcal{A}u(t) + \mathcal{F}(u(t)), \quad t \geqslant 0, \\ u(0) = u_0, \end{cases} \tag{2.1}$$

where $u_0 = (T_0, i_0(a), V_0, 0)^\top$.

In general, it is difficult to find a strong solution for an abstract differential equation like (2.1). So, we consider its integral form

$$u(t) = u_0 + \mathcal{A}\int_0^t u(s)ds + \int_0^t \mathcal{F}(u(s))ds. \tag{2.2}$$

A solution of (2.2) is called a mild solution of (2.1).

Set

$$X_0 = \overline{D(\mathcal{A})} = \mathbb{R} \times L^1((0,+\infty),\mathbb{R}) \times \mathbb{R} \times \{0\},$$

$$X_{0+} = \mathbb{R}_+ \times L^1_+((0,+\infty),\mathbb{R}) \times \mathbb{R}_+ \times \{0\}.$$

Then we can prove the following theorem.

Theorem 2.1 *The operator $(\mathcal{A}, D(\mathcal{A}))$ is a Hille–Yosida operator.*

Proof For $(\alpha,\varphi,\omega,\psi) \in X$, $(\tilde{\alpha},\tilde{\varphi},\tilde{\omega},0) \in D(\mathcal{A})$, $\lambda \in \Omega := \{\lambda \in \mathbb{C} : \mathrm{Re}(\lambda) > -\xi\}$, where $\xi := \min\{d_1,\mu,d_3\} > 0$, we have

$$(\lambda - \mathcal{A})^{-1}\begin{pmatrix} \alpha \\ \varphi \\ \omega \\ \psi \end{pmatrix} = \begin{pmatrix} \tilde{\alpha} \\ \tilde{\varphi} \\ \tilde{\omega} \\ 0 \end{pmatrix} \quad \Leftrightarrow \quad \begin{cases} (\lambda + d_1)\tilde{\alpha} = \alpha, \\ \tilde{\varphi}' = -(\lambda+\mu)\tilde{\varphi} + \varphi, \\ (\lambda + d_3)\tilde{\omega} = \omega, \\ \tilde{\varphi}(0) = \psi. \end{cases}$$

It then follows that

$$\begin{cases} \tilde{\alpha} = \frac{1}{\lambda+d_1}\alpha, \\ \tilde{\varphi} = e^{-(\lambda+\mu)a}\psi + \int_0^a e^{-(\lambda+\mu)(a-\theta)}\varphi(\theta)d\theta, \\ \tilde{\omega} = \frac{1}{\lambda+d_3}\omega. \end{cases} \tag{2.3}$$

Integrating the second equation in (2.3) with regard to the age variable a and adding all equations we obtain that

$$|\tilde{\alpha}| + \|\tilde{\varphi}\|_{L^1} + |\tilde{\omega}| \leq \frac{1}{\lambda + \xi}(|\alpha| + \|\varphi\|_{L^1} + |\omega| + |\psi|) \quad \text{for} \quad \lambda \in \Omega.$$

Thus, we have

$$\|(\lambda - \mathcal{A})^{-1}\| \leq \frac{1}{\lambda + \xi}, \quad \textit{for all} \ \ \lambda \in \Omega,$$

which shows that $(\mathscr{A}, D(\mathcal{A}))$ is a Hille–Yosida operator. □

By this theorem and Lemma 2.2, we know that $(\mathcal{A}, D(\mathcal{A}))$ generates a C_0-semigroup on X_0. As a result, we have the following existence theorem for the System (2.1).

Theorem 2.2 *For any $u_0 \in X_{0+}$, the system of equations (1.6) has a unique continuous solution represented by the integral equation (2.2) with values in X_{0+}. Moreover, the map $\Phi : [0, +\infty) \times X_{0+} \mapsto X_{0+}$ defined by $\Phi(t, u_0) = u(t, u_0)$ is a continuous semi-flow, i.e., the map Φ is continuous and satisfies that $\Phi(0, \cdot)$ is the identity map and $\Phi(t, \Phi(s, \cdot)) = \Phi(t + s, \cdot)$ on X_{0+}.*

Because of the biological interpretation of model (1.6), only non-negative and bounded solutions are meaningful. The following result reveals that $(T(t), i(t, a), V(t))$ associated with non-negative initial condition does remain non-negative and bounded ultimately.

Theorem 2.3 *All solutions of System (1.6) with non-negative initial condition remain non-negative for all $t \geq 0$ and are ultimately bounded.*

Proof First of all, we show that $T(t)$ is non-negative for all $t \geq 0$. In fact, if there exists t_1 such that $T(t_1) = 0$, and $T(t) > 0$ *for* $t \in (0, t_1)$. Then by the first equation of System (1.6) we see $T'(t_1) = h > 0$, which together with $T(t_1) = 0$ implies that $T(t) < 0$ for $t < t_1$ but very close to t_1, a contradiction. This means that $T(t) \geq 0$, for all $t \geq 0$.

Rewrite the second equation in (1.6) as the Gaussian form

$$\frac{\partial i(t, a)}{\partial t} + \frac{\partial i(t, a)}{\partial a} = i(t, a)\left[-\mu - r_2 \frac{T(t) + q\int_0^{+\infty} i(t, a)da}{K}\right].$$

The non-negative initial condition (1.5) together with the method of characteristics then implies that $i(t, a) \geq 0$ for all $t \geq 0$.

The positivity of $V(t)$ for $t \geq 0$ can be similarly proved: if there exits t_2 such that $V(t_2) = 0$, and $V(t) > 0$ for any $t \in (0, t_2)$, then from the third equation of System (1.6), we find $V'(t_2) = \int_0^{+\infty} p(a)i(t_2, a)da > 0$, a contradiction.

Next, we show the boundedness of solutions of (1.6). Firstly, from the first equation of (1.6), it follows that

$$\frac{dT(t)}{dt} \leq h - d_1 T(t) + rT(t)\left(1 - \frac{T(t)}{K}\right),$$

then we have

$$\limsup_{t \to +\infty} T(t) \leq \overline{T}_0,$$

where

$$\overline{T}_0 = \frac{-K(d_1 - r_1) + \sqrt{K^2(d_1 - r_1)^2 + 4Khr_1}}{2r_1} > 0. \tag{2.4}$$

Let $I(t) = \int_0^{+\infty} i(t, a)da$, which represents the total number of infected cells at time t. From the second equation in (1.6) and the fact that $\mu > 0$, it is easy to show that $\lim_{a\to+\infty} i(t, a) = 0$. Making use of this limit and (1.6), we then obtain

$$\begin{aligned}(T(t) + I(t))' &= h - d_1 T(t) + r_1 T(t)\left(1 - \tfrac{T(t)+qI(t)}{K}\right) - \mu I(t) - r_2 I(t)\tfrac{T(t)+qI(t)}{K} \\ &\le h - d_1 T(t) - \mu I(t) + r_1 T(t) \\ &\le h - d_1 T(t) - \mu I(t) + r_1 \overline{T}_0 \\ &\le h + r_1 \overline{T}_0 - \min\{d_1, \mu\}(T(t) + I(t)),\end{aligned}$$

implying

$$\limsup_{t\to+\infty}(T(t) + I(t)) \le \frac{h + r_1 \overline{T}_0}{\min\{d_1, \mu\}}.$$

It then follows from the third equation of System (1.6) that

$$\frac{dV(t)}{dt} \le \bar{p}\int_0^{+\infty} i(t, a)da - d_3 V(t) = \bar{p} I(t) - d_3 V(t)$$

where $\bar{p} := \sup p(a) < \infty$, and hence

$$\limsup_{t\to+\infty} V(t) \le \frac{\bar{p}(h + r_1 \overline{T}_0)}{d_3 \min\{d_1, \mu\}}.$$

Consequently, $T(t)$, $i(t, a)$ and $V_I(t)$ are ultimately bounded. □

Remark 2.1 *From the proof of Theorem 2.3, we have actually also proved that the omega limit set of System* (1.6) *is contained in the following bounded feasible region:*

$$\Gamma = \left\{(T, i, V) : T, V \ge 0, i \in L^1_+(0, +\infty), T + I \le \frac{h + r_1 \overline{T}_0}{\min\{d_1, \mu\}}, V \le \frac{\bar{p}(h + r_1 \overline{T}_0)}{d_3 \min\{d_1, \mu\}}\right\}.$$

Obviously, Γ *is positively invariant with respect to System* (1.6).

3 Basic reproduction number R_0 and local stability of the infection free equilibrium E_0

In this section, we identify the basic reproduction number R_0 for the model, which plays an important role in characterising the virus dynamics. It is closely related to the local stability of the *unique* infection-free equilibrium $E_0 = (\overline{T}_0, 0, 0)$, where $\overline{T}_0$ is given by (2.4), which is obtained by setting the right-hand side terms of (1.6) to 0 and setting $i = 0 = V$, leading to the quadratic equation for T: $h - d_1 T + r_1 T(1 - T/k) = 0$ which has a unique positive solution defining the above $\overline{T}_0$.

Note that the model (1.6) contains two infection modes: virus-to-cell and cell-to-cell. Thus, the basic reproduction number should be a result of combining the production of virus and infections

cells through these two channels. Tracking the two channels, we can obtain the following formula for the basic reproduction number:

$$R_0 := \frac{k\overline{T}_0}{d_3}\int_0^\infty p(a)e^{-\mu_0 a}da + m\overline{T}_0\int_0^\infty n(a)e^{-\mu_0 a}da := \frac{kN\overline{T}_0}{d_3} + mM\overline{T}_0. \tag{3.1}$$

where

$$\mu_0 = \left(\mu + \frac{r_2\overline{T}_0}{K}\right), \quad N = \int_0^\infty p(a)e^{-\mu_0 a}da, \quad M = \int_0^\infty n(a)e^{-\mu_0 a}da.$$

This can be seen by considering the decoupled equations for $i(t,a)$ and $V(t)$ in the linearisation of (1.6) at the infection-free equilibrium E_0:

$$\begin{cases} \dfrac{\partial i(t,a)}{\partial t} + \dfrac{\partial i(t,a)}{\partial a} = -\mu_0 i(t,a), \quad t \geq 0,\ a \geq 0, \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^{+\infty} p(a)i(t,a)da - d_3V(t), \quad t \geq 0, \\ i(t,0) = k\overline{T}_0V(t) + m\overline{T}_0\displaystyle\int_0^{+\infty} n(a)i(t,a)da, \quad t \geq 0. \end{cases} \tag{3.2}$$

which govern the evolution of $i(t,a)$ and $V(t)$ in the *neighbourhood of* E_0. From (3.2), we obtain

$$i(t,a) = \begin{cases} i(0,a-t)e^{-\mu_0 t} =: i_0(a-t)e^{-\mu_0 t}, & t < a; \\ i(t-a,0)e^{-\mu_0 t} =: b(t-a)e^{-\mu_0 a}, & t > a. \end{cases} \tag{3.3}$$

$$V(t) = V_0e^{-d_3t} + \int_0^t e^{-d_3(t-s)}\int_0^{+\infty} p(a)i(s,a)da\,ds \tag{3.4}$$

Plugging (3.3)–(3.4) into the third equation in (3.2), we find that the renewal equation for $b(t) = i(t,0)$ at large t (as $t \to \infty$, or asymptotical renewal equation) is actually governed by the following linear integral equation for $b(t) = i(t,0)$:

$$b(t) = \frac{K\overline{T}_0}{d_3}\int_0^t p(a)b(t-a)e^{-\mu_0 a}da + m\overline{T}_0\int_0^t n(a)b(t-a)e^{-\mu_0 a}da. \tag{3.5}$$

Following the line of [1] on pages 38–39, the basic reproduction number R_0 is then obtained by setting $b(t-a) = 1$ and changing the upper limits of the integrals to ∞ on the right-hand side of (3.5), resulting in the formula in (3.1).

Biologically, the first term $\frac{kN\overline{T}_0}{d_3}$ accounts for the total number of newly infected cells resulted from a single viron through the virus-to-cell infection mode, which is the basic reproduction number for the corresponding model with virus-to-cell infection only. Similarly, the second term $mM\overline{T}_0$ gives the total number of newly infected cells that arise from a single infected cell, and it is the basic reproduction number for the corresponding model with cell-to-cell transmission only. Therefore, R_0 is a consequence of superposition of the two infection channels. The two composed parameters M and N also have their biological meanings, with M denoting the average infectivity of an infected cell over its lifespan and N representing the total number of virus particles produced by an infected cell during its lifespan and

Next, we investigate the local stability of the infection-free equilibrium E_0. Typically, it is related to the threshold value of R_0, i.e., $R_0 = 1$. Let $x(t) = T(t) - \overline{T}_0$, $y(t,a) = i(t,a)$, $z(t) = V(t)$. Then, the linearisation of System (1.6) at E_0 turns out to the following linear system

$$\begin{cases} x'(t) = -d_1 x(t) - k\overline{T}_0 z(t) + r_1\left(1-\dfrac{2\overline{T}_0}{K}\right)x(t) - \dfrac{r_1 q}{K}\overline{T}_0 \displaystyle\int_0^{+\infty} y(t,a)da - m\overline{T}_0 \int_0^{+\infty} n(a)y(t,a)da, \\ \dfrac{\partial y(t,a)}{\partial t} + \dfrac{\partial y(t,a)}{\partial a} = -\mu y(t,a) - \dfrac{r_2\overline{T}_0}{K} y(t,a), \\ z'(t) = \displaystyle\int_0^{+\infty} p(a)y(t,a)da - d_3 z(t), \\ y(t,0) = k\overline{T}_0 z(t) + m\overline{T}_0 \displaystyle\int_0^{+\infty} n(a)y(t,a)da. \end{cases} \tag{3.6}$$

Substituting $x(t) = x_0 e^{\lambda t}$, $y(t,a) = y_0(a)e^{\lambda t}$, $z(t) = z_0 e^{\lambda t}$ into the equations (3.6) gives

$$\begin{cases} (\lambda + d_1)x_0 = -k\overline{T}_0 z_0 + r_1\left(1 - \dfrac{2\overline{T}_0}{K}\right)x_0 - \dfrac{r_1 q}{K}\overline{T}_0 \displaystyle\int_0^{+\infty} y_0(a)da - m\overline{T}_0 \int_0^{+\infty} n(a)y_0(a)da, \\ \dfrac{dy_0(a)}{da} = -(\lambda+\mu)y_0(a) - \dfrac{r_2\overline{T}_0}{K} y_0(a), \\ (\lambda + d_3)z_0 = \displaystyle\int_0^{+\infty} p(a)y_0(a)da, \\ y_0(0) = k\overline{T}_0 z_0 + m\overline{T}_0 \displaystyle\int_0^{+\infty} n(a)y_0(a)da. \end{cases} \tag{3.7}$$

Solving (3.7), we obtain that

$$y_0(a) = y_0(0)e^{-(\lambda+\mu+\frac{r_2\overline{T}_0}{K})a}, \quad z_0 = \frac{y_0(0)}{\lambda + d_3}\int_0^{+\infty} p(a)e^{-(\lambda+\mu+\frac{r_2\overline{T}_0}{K})a}da.$$

Substituting z_0 into the last equation of (3.7) and noting that $y_0(0)$ is arbitrary, we then obtain the equation:

$$\Delta_0(\lambda) := \frac{k\overline{T}_0}{\lambda + d_3}\int_0^{+\infty} p(a)e^{-(\lambda+\mu+\frac{r_2\overline{T}_0}{K})a}da + m\overline{T}_0 \int_0^{+\infty} n(a)e^{-(\lambda+\mu+\frac{r_2\overline{T}_0}{K})a}da - 1 = 0, \tag{3.8}$$

which is the characteristic equation of (3.6). Analys ing this equation, the threshold role of R_0 on local stability of E_0 is established in the following theorem.

Theorem 3.1 *If $R_0 < 1$, then the uninfected steady state $E_0 = (\overline{T}_0, 0, 0)$ of System (1.6) is locally asymptotically stable. If $R_0 > 1$, E_0 is unstable.*

Proof Obviously, if λ is restricted to $\mathbb{R}$, $\Delta_0(\lambda)$ is a continuous, strictly decreasing and real function satisfying

$$\lim_{\lambda\to+\infty} \Delta_0(\lambda) = -1, \quad \Delta_0(0) = R_0 - 1.$$

Hence, when $R_0 > 1$, the characteristic equation (3.8) has at least one positive real root, and thus, the infection-free steady state E_0 is unstable. If $R_0 < 1$, we can show that (3.8) has no

solution with non-negative real part. By way of contradiction, we assume that $\lambda = \alpha + \omega i$ is a complex root with $\alpha \geq 0$. Note that if λ is restricted to $\mathbb{R}$, $\Delta_0(\lambda)$ is strictly decreasing, therefore $\Delta_0(\alpha) \leq \Delta_0(0)$. Therefore,

$$
\begin{aligned}
1 = |\Delta_0(\lambda)+1| &= \left| \frac{k\overline{T}_0}{\alpha+\omega i+d_3} \int_0^{+\infty} p(a) e^{-(\alpha+\omega i+\mu+\frac{r_2\overline{T}_0}{K})a} da + m\overline{T}_0 \int_0^{+\infty} n(a) e^{-(\alpha+\omega i+\mu+\frac{r_2\overline{T}_0}{K})a} da \right| \\
&\leq \frac{k\overline{T}_0}{|\alpha+\omega i+d_3|} \int_0^{+\infty} p(a) \left| e^{-(\alpha+\omega i+\mu+\frac{r_2\overline{T}_0}{K})a} \right| da + m\overline{T}_0 \int_0^{+\infty} n(a) \left| e^{-(\alpha+\omega i+\mu+\frac{r_2\overline{T}_0}{K})a} \right| da \\
&= \frac{k\overline{T}_0}{\sqrt{(\alpha+d_3)^2+\omega^2}} \int_0^{+\infty} p(a) e^{-(\alpha+\mu+\frac{r_2\overline{T}_0}{K})a} da + m\overline{T}_0 \int_0^{+\infty} n(a) e^{-(\alpha+\mu+\frac{r_2\overline{T}_0}{K})a} da \\
&\leq \frac{k\overline{T}_0}{\alpha+d_3} \int_0^{+\infty} p(a) e^{-(\alpha+\mu+\frac{r_2\overline{T}_0}{K})a} da + m\overline{T}_0 \int_0^{+\infty} n(a) e^{-(\alpha+\mu+\frac{r_2\overline{T}_0}{K})a} da \\
&= \Delta_0(\alpha) + 1 \leq \Delta_0(0) + 1 = R_0 < 1,
\end{aligned}
$$

which is a contradiction. Thus, if $R_0 < 1$, all roots of of the characteristic equation $\Delta_0(\lambda) = 0$ must have negative real parts, implying the infection-free steady state E_0 is locally asymptotically stable. □

4 The existence of positive equilibrium

Up to now, we have established basic results on the well-posedness of the System (1.6), identified the basic reproduction number and illustrated its relation to the stability of the infection-free steady state E_0, all for the *general* distribution functions $p(a)$ and $n(a)$. It becomes very challenging to perform further analysis, regrading to the existence and number of positive equilibria for this general kernel. In this section, we proceed with a special form for the two distribution functions $p(a)$ and $n(a)$:

$$
p(a) = p_*(1 - e^{-\theta_1 a}), \quad n(a) = n_*(1 - e^{-\theta_2 a}), \tag{4.1}
$$

with p_* representing the maximum production rate, θ_1 indicating how quickly virions can be produced, n_* denoting the maximum infectivity rate of infected cell and θ_2 accounting for how quickly the uninfected target T cells can be infected.

With $p(a)$ and $n(a)$ specified in (4.1), the model system (1.6) becomes

$$
\begin{cases}
\dfrac{dT(t)}{dt} = h - d_1 T(t) - kT(t)V(t) - mT(t)n_* \displaystyle\int_0^{+\infty} (1 - e^{-\theta_2 a}) i(t,a) da \\
\qquad\qquad\qquad\qquad + r_1 T(t) \left(1 - \dfrac{T(t) + q\int_0^{+\infty} i(t,a) da}{K} \right), \\
\dfrac{\partial i(t,a)}{\partial t} + \dfrac{\partial i(t,a)}{\partial a} = -\mu i(t,a) - r_2 \dfrac{T(t) + q\int_0^{+\infty} i(t,a) da}{K} i(t,a), \quad t \geq 0,\ a \geq 0, \\
\dfrac{dV(t)}{dt} = p_* \displaystyle\int_0^{+\infty} (1 - e^{-\theta_1 a}) i(t,a) da - d_3 V(t), \quad t \geq 0, \\
i(t,0) = kT(t)V(t) + mT(t)n_* \displaystyle\int_0^{+\infty} (1 - e^{-\theta_2 a}) i(t,a) da, \quad t \geq 0.
\end{cases} \tag{4.2}
$$

Now, we find the positive equilibrium $E_* = (T_*, i_*(a), V_*)$ of (4.2) which is governed by following hybrid equations:

$$\begin{cases} h - d_1 T_* - kT_* V_* - mT_* n_* \int_0^{+\infty} (1 - e^{-\theta_2 a}) i_*(a) da + r_1 T_* \left(1 - \dfrac{T_* + qI_*}{K}\right) = 0, \\ \dfrac{di_*(a)}{da} = -\mu i_*(a) - r_2 \dfrac{T_* + qI_*}{K} i_*(a), \\ p_* \int_0^{+\infty} (1 - e^{-\theta_1 a}) i_*(a) da - d_3 V_* = 0, \\ i_*(0) = kT_* V_* + mT_* n_* \int_0^{+\infty} (1 - e^{-\theta_2 a}) i_*(a) da, \end{cases} \tag{4.3}$$

where $I_* = \int_0^{+\infty} i_*(a) da$. Solving the second equation of (4.3) for $i_*(a)$, we obtain

$$i_*(a) = i_*(0) e^{-(\mu + r_2 \frac{T_* + qI_*}{K})a}. \tag{4.4}$$

From the third equation in (4.3), we have

$$V_* = \frac{i_*(0)}{d_3} p_* \int_0^{+\infty} (1 - e^{-\theta_1 a}) e^{-(\mu + r_2 \frac{T_* + qI_*}{K})a} da.$$

Substituting $i_*(a)$ and V_* into the last equation of (4.3) leads to

$$i_*(0) = kT_* \frac{i_*(0) p_*}{d_3} \int_0^{+\infty} (1 - e^{-\theta_1 a}) e^{-(\mu + r_2 \frac{T_* + qI_*}{K})a} da + mT_* n_* i_*(0) \int_0^{+\infty} (1 - e^{-\theta_2 a}) e^{-(\mu + r_2 \frac{T_* + qI_*}{K})a} da.$$

Hence, T_* and I_* satisfy the following equation

$$1 = \frac{kT_* p_*}{d_3} \int_0^{+\infty} (1 - e^{-\theta_1 a}) e^{-(\mu + r_2 \frac{T_* + qI_*}{K})a} da + mT_* n_* \int_0^{+\infty} (1 - e^{-\theta_2 a}) e^{-(\mu + r_2 \frac{T_* + qI_*}{K})a} da. \tag{4.5}$$

On the other hand, integrating (4.4) from $a = 0$ to $a = \infty$, we have $i_*(0) = (\mu + r_2 \frac{T_* + qI_*}{K}) I_*$. This together with the first and last equations in (4.3) yields

$$h - d_1 T_* + r_1 T_* (1 - \frac{T_* + qI_*}{K}) = (\mu + r_2 \frac{T_* + qI_*}{K}) I_*. \tag{4.6}$$

Equations (4.5) and (4.6) form a system of equations for T_* and I_* which is not easy at all, if not impossible, to solve explicitly for general case. In the sequel, we *only consider a simplified case with* $q = 0$.

When $q = 0$, (4.3) reduces to

$$\begin{cases} h - d_1 T_* - kT_* V_* - mT_* n_* \int_0^{+\infty} (1 - e^{-\theta_2 a}) i_*(a) da + r_1 T_* \left(1 - \frac{T_*}{K}\right) = 0, \\ \dfrac{di_*(a)}{da} = -\mu i_*(a) - r_2 \dfrac{T_*}{K} i_*(a), \\ p_* \int_0^{+\infty} (1 - e^{-\theta_1 a}) i_*(a) da - d_3 V_* = 0, \\ i_*(0) = kT_* V_* + mT_* n_* \int_0^{+\infty} (1 - e^{-\theta_2 a}) i_*(a) da. \end{cases} \tag{4.7}$$

By the first and the last equations in (4.7), we have

$$i_*(0) = h - d_1 T_* + r_1 T_* \left(1 - \frac{T_*}{K}\right) = (r_1 - d_1) T_* + h - \frac{r_1}{K} T_*^2.$$

Noting that $r_1 - d_1 = \frac{r_1}{K}\overline{T}_0 - \frac{h}{\overline{T}_0}$, we then obtain

$$i_*(0) = (\overline{T}_0 - T_*)\left(\frac{h}{\overline{T}_0} + \frac{r_1}{K}T_*\right) > 0.$$

By solving the second equation in (4.7) with $i_*(0)$ given by the above, we have

$$i_*(a) = i_*(0)e^{-(\mu + r_2\frac{T_*}{K})a} = (\overline{T}_0 - T_*)\left(\frac{h}{\overline{T}_0} + \frac{r_1}{K}T_*\right)e^{-(\mu + r_2\frac{T_*}{K})a} > 0,$$

and

$$\begin{aligned} V_* &= \tfrac{i_*(0)}{d_3}p_*\textstyle\int_0^{+\infty}(1 - e^{-\theta_1 a})e^{-(\mu + r_2\frac{T_*}{K})a}da \\ &= \tfrac{\overline{T}_0 - T_*}{d_3}\left(\tfrac{h}{\overline{T}_0} + \tfrac{r_1}{K}T_*\right)p_*\textstyle\int_0^{+\infty}(1 - e^{-\theta_1 a})e^{-(\mu + r_2\frac{T_*}{K})a}da > 0. \end{aligned}$$

Plugging the above expressions of $i_*(0)$, $i_*(a)$ and V_* in terms of T_* into (4.5) with $q = 0$, we obtain the following equation for T_* only:

$$1 = \frac{kT_*p_*}{d_3}\int_0^{+\infty}(1 - e^{-\theta_1 a})e^{-(\mu + r_2\frac{T_*}{K})a}da + mT_*n_*\int_0^{+\infty}(1 - e^{-\theta_2 a})e^{-(\mu + r_2\frac{T_*}{K})a}da. \tag{4.8}$$

After evaluating the two integrals in this equation, we finally arrive at the following pure scalar non-linear algebraic equation for T_*:

$$1 = \frac{kT_*p_*\theta_1}{d_3(\mu + \frac{r_2T_*}{K})(\theta_1 + \mu + \frac{r_2T_*}{K})} + \frac{mT_*n_*\theta_2}{(\mu + \frac{r_2T_*}{K})(\theta_2 + \mu + \frac{r_2T_*}{K})}. \tag{4.9}$$

To proceed further, we distinguish two cases: (I) $\theta_1 = \theta_2 =: \theta$; (II) $\theta_1 \neq \theta_2$. It turns out that the two cases will have different outcomes, as analysed below.

Case (I) $\theta_1 = \theta_2 =: \theta$. In this case, (4.9) has the form:

$$1 = \left(\frac{kT_*p_*}{d_3} + mT_*n_*\right)\frac{\theta}{(\mu + \frac{r_2T_*}{K})(\theta + \mu + \frac{r_2T_*}{K})},$$

which is equivalent to

$$\left(\mu + \frac{r_2T_*}{K}\right)\left(\theta + \mu + \frac{r_2T_*}{K}\right) - \left(\frac{kT_*p_*}{d_3} + mT_*n_*\right)\theta = 0. \tag{4.10}$$

Let

$$\begin{aligned} f(x) &= \left(\mu + \frac{r_2x}{K}\right)\left(\theta + \mu + \frac{r_2x}{K}\right) - \left(\frac{kxp_*}{d_3} + mxn_*\right)\theta \\ &= \left(\frac{r_2}{K}\right)^2x^2 + \left[\frac{r_2}{K}(2\mu + \theta) - \left(\frac{kp_*}{d_3} + mn_*\right)\theta\right]x + \mu(\theta + \mu). \end{aligned}$$

Note that $f(x)$ is a concave-up quadratic function with $f(0) = \mu(\theta + \mu) > 0$ and by (4.10),

$$\begin{aligned} f(\overline{T}_0) &= \left(\mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta + \mu + \frac{r_2\overline{T}_0}{K}\right) - \left(\frac{k\overline{T}_0p_*}{d_3} + m\overline{T}_0n_*\right)\theta \\ &= \left(\mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta + \mu + \frac{r_2\overline{T}_0}{K}\right)\left(1 - \frac{\left(\frac{k\overline{T}_0p_*}{d_3} + m\overline{T}_0n_*\right)\theta}{\left(\mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta + \mu + \frac{r_2\overline{T}_0}{K}\right)}\right). \end{aligned}$$

Substituting (4.1) into the formula of R_0 in Section 3 and evaluating the two resulting integrals, we find

$$R_0 = \frac{\left(\frac{k\overline{T}_0 p_*}{d_3} + m\overline{T}_0 n_*\right)\theta}{\left(\mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta + \mu + \frac{r_2\overline{T}_0}{K}\right)},$$

and therefore,

$$f(\overline{T}_0) = \left(\mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta + \mu + \frac{r_2\overline{T}_0}{K}\right)(1 - R_0).$$

and

$$f'(0) = \frac{r_2}{K}(2\mu + \theta) - \left(\frac{kp_*}{d_3} + mn_*\right)\theta.$$

Thus, if $R_0 > 1$, then $f(\overline{T}_0) < 0$, and thus, (4.10) has a unique positive solution $T_* \in (0, \overline{T}_0)$ such that $f(T_*) = 0$. Hence, we have the following result.

Theorem 4.1 *If $R_0 > 1$, then the System (4.2) with $q = 0$ has only one positive equilibrium $E_* = (T_*, i_*, V_*)$.*

Now we consider the case $R_0 < 1$ implying $f(\overline{T}_0) > 0$. Since $f(0) > 0$ and $f(x)$ is a concave-up function, $f(x) = 0$ has at most two positive roots *between* 0 and $\overline{T}_0$. It is precisely when there are two positive roots in $(0, \overline{T}_0)$ that represents the *case of backward bifurcation*. By the properties of quadratic functions, together with the fact $f(0) > 0$ and the assumption $f(\overline{T}_0) > 0$, we can easily obtain conditions that characterise this case in the following theorem.

Theorem 4.2 *The System (4.2) with $q = 0$ exhibits backward bifurcation for R_0 at $R_0 = 1$ if and only if the following three conditions hold simultaneously:*

(a) $f'(0) = (2\mu + \theta)\frac{r_2}{K} - \left(\frac{kp_*}{d_3} + mn_*\right)\theta < 0$,

(b) $f'(\overline{T}_0) = 2\overline{T}_0\left(\frac{r_2}{K}\right)^2 + (2\mu + \theta)\frac{r_2}{K} - \left(\frac{kp_*}{d_3} + mn_*\right)\theta > 0$,

(c) *the discriminant* $\Delta = \left[(2\mu + \theta)\frac{r_2}{K} - \left(\frac{kp_*}{d_3} + mn_*\right)\theta\right]^2 - 4\mu(\mu + \theta)\left(\frac{r_2}{K}\right)^2 > 0$.

The three conditions (a)–(c) in Theorem 4.2 give the range of parameters within which backward bifurcation will occur, leading to a bistability scenario will happen. Depending on the focus of parameters, one can solve the set of inequalities (a)–(c) to obtain explicit conditions of a particular parameters in terms of another. For example, from the above three conditions, we can obtain the relations between n_* and θ:

$$n_* > \frac{2\mu\frac{r_2}{K}}{m\theta} + \frac{\frac{r_2}{K} - \frac{kp_*}{d_3}}{m}, \tag{4.11}$$

$$n_* < \frac{2\overline{T}_0\left(\frac{r_2}{K}\right)^2 + 2\mu\frac{r_2}{K}}{m\theta} + \frac{\frac{r_2}{K} - \frac{kp_*}{d_3}}{m}, \tag{4.12}$$

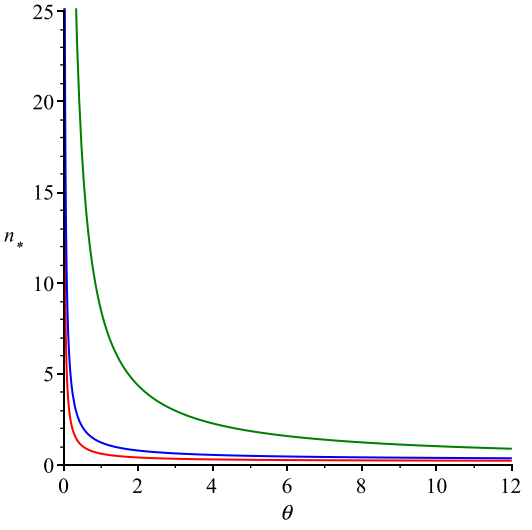

FIGURE 1. (colour online) Boundaries of the region in the $\theta - n_*$ plane given by (4.11)–(4.13) with $p_* = 0.91$ and other parameters given by (4.17): red curve represents the equality in (4.11), green curve represents the equality in (4.12), blue curve represents the equality in (4.13).

$$n_* > \frac{2\mu\frac{r_2}{K}}{m\theta} + \frac{\frac{r_2}{K} - \frac{kp_*}{d_3}}{m} + \frac{\sqrt{4\mu\left(\mu+\theta\right)\left(\frac{r_2}{K}\right)^2}}{m\theta}. \tag{4.13}$$

Similarly, from (a)–(c), we can obtain the relations between p_* and θ:

$$p_* > \frac{2\mu\frac{r_2}{K}\frac{d_3}{k}}{\theta} + \frac{d_3}{k}\left(\frac{r_2}{K} - mn_*\right), \tag{4.14}$$

$$p_* < \frac{\left(2\overline{T}_0\left(\frac{r_2}{K}\right)^2 + 2\mu\frac{r_2}{K}\right)\frac{d_3}{k}}{\theta} + \frac{d_3}{k}\left(\frac{r_2}{K} - mn_*\right), \tag{4.15}$$

$$p_* > \frac{2\mu\frac{r_2}{K}\frac{d_3}{k}}{\theta} + \frac{d_3}{k}\left(\frac{r_2}{K} - mn_*\right) + \frac{\sqrt{4\mu\left(\mu+\theta\right)\left(\frac{r_2}{K}\right)^2\frac{d_3}{k}}}{\theta}. \tag{4.16}$$

Given the values of all parameters, either (4.11)–(4.13) or (4.14)–(4.16) can be easily verified (true or not). Particularly, if other parameters are fixed, one can conveniently explore the range of n_* in terms of θ, or the range of p_* in terms of θ, within which backward bifurcation will occur. To illustrate, we fix

$$\begin{aligned} &K = 50,\ r_1 = 0.1,\ r_2 = 2.954,\ d_1 = 0.5,\ \mu = 0.9,\ d_3 = 1/3,\\ &k = 1/200,\ m = 0.25,\ h = 0.4. \end{aligned} \tag{4.17}$$

Then for $p_* = 0.91$, Figure 1 demonstrates the three curves on the θ-n_* plane that are obtained by changing the inequalities to equalities in (4.11)–(4.13), while for $n_* = 0.520$, Figure 2 gives the three curves in the θ-p_* plane obtained by changing the inequalities to equalities in (4.14)–(4.16).

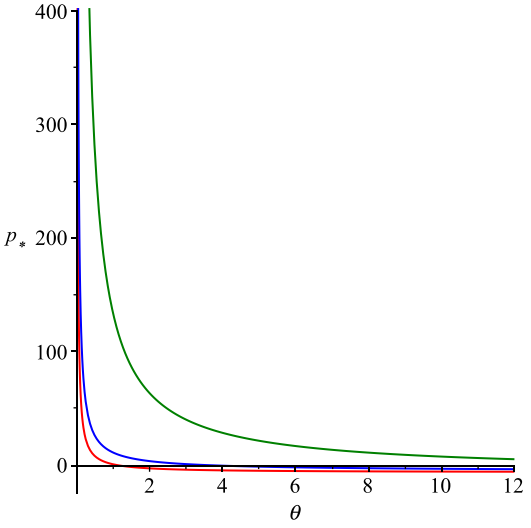

FIGURE 2. (colour online) Boundaries of the region in the $\theta - p_*$ plane given by (4.14)–(4.16) with $n_* = 0.520$ and other parameters given by (4.17): red curve represents the equality in (4.14), green curve represents the equality in (4.15), blue curve represents the equality in (4.16).

Case (II) $\theta_1 \neq \theta_2$. In this case, through tedious computations, the equation (4.9) has the simplified form $B_0 T_*^3 + B_1 T_*^2 + B_2 T_* + B_3 = 0$ where

$$
\begin{aligned}
B_0 &= \left(\frac{r_2}{K}\right)^3 > 0,\\
B_1 &= \frac{r_2}{K}\left[(3\mu + \theta_1 + \theta_2)\frac{r_2}{K} - \left(\frac{kp_*\theta_1}{d_3} + mn_*\theta_2\right)\right],\\
B_2 &= \left[\theta_1\theta_2 + 2\mu(\theta_1 + \theta_2) + 3\mu^2\right]\frac{r_2}{K} - \frac{kp_*\theta_1}{d_3}(\theta_2 + \mu) - mn_*\theta_2(\theta_1 + \mu),\\
B_3 &= \theta_1\theta_2\mu + (\theta_1 + \theta_2)\mu^2 + \mu^3 > 0.
\end{aligned}
$$

Let $g(y) = B_0 y^3 + B_1 y^2 + B_2 y + B_3$. Since $g(0) = B_3 > 0$ and $g(-\infty) = -\infty$, $g(y)$ has at least one negative (real) root $y_1 < 0$. Note that complex roots of $g(y)$ must appear in conjugate pairs. Thus, either $g(y)$ only has one real root which is negative, or it has three real roots. If $g(y)$ has three real roots (counting multiplicity), denoted by y_i, $i = 1, 2, 3$ with $y_1 < 0$, then there hold

$$
\sum_{i=1}^{3} y_i = -\frac{B_1}{B_0}, \qquad \prod_{i=1}^{3} y_i = -\frac{B_3}{B_0} < 0,
$$

and therefore, y_2 and y_3 must have the same sign: either (A) both are positive or (B) both are negative. It is clear that (A) holds if and only if $B_1 < 0$.

Assume $B_1 < 0$ so that $g(y)$ has two positive roots $0 < y_2 < y_3$. Only when a positive root is in $(0, \overline{T}_0)$ does it correspond to a positive equilibrium for (4.2). So we need to confine ourselves to $(0, \overline{T}_0)$. Note that

$$
g(\overline{T}_0) = \left(\mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta_1 + \mu + \frac{r_2\overline{T}_0}{K}\right)\left(\theta_2 + \mu + \frac{r_2\overline{T}_0}{K}\right)(1 - R_0).
$$

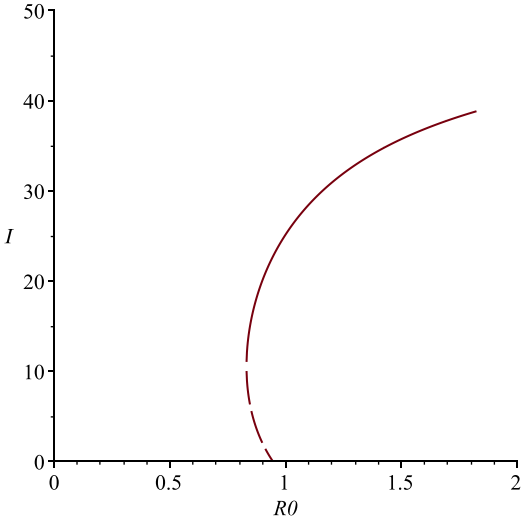

FIGURE 3. Backward bifurcation diagram of (4.2) with $q = 0$ w.r.t. R_0 with the parameter values given in (4.18). By varying n_* in (0.4409, 0.5046), we have R_0 varying in (0.83737, 1) – the range for (4.2) with $q = 0$ to have two positive equilibria, in addition to the infection-free equilibrium E_0. For $n_* > 0.5046$ leading to $R_0 > 1$, there is only one infection steady state.

Thus, if $R_0 > 1$, then $g(\overline{T}_0) < 0$, implying that there exists a unique positive solution $T_* \in (0, \overline{T}_0)$ such that $g(T_*) = 0$. Hence, we have proved the following result.

Theorem 4.3 *If $B_1 < 0$ and $R_0 > 1$, then the System (4.2) with $q = 0$ has only one positive equilibrium $E_* = (T_*, i_*, V_*)$.*

If $R_0 < 1$ (still assuming $B_1 < 0$), then $g(\overline{T}_0) > 0$. This is the case that allows $g(y)$ to either have none or two positive roots in $(0, \overline{T}_0)$. It is easy to see that for the latter to happen if and only if $g(y)$ has a *negative minimum* in $(0, \overline{T}_0)$. Therefore, we have actually proved the following theorem on the existence of *backward bifurcation*.

Theorem 4.4 *Assume that $B_1 < 0$. Then the System (4.2) with $q = 0$ exhibits backward bifurcation for R_0 at $R_0 = 1$ if there exists a $\check{T} \in (0, \overline{T}_0)$ such that $g'(\check{T}) = 0$ and $g(\check{T}) < 0$.*

To demonstrate the feasibility of the conditions in Theorem 4.4 for the existence of backward bifurcation, we choose the parameter values as below:

$$\begin{aligned} &\theta_1 = 0.62,\ \ \theta_2 = 0.9,\ \ K = 100,\ \ r_1 = 0.001,\ \ r_2 = 2.954,\ \ d_1 = 0.5,\\ &\mu = 0.9,\ \ d_3 = 1/3,\ \ k = 0.005,\ \ m = 0.35,\ \ h = 46,\ \ p_* = 0.918,\ \ n_* = 0.482. \end{aligned} \tag{4.18}$$

For these parameter values, we can calculate to obtain $\overline{T}_0 = 92.01407$ and find the local minimal point for $g(y)$ to be $\check{T} = 33.8245 \in (0, \overline{T}_0)$ with $g(\check{T}) < 0$, verifying the conditions in Theorem 4.4. The corresponding bifurcation diagram with respect to R_0 is given in Figure 3.

5 Stability of the infection equilibrium E_*

In this section, we study the stability of the infection equilibrium $E_* = (T_*, i_*(a), V_*)$. To analyse the local stability of E_*, we linearise the System (4.2) around the infection steady state E_* to obtain the following linear system:

$$\begin{cases} x'(t) = \left(-d_1 - kV_* - m\displaystyle\int_0^{+\infty} n(a)i_*(a)da + r_1\left(1-\frac{2T_*}{K}\right)\right)x(t) - mT_*\displaystyle\int_0^{+\infty} n(a)y(t,a)da - kT_*z(t), \\ \dfrac{\partial y(t,a)}{\partial t} + \dfrac{\partial y(t,a)}{\partial a} = -\left(\mu + \dfrac{r_2T_*}{K}\right)y(t,a) - \dfrac{r_2 i_*(a)}{K}x(t), \\ z'(t) = \displaystyle\int_0^{+\infty} p(a)y(t,a)da - d_3z(t), \\ y(t,0) = \left(kV_* + m\displaystyle\int_0^{+\infty} n(a)i_*(a)da\right)x(t) + mT_*\displaystyle\int_0^{+\infty} n(a)y(t,a)da + kT_*z(t), \end{cases}$$

where $x(t) = T(t) - T_*$, $y(t,a) = i(t,a) - i_*(a)$ and $z(t) = V(t) - V_*$ are the deviation variables. By plugging the trial functions $x(t) = x_0e^{\lambda t}$, $y(t,a) = y_0(a)e^{\lambda t}$, $z(t) = z_0e^{\lambda t}$ into the above linearisation, we can obtain the following eigenvalue problem:

$$\begin{cases} \left[\lambda + d_1 - r_1\left(1 - \dfrac{2T_*}{K}\right)\right]x_0 = \left(-kV_* - m\displaystyle\int_0^{+\infty} n(a)i_*(a)da\right)x_0 \\ \qquad\qquad - mT_*\displaystyle\int_0^{+\infty} n(a)y_0(a)da - kT_*z_0, \\ \dfrac{dy_0(a)}{da} = -\left(\lambda + \mu + \dfrac{r_2T_*}{K}\right)y_0(a) - \dfrac{r_2i_*(a)}{K}x_0, \\ (\lambda + d_3)z_0 = \displaystyle\int_0^{+\infty} p(a)y_0(a)da, \\ y_0(0) = \left(kV_* + m\displaystyle\int_0^{+\infty} n(a)i_*(a)da\right)x_0 + mT_*\displaystyle\int_0^{+\infty} n(a)y_0(a)da + kT_*z_0. \end{cases} \tag{5.1}$$

Solving the second and third equations in (5.1), we obtain that

$$y_0(a) = y_0(0)e^{-\left(\lambda+\mu+\frac{r_2T_*}{K}\right)a} - \int_0^a e^{-\left(\lambda+\mu+\frac{r_2T_*}{K}\right)(a-s)}\frac{r_2i_*(s)}{K}x_0ds, \quad z_0 = \frac{1}{\lambda + d_3}\int_0^{+\infty} p(a)y_0(a)da. \tag{5.2}$$

Then the first equation in (5.1) implies that

$$\left[\lambda + d_1 - r_1\left(1 - \frac{2T_*}{K}\right)\right]x_0 = -y_0(0). \tag{5.3}$$

Multiplying both sides of the last equation in (5.1) by $\left[\lambda + d_1 - r_1\left(1 - \frac{2T_*}{K}\right)\right]$ and combining the resulting equation with (5.2) and (5.3), we obtain (after cancelling $y_0(0)$)

$$\left[\lambda + d_1 - r_1\left(1 - \frac{2T_*}{K}\right)\right] = -\left(kV_* + m\int_0^{+\infty} n(a)i_*(a)da\right)$$

$$+\left(\lambda+d_1-r_1\left(1-\frac{2T_*}{K}\right)\right)mT_*\int_0^{+\infty}n(a)e^{-(\lambda+\mu+\frac{r_2T_*}{K})a}da$$
$$+mT_*\int_0^{+\infty}n(a)e^{-(\lambda+\mu+\frac{r_2T_*}{K})(a-s)}\frac{r_2i_*(s)}{K}ds$$
$$+\left(\lambda+d_1-r_1\left(1-\frac{2T_*}{K}\right)\right)\frac{kT_*}{\lambda+d_3}\int_0^{+\infty}p(a)e^{-(\lambda+\mu+\frac{r_2T_*}{K})a}da$$
$$+\frac{kT_*}{\lambda+d_3}\int_0^{+\infty}p(a)e^{-(\lambda+\mu+\frac{r_2T_*}{K})}(a-s)\frac{r_2i_*(s)}{K}ds.$$

Substituting the function forms (4.1) for $p(a)$ and $n(a)$ into the above equation and by direct evaluations of the involving integrals, we are led to the following characteristic equation for (4.2) at E_*:

$$\begin{aligned}\Delta_1(\lambda):=&\left[\lambda+d_1-r_1\left(1-\frac{2T_*}{K}\right)\right]+kV_*+mn_*(I_*-I_2)\\&-\frac{mT_*n_*\theta_2\left[\lambda+d_1-r_1\left(1-\frac{2T_*}{K}\right)\right]}{\left(\lambda+\mu+\frac{r_2T_*}{K}\right)\left(\lambda+\mu+\frac{r_2T_*}{K}+\theta_2\right)}\\&-\frac{mT_*n_*r_2}{K}\left[\frac{I_*}{\lambda+\mu+\frac{r_2T_*}{K}}-\frac{I_2}{\lambda+\mu+\frac{r_2T_*}{K}+\theta_2}\right]\\&-\frac{kT_*p_*\theta_1\left[\lambda+d_1-r_1\left(1-\frac{2T_*}{K}\right)\right]}{\left(\lambda+\mu+\frac{r_2T_*}{K}\right)\left(\lambda+\mu+\frac{r_2T_*}{K}+\theta_1\right)(\lambda+d_3)}\\&-\frac{kT_*p_*r_2}{K}\left[\frac{I_*}{\left(\lambda+\mu+\frac{r_2T_*}{K}\right)(\lambda+d_3)}-\frac{I_1}{\left(\lambda+\mu+\frac{r_2T_*}{K}+\theta_1\right)(\lambda+d_3)}\right]=0,\end{aligned}$$

where

$$I_*=\int_0^\infty i_*(a)da,\quad I_1=\int_0^\infty e^{-\theta_1a}i_*(a)da,\quad I_2=\int_0^\infty e^{-\theta_2a}i_*(a)da.$$

Now, by straightforward but very tedious calculations, we find that $\Delta_1(\lambda)=0$ is equivalent to the following polynomial equation:

$$\Delta_1(\lambda):=\lambda^5+A_1\lambda^4+A_2\lambda^3+A_3\lambda^2+A_4\lambda+A_5=0, \tag{5.4}$$

where

$$\begin{aligned}A_1&=d_3+a_1+a_2+a_3+a_4+b_1,\\A_2&=d_3a_3+(d_3+a_3)(a_1+a_2+a_4+b_1)+a_2a_4+(a_2+a_4)(a_1+b_1)+(I_*-I_2)b_3+b_2,\\A_3&=d_3a_3(a_1+a_2+a_4+b_1)+(d_3+a_3)[a_2a_4+(a_2+a_4)(a_1+b_1)+(I_*-I_2)b_3+b_2],\\A_4&=d_3a_3\left[(a_1+a_2+b_1)a_4+(a_1+b_1)a_2+(I_*-I_2)b_3+b_2\right]+(a_1b_2-I_2a_2b_3+I_*b_5)a_3\\&\quad+\{[(a_1+b_1)a_2+I_*b_3]a_4-I_2a_2b_3+a_1b_2\}\,d_3-I_1a_2b_5+a_1b_4\\&\quad+\{[(a_1+b_1)a_2+I_*b_3]a_3+(I_*-I_1)b_5+b_4\}\,a_4,\\A_5&=d_3a_3\,\{[(a_1+b_1)a_2+I_*b_3]a_4-I_2a_2b_3+a_1b_2\}+a_4(I_*a_3b_5-I_1a_2b_5+a_1b_4,\end{aligned}$$

$$a_1 = d_1 - r_1\left(1 - \frac{2T_*}{K}\right), \quad a_2 = \mu + \frac{r_2 T_*}{K}, \quad a_3 = a_2 + \theta_1, \quad a_4 = a_2 + \theta_2,$$
$$b_1 = mn_*(I_* - I_2), \quad b_2 = mT_* n_* \theta_2, \quad b_3 = \frac{mT_* n_* r_2}{K}, \quad b_4 = kT_* p_* \theta_1, \quad b_5 = \frac{kT_* p_* r_2}{K}.$$

Noticing that

$$\lim_{\lambda \to +\infty} \Delta_1(\lambda) = +\infty, \quad \lim_{\lambda \to -\infty} \Delta_1(\lambda) = -\infty, \quad \Delta_1(0) = A_5.$$

Thus, if $\Delta_1(0) < 0$, then there will be a positive root for $\Delta_1(\lambda)$, implying that E_* is unstable. Therefore, we have proved the following theorem on *instability* of E_*.

Theorem 5.1 *The following statement holds*

(i) *When $\theta_1 = \theta_2$, if $R_0 > 1$ and $\Delta_1(0) < 0$, then the positive equilibrium $E_* = (T_*, i_*, V_*)$ of the System (4.2) with $q = 0$ is unstable;*
(ii) *While $\theta_1 \neq \theta_2$, if $B_1 < 0$, $R_0 > 1$ and $\Delta_1(0) < 0$, then the positive equilibrium E_* is unstable as well.*

As for the conditions for *stability* of E_*, one can apply the Routh–Hurwitz criteria (e.g., [9]) to (5.4) to conclude that all eigenvalues of (5.4) have negative real parts if and only if:

$A_i > 0$ $(i = 1, 2, 3, 4, 5)$,

$$D_1 = A_1 > 0,$$

$$D_2 = \begin{vmatrix} A_1 & A_3 \\ 1 & A_2 \end{vmatrix} = A_1 A_2 - A_3 > 0,$$

$$D_3 = \begin{vmatrix} A_1 & A_3 & A_5 \\ 1 & A_2 & A_4 \\ 0 & A_1 & A_3 \end{vmatrix} = A_1 A_2 A_3 - A_1^2 A_4 - A_3^2 + A_1 A_5 > 0,$$

$$D_4 = \begin{vmatrix} A_1 & A_3 & A_5 & 0 \\ 1 & A_2 & A_4 & 0 \\ 0 & A_1 & A_3 & A_5 \\ 0 & 1 & A_2 & A_4 \end{vmatrix} = D_2(A_3 A_4 - A_2 A_5) - (A_1 A_4 - A_5)^2 > 0,$$

$$D_5 = \begin{vmatrix} A_1 & A_3 & A_5 & 0 & 0 \\ 1 & A_2 & A_4 & 0 & 0 \\ 0 & A_1 & A_3 & A_5 & 0 \\ 0 & 1 & A_2 & A_4 & 0 \\ 0 & 0 & A_1 & A_3 & A_5 \end{vmatrix} = A_1 A_4 A_5 (A_2 A_3 - A_1 A_4) + (2A_1 A_4 + A_2 A_3 - A_1 A_2^2 - 1) A_5^2 - A_4 A_5 A_3^2 > 0.$$

Therefore, we have obtained the following results on the local stability of the positive equilibrium E_*.

Theorem 5.2 *The following statements hold.*

(i) *When* $\theta_1 = \theta_2$, *if* $R_0 > 1$, $A_i > 0$ *and* $D_i > 0$, *(i=1,2,3,4,5), then the positive equilibrium* $E_* = (T_*, i_*, V_*)$ *of the System* (4.2) *with* $q = 0$ *is locally asymptotically stable;*

(ii) *When* $\theta_1 \neq \theta_2$, *if* $B_1 < 0$, $R_0 > 1$ *and* $A_i > 0$, $D_i > 0$, *then the positive equilibrium* E_* *is locally asymptotically stable.*

6 Conclusion and discussion

In this paper, motivated by some existing works on HIV in-host dynamics, we propose a very general age-structured HIV infection model (1.6) that contains (i) both virus-to-cell infection and cell-to-cell transmission modes; (ii) proliferations of both uninfected and infected T cells in the form of logistic growths. The model turns out to be a hybrid system consisting of two differential-integral equations for uninfected cells and free virus, as well as a partial differential equation for age-structured infected cells. By carefully choosing an appropriate working phase space and introducing some suitable preliminaries, we have established the well-posedness of the model (1.6). We have also identified the basic reproduction number R_0 of the model and discussed the structure of equilibria and their stability in terms of the basic reproduction number. Particularly, we have found that, due to the incorporation of the proliferation of the infected cells (i.e., $r_2 > 0$), it is possible for the model to have two infection equilibria accounting for a backward bifurcation in terms of the basic reproduction number R_0, which leads to a bistability scenario within certain ranges of parameters. This can be seen, for example, from (4.11)–(4.13) and Theorem 4.2 by comparing the case of $r_2 = 0$ (no proliferation for infected cells) and the case $r_2 > 0$: when $r_2 = 0$ (4.12) is impossible and hence there will be no backward bifurcation, while for $r_2 > 0$ there can be a range for other parameters within which backward bifurcation will occur. This is an interesting and important finding because the existence of backward bifurcation for the basic reproduction number R_0 at $R_0 = 1$ implies that even when $R_0 < 1$, it is still possible for the virus to persist provided that the initial implantation of virus is large.

Comparing our model with other HIV in-host models that also contain logistic growth terms (e.g., [3, 7, 12, 13]) but do not include infection age to characterise the viral production variations, the dynamics of our model are richer and more complicated, and the analysis brings challenges. Moreover, comparing our results with those HIV models without cell-to-cell infection [2, 7, 19, 26], we found that the maximum infectivity rate of infected cell is also one of the important reasons that cause backward bifurcation. This can be easily seen, also from Theorem 4.2 and the conditions (4.11)–(4.13): if $n_* = 0$ (hence $n(t, a) \equiv 0$) (4.11) and (4.13) become impossible, but when n_* is within certain range (between blue and green curves in Figure 1), backward bifurcation will occur. One can also discuss the biological implications from our mathematical results in terms of other parameters, depending on one's focus and need, and we will omit further discussions here.

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Conflicts of interest

None.

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