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CELL-FREE INFECTION AND CELL-CELL TRANSMISSION HIV-1 DYNAMICS MODEL WITH CURE RATE

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Abstract. Direct cell-to-cell transmission of HIV-1 is found to be a more efficient means of virus propagation than virus-to-cell infection. In this paper, a mathematical model combining these two modes of viral infection with cure rate is investigated. Through calculation, the explicit expression of the basic reproduction number of the model is obtained. By analyzing the characteristic equations, the local stability of equilibria of the model is established. It is proven that the model is permanent if the chronic-infection equilibrium exists. By means of the second additive compound matrix theory, we show that the chronic-infection equilibrium is globally stable if the basic reproduction number is greater than one. By using Lyapunov function, a sufficient condition of global stability for the infection-free equilibrium is obtained if the basic reproduction number is less than one.

Keywords: Cell-to-cell transmission; Virus-to-cell infection; Cure rate; Basic reproduction number; Local stability.

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1. Introduction

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In recent years, compared to the cell-free infection mode, direct cell-to-cell transmission is tending to draw more attention. In the virus-to-cell infection mode, viral particles are released from infected cells and travel to find new targets to infect. The infection happens during the process of the attachment between viral particles and T cells. Traditionally, the viral particles invade the T cells and produce new viral particle fusions inside the target cells. Finally, new viral particles are released outside the T cells and find new T cells to infect. However, recent studies revealed a new infection mode, cell-to-cell transmission also played an important role in the viral spreading and even was found to be a more effective infection mode than the virus-to-cell infection mode[1]. Cell-to-cell spread not only facilitates rapid viral dissemination but may also promote immune invasion and, thereby, influence the disease [2]. Actually, through the contact between cells, multiple viral particles can be transformed from infected cells to uninfected cells via some structures on cells named virological synapses [3-5]. Dimitrov et.al. [6] studied the kinetics of HIV-1 accumulation in cell culture supernatants during multiple rounds of infections by viral production models. They found that the infection rate constant is the critical parameter that affects the kinetics of HIV-1 infection, and furthermore the infectivity of HIV-1 during cell-to-cell transmission is greater than the infectivity of cell-to-cell infection. Dixit and Perelson [7] studied the kinetics of HIV-1 infection by exploring the mechanisms of multiple infections. They found that multiple infections can be caused by both cell-free infection mode and cell-to-cell transmission mode. In cell-to-cell transfer mode, by contact of a target cell, an infectious cell can transfer multiple virions or genomes. However, in cell-free mode, multiple genomes are acquired one by one in a series of infectious contacts of a target cell with free virions.

In terms of cell-to-cell transmission, Lai and Zou [16] studied the both cell-to-cell transmission and virus-to-cell infection of HIV-1 by the model

$$\begin{aligned} \dot{x}(t) &= sx(t)\left(1-\tfrac{x(t)+\alpha y(t)}{x_m}\right)-\beta x(t)v(t)-\beta_1 x(t)y(t), \\ \dot{y}(t) &= \beta x(t)v(t)+\beta_1 x(t)y(t)-ay(t), \\ \dot{v}(t) &= ky(t)-uv(t), \end{aligned} \tag{1.1}$$

where $x(t), y(t), v(t)$ denote the amount of susceptible $CD4^+$ T cells, productively infected T cells and free viral particles at time T. s represents a target cell growth rate and this growth rate is limited by a carrying capacity of target cells x_m. The constant α represents the limitation

of infected cells imposed on the cell growth of target cells, generally $\alpha > 1$. $\beta x(t)v(t)$ is the infection rate of free virus and $\beta_1 x(t)y(t)$ is the infection rate of productively infected cells. The free viral particles are produced from the infected cells at a rate $ky(t)$. The losing rate of productive infected cells and free viral is $ay(t)$ and $uv(t)$ respectively.

In this paper, based on model (1.1), we study a virus dynamic model that incorporates both cell-to-cell transmission mechanism and virus-to-cell infection mode. In addition, we also take account the cure rate of infected cells to uninfected cells. Cure rate is an assumption in many viral dynamic models and is not clearly possible in the case of HIV as in [8-11]. However, this assumption gives some desirable features of these models. For example, the speed of the virus infection is slower and the disease can be controlled if the rate is improved [11-12]. In addition, Zhang also investigated the global dynamics of cell-cell transmission model with cure rate[27]. In comparison with the work of Zhang, we prove the global stability of chronic-infection equilibrium by means of the second additive compound matrix. Here we will adopt a simpler production mechanism for susceptible cells instead of the logistic growth function. All these considerations lead to the following model:

$$\begin{aligned} \dot{x}(t) &= s - dx(t) - \beta x(t)v(t) - \beta_1 x(t)y(t) + \rho y(t), \\ \dot{y}(t) &= \beta x(t)v(t) + \beta_1 x(t)y(t) - ay(t) - \rho y(t), \\ \dot{v}(t) &= ky(t) - uv(t), \end{aligned} \tag{1.2}$$

where target cells are recruited at a constant rate s. The infected cells will transform to susceptible cells at the rate $\rho y(t)$ under certain therapy.

In the rest of the paper, we will analyze the model (1.2). In Section 2, by analyzing the corresponding characteristic equations, the local stability of each feasible equilibria of model (1.2) is discussed. In Section 3, by using the persistence theory developed in [13], we prove that model (1.2) is permanent if the chronic-infection equilibrium exists. In Section 4, by using Lyapunov function and the second additive compound matrix in [14,15,21], we show that if chronic-infection equilibrium is not feasible, the infection-free equilibrium is globally asymptotically stable, else the chronic-infection equilibrium is globally asymptotically stable.

2. The basic reproduction number and local stability of equilibria

In this section, we discuss the local stability of an infection-free equilibrium and a chronic-infection equilibrium of the model (1.2) by analyzing the corresponding characteristic equations, respectively.

Through calculation, model (1.2) always has an infection-free equilibrium $E_0\left(\frac{s}{d},0,0\right)$. If $s(\beta k+\beta_1 u)>du(a+\rho)$, then system has a unique chronic-infection equilibrium $E^*(x^*,y^*,v^*)$, where

$$x^*=\frac{(a+\rho)u}{(\beta k+\beta_1 u)},y^*=\frac{(\beta k+\beta_1 u)s-du(a+\rho)}{(\beta k+\beta_1 u)((a+\rho)-\rho)},v^*=\frac{k}{u}\frac{(\beta k+\beta_1 u)s-du(a+\rho)}{(\beta k+\beta_1 u)((a+\rho)-\rho)}.$$

Let

$$R_0=\frac{s(\beta k+\beta_1 u)}{du(a+\rho)}.$$

R_0 is called the basic reproduction number of model (1.2). It is easy to show that if $R_0>1$, the chronic-infection equilibrium E^* exists, else E^* is not feasible.

The characteristic equation of model (1.2) at the infection-free equilibrium E_0 takes the form

$$(\lambda+d)[(\lambda-\beta_1 x_0+(a+\rho))(\lambda+u)-k\beta x_0]=0. \tag{2.1}$$

Clearly, Eq. (2.1) always has a real root $\lambda=-d<0$. Other roots of (2.1) are given by the following equation:

$$(\lambda-\beta_1 x_0+a+\rho)(\lambda+u)-k\beta x_0=0. \tag{2.2}$$

Let $f(\lambda)=(\lambda-\beta_1 x_0+a+\rho)(\lambda+u)-k\beta x_0$.

Dividing each side of (2.2) by $\lambda+u$ when $\lambda\neq u$, it follows that

$$\lambda+(a+\rho)=\frac{k\beta x_0}{(\lambda+u)}+\beta_1 x_0. \tag{2.3}$$

For $f(\lambda)=0$, we assume that the real parts of its roots are positive or zero, and then take modulo for each side of (2.3), it follows that

$$|\lambda+(a+\rho)|>a+\rho, \tag{2.4}$$

when $R_0<1$

$$\left|\frac{k\beta x_0}{(\lambda+u)}+\beta_1 x_0\right|<(k\beta+\beta_1 u)\frac{s}{du}<a+\rho. \tag{2.5}$$

Here Eq. (2.5) contradicts Eq. (2.4). Hence all roots of $f(\lambda)=0$ possess negative real parts, and we can conclude that the infection-free equilibrium is stable when $R_0<1$.

$f(0) = u(a+\rho) - (\beta_1 u + k\beta)\frac{s}{d} < 0, f(+\infty) = +\infty$. Hence Eq. (2.2) has at least a positive real root when $R_0 > 1$, and then the infection-free equilibrium is unstable.

The characteristic equation of model (1.2) at the chronic-infection equilibrium E^* takes the form

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0, \tag{2.6}$$

where

$$\begin{aligned} A &= a+\rho+u+d+\beta v^*+\beta_1 y^*-\beta_1 x^*, \\ B &= d\left(\tfrac{\beta k(a+\rho)}{\beta k+\beta_1 u}+u\right)+(\beta v^*+\beta_1 y^*)(a+u), \\ C &= au(\beta v^*+\beta_1 y^*). \end{aligned}$$

When $R_0 > 1$

$$\begin{aligned} A &= \tfrac{\beta k(a+\rho)}{\beta k+\beta_1 u}+u+d+\beta v^*+\beta_1 y^* > 0, \\ B &= d\left(\tfrac{\beta k(a+\rho)}{\beta k+\beta_1 u}+u\right)+(\beta v^*+\beta_1 y^*)(a+u) > 0, \\ C &= au(\beta v^*+\beta_1 y^*) > 0, \end{aligned}$$

$$\begin{aligned} AB-C = &\left(\tfrac{\beta k(a+\rho)}{\beta k+\beta_1 u}+\beta v^*+\beta_1 y^*\right)B+du\left(\tfrac{\beta k(a+\rho)}{\beta k+\beta_1 u}+u\right)+u^2(\beta v^*+\beta_1 y^*) \\ &+d^2\left(\tfrac{\beta k(a+\rho)}{\beta k+\beta_1 u}+u\right)+d(a+u)(\beta v^*+\beta_1 y^*). \end{aligned}$$

Obviously, $AB - C > 0$ always holds. Hence by Routh-Hurwitz criterion, we see that the chronic-infection equilibrium E^* is locally asymptotically stable when $R_0 > 1$.

3. Permanence

In this section, we are concerned with the permanence of model (1.2) referring to the method in [13,17].

Definition 3.1. Model (1.2) is permanent (uniformly persistent) if there are positive constants $m_1, m_2, m_3, M_1, M_2, M_3$ such that each positive solution of model (1.2) satisfies

$$\begin{aligned} m_1 \le \liminf_{t\to+\infty} x(t) \le \limsup_{t\to+\infty} x(t) \le M_1, \\ m_2 \le \liminf_{t\to+\infty} y(t) \le \limsup_{t\to+\infty} y(t) \le M_2, \\ m_3 \le \liminf_{t\to+\infty} v(t) \le \limsup_{t\to+\infty} v(t) \le M_3. \end{aligned}$$

In order to study the permanence of model (1.2), we refer to the persistence theory developed by Hale and Waltman [13].

Let X be a complete metric space with metric d. Suppose that T is a continuous semiflow on X, i.e., a continuous mapping $T:[0,\infty)\times X\to X$ with the following properties

$$T_t\circ T_s=T_{t+s},t,s\geq 0,T_0(x)=x,x\in X,$$

where T_t denotes the mapping from X to X given by $T_t(x)=T(t,x)$. The distance $d(x,Y)$ of a point $x\in X$ from a subset Y of X is defined by

$$d(x,Y)=\inf_{y\in Y}d(x,y).$$

Recall that the positive orbit $\gamma^+(x)$ through x is defined as $\gamma^+(x)=\cup_{t\geq 0}\{T(t)x\}$, and its ω-limit set is $\omega(x)=\cap_{s\geq 0}\overline{\cup_{t\geq s}\{T(t)x\}}$. Define $W^s(A)$ the strong stable set of a compact invariant set A as

$$W^s(A)=\{x:x\in A,\omega(x)\neq\phi,\omega(x)\subset A\}.$$

$(C1)$ Assume that X^0 is open and dense in X and $X^0\cup X_0=X,X^0\cap X_0=\phi$. Moreover, the C^0-semigroup $T(t)$ on X satisfies

$$T(t):X^0\to X^0,T(t):X_0\to X_0.$$

Let $T_b(t)=T(t)|_{X0}$ and A_b be the global attractor for $T_b(t)$. Define $\overline{A}_b=\cup_{x\in A_b}\omega(x)$.

Lemma 3.1. *Suppose that $T(t)$ satisfies $(C1)$ and the following conditions:*

i. There is a $t_0\geq 0$ such that $T(t)$ is compact for $t>t_0$.

ii. $T(t)$ is dissipative in X.

iii. $\overline{A}_b$ is isolated and has an acyclic covering $\overline{M}=\{\overline{M}_1,\overline{M}_2,\ldots,\overline{M}_n\}$.

iv. $W^s(\overline{M}_i)\cap X_0=\phi$ for $i=1,2,\ldots,n$.

Then X_0 is a uniform repeller with respect to X^0, that is, there is an $\varepsilon>0$ such that for any $x\in X^0$, $\liminf_{t\to+\infty}d(T(t)x,X_0)\geq\varepsilon$ holds.

To study the permanence of model (1.2), we also need the following result.

Lemma 3.2. *There is positive constant M such that for any positive solution $(x(t),y(t),v(t))$ of model (1.2), the following inequations hold*

$$\limsup_{t\to+\infty}x(t)\leq M,\limsup_{t\to+\infty}y(t)\leq M,\limsup_{t\to+\infty}v(t)\leq M.$$

Proof. Let $(x(t), y(t), v(t))$ be any positive solution of (1.2). Denote $\mu = \min\{d, a-kk_1, k_1u\}$. Define

$$V(t) = x(t) + y(t) + k_1 v(t).$$

Calculating the derivative of $V(t)$ along positive solutions of model (1.2), it follows that

$$\frac{dV(t)}{dt} = s - dx(t) - ay(t) + k_1 ky(t) - k_1 uv(t) \leq s - \mu V(t).$$

Take k_1 such that $0 < k_1 < \frac{a}{k}$, which yields $\limsup_{t\to+\infty} V(t) = \frac{s}{\mu}$. Denote $M = \max\{\frac{s}{\mu}, \frac{s}{k_1\mu}\}$, so we have the result of Lemma 3.2. Thus we complete the proof.

Particularly, when $k_1 = 0, a > d$, it follows that

$$V_0(t) = x(t) + y(t).$$

Calculating the derivative of V_0 along the positive solutions of model (1.2), it follows that

$$\frac{dV_0(t)}{dt} = s - dx(t) - ay(t) \leq s - dV_0(t),$$

which yields $\limsup_{t\to+\infty} V_0(t) = \frac{s}{d}$, denote $M_0 = \frac{s}{d}$, it follows that

$$\limsup_{t\to+\infty} x(t) \leq M_0, \limsup_{t\to+\infty} y(t) \leq M_0. \tag{3.1}$$

This result will be used in Section 4 to prove the global stability of infection-free equilibrium. We are now in a position to state and prove our result on the permanence of model (1.2).

Theorem 3.1. *If $R_0 > 1$, model (1.2) is permanent.*

Proof. We need only to show that the boundaries of R^3_{+0} repel positive solutions of model (1.2) uniformly.

Define

$$C_1 = \left\{(\phi, \psi_1, \psi_2) \in R^3_{+0} : \phi \equiv 0\right\},$$
$$C_2 = \left\{(\phi, \psi_1, \psi_2) \in R^3_{+0} : \psi_i \equiv 0, i = 1, 2\right\}.$$

Denote $C_0 = C_1 \cup C_2$ and $C^0 = \text{int}R^3_{+0}$. By the definition of C_0 and C^0, it is easy to see that C_0 and C^0 are positively invariant and the condition *ii* in Lemma 3.1 is clearly satisfied. Noting that the functions in the right side of model (1.2) are C^1, and the solution of model (1.2) is ultimately bounded, using the smoothing property of solutions of delay differential equations introduced in Kuang [18] (Theorem 2.2.8), it follows that condition *i* in Lemma 3.1 is satisfied.

Thus, we need only to show that the conditions *iii* and *iv* hold. Clearly, there are two constant solutions E_1 and E_2 in C_0, to $x(t)=y(t)=v(t)=0$ and $x(t)=\frac{s}{d}, y(t)=v(t)=0$, respectively. If $(x(t),y(t),v(t))$ is a solution of model (1.2) with initial condition C_1, it follows that $y'(t)=-(a+\rho)y$, which yields $y(t)\to 0$ when $t\to+\infty$. If $(x(t),y(t),v(t))$ is a solution of model (1.2) with initiating from C_2 with $x(0)>0$, it follows that $x(t)\to\frac{s}{d}$ when $t\to+\infty$. This shows that if invariant set E_1 and E_2 are isolated, $\{E_1,E_2\}$ is isolated and an acyclic covering.

We now show that $W^s(E_1)\cap C^0=\phi$ and $W^s(E_2)\cap C^0=\phi$. We restrict our attention to the second equation, since the proof for the first is simple. Assume the contrary, then there exists a positive solution $(\overline{x}(t),\overline{y}(t),\overline{v}(t))$, such that

$$(\overline{x}(t),\overline{y}(t),\overline{v}(t))\to\left(\frac{s}{d},0,0\right),t\to+\infty.$$

Choose $\varepsilon>0$ small enough such that

$$\frac{s}{d}-\varepsilon>\frac{(a+\rho)u}{\beta_1 u+\beta k}. \tag{3.2}$$

Let $t_0>0$ be sufficiently large such that

$$\frac{s}{d}-\varepsilon<\overline{x}(t)<\frac{s}{d}+\varepsilon,t\geq t_0,$$

then we have, for $t>t_0$

$$\begin{aligned}\overline{y}'(t)&\geq\left[\beta_1\left(\tfrac{s}{d}-\varepsilon\right)-(a+\rho)\right]y(t)+\beta\left(\tfrac{s}{d}-\varepsilon\right)v(t),\\ \overline{v}'(t)&=ky(t)-uv(t).\end{aligned} \tag{3.3}$$

Consider the matrix

$$A_\varepsilon=\begin{bmatrix}\beta_1\left(\frac{s}{d}-\varepsilon\right)-(a+\rho) & \beta\left(\frac{s}{d}-\varepsilon\right)\\ k & -u\end{bmatrix},$$

since A_ε admits positive off-diagonal elements, the Perron-Frobenius theorem implies that there is a positive eigenvector η for the maximum eigenvalue α of A_ε. By a simple computation we see that the maximum eigenvalue α is a positive since we have (3.1).

Consider

$$\begin{aligned}y'(t)&=\left[\beta_1\left(\tfrac{s}{d}-\varepsilon\right)-(a+\rho)\right]y(t)+\beta\left(\tfrac{s}{d}-\varepsilon\right)v(t),\\ v'(t)&=ky(t)-uv(t).\end{aligned} \tag{3.4}$$

let $\eta = (\eta_1, \eta_2)$ and $l > 0$ be small enough such that

$$l\eta_1 < \overline{y}(t),$$
$$l\eta_2 < \overline{v}(t).$$

If $(y(t), v(t))$ is a solution of model (3.4) satisfying $y(t) = l\eta_1, v(t) = l\eta_2$, since the semiflow of (3.4) is monotone and $A_\varepsilon \eta > 0$, it follows from papers [19-20] that $y(t), v(t)$ are strictly increasing and $y(t) \to +\infty, v(t) \to +\infty$. Note that $\overline{y}(t) > y(t), \overline{v}(t) > v(t)$ for $t > t_0$. We have $\overline{y}(t) \to +\infty, \overline{v}(t) \to +\infty$ as $t \to +\infty$. This contradicts Lemma 3.2. The above assertion is thus proved. Now we are able to conclude from Lemma 3.1 that C_0 repels the positive solution of (1.2) uniformly, and the proof of Theorem 3.1 is complete.

4. Global stability of equilibria

In this section, we study the global stability of each feasible equilibria of model (1.2) by using Lyapunov function and the second additive compound matrix [14,15,21].

Theorem 4.1. *The infection-free equilibrium is globally asymptotically stable if* $R_0 > 1$ *and* $a > d$.

Proof. Define

$$V_1(t) = x(t) - x_0 - x_0 \ln \frac{x}{x_0} + y(t) + \frac{\beta s}{du} v(t).$$

Calculating the derivative of $V_1(t)$ along positive solutions of model (1.2), it follows that

$$\begin{aligned}
\tfrac{d}{dt}V_1(t) &= \left(1 - \tfrac{x_0}{x}\right)(s - dx(t) - \beta xv - \beta_1 xy + \rho y) + \beta xv + \beta_1 xy - (a+\rho)y + \tfrac{\beta s}{du}(ky - uv) \\
&= dx_0\left(2 - \tfrac{x}{x_0} - \tfrac{x_0}{x}\right) + \beta x_0 v + \beta_1 x_0 y - ay - \tfrac{x_0}{x}\rho y + \tfrac{\beta s}{du}(ky - uv) \\
&= dx_0\left(2 - \tfrac{x}{x_0} - \tfrac{x_0}{x}\right) + \beta_1 x_0 y + \tfrac{\beta k s}{du} y - ay - \tfrac{x_0}{x}\rho y \\
&= dx_0\left(2 - \tfrac{x}{x_0} - \tfrac{x_0}{x}\right) + \left[\tfrac{(\beta k + \beta_1 u)s}{du} - \left(a + \tfrac{x_0}{x}\rho\right)\right] y.
\end{aligned}$$

When $a > d$, we have (3.1), which means $x \le x_0 = \frac{s}{d}$. It follows that

$$\begin{aligned}
\tfrac{d}{dt}V_1(t) &\le dx_0\left(2 - \tfrac{x}{x_0} - \tfrac{x_0}{x}\right) + \left[\tfrac{(\beta k + \beta_1 u)s}{du} - (a+\rho)\right] y \\
&= dx_0\left(2 - \tfrac{x}{x_0} - \tfrac{x_0}{x}\right) + (a+\rho)(R_0 - 1)\, y.
\end{aligned}$$

Notice that

$$2 - \frac{x}{x_0} - \frac{x_0}{x} \le 0$$

holds for all $x(t) \geq 0$, and the equality holds if and only if $x(t) = x_0$. Hence if $R_0 < 1$, then ${V_1}'(t) \leq 0$. Let $E = \{x(t), y(t), v(t), {V_1}'(t) = 0\}$ and Ω be the largest invariant set in E. By the LaSalles invariance principle, all nonnegative solutions tend to Ω. Note that ${V_1}'(t) = 0$ if and only if $x(t) = x_0$ and $y = 0$, thus the infection-free equilibrium is globally asymptotically stable by the LaSalle invariance principle. This completes the proof.

Lemma 4.1. [15] *Assume that D is a convex bounded set in R^3_+. If model (1.2) satisfies the conditions in D*

i. Model (1.2) is competitive.

ii. Model (1.2) is permanent.

iii. Any periodic orbit of model (1.2) is to be asymptotically orbitally stable.

iv. Model (1.2) has a unique equilibrium E^*, which is locally asymptotically stable.

E^* is globally asymptotically stable in D.

Theorem 4.2. *The chronic-infection equilibrium is globally asymptotically stable if $R_0 > 1$.*

Proof. First of all, we need to verify that the model (1.2) is competitive. The jacobian matrix of model (1.2) is as follows

$$J = \begin{bmatrix} -d - \beta v - \beta_1 y & -\beta_1 x + \rho & -\beta x \\ \beta v + \beta_1 y & \beta_1 x - (a + \rho) & \beta x \\ 0 & k & -u \end{bmatrix}.$$

Take the diagonal matrix $H = (1, -1, 1)$. Obviously, the diagonal element of HJH is negative. Thus model (1.2) is competitive in D, and the condition i in Lemma 4.1 is satisfied. In Section 3, we have proved that model (1.2) is permanent when $R_0 > 1$, thus condition ii in Lemma 4.1 is clearly satisfied. Now we are in position to verify the condition iii in Lemma 4.1. The second compound matrix $J^{[2]}(p)$ of the Jacobian matrix $J(p)$ is

$$\begin{bmatrix} -d - a - \rho - \beta v - \beta_1 y + \beta_1 x & \beta x & \beta x \\ k & -d - u - \beta v - \beta_1 y & -\beta_1 x + \rho \\ 0 & \beta v + \beta_1 y & \beta_1 x - a - \rho - u \end{bmatrix}.$$

Here, we refer Theorem 6.3 and Proposition 6.4 in [21] to prove our result.

Theorem 4.3. *A sufficient condition for a periodic orbit of model (1.2) to be asymptotically orbitally stable with asymptotic phase is that the periodic linear model*

$$W'(t) = \left(J^{[2]} p(t)\right) W(t) \tag{4.1}$$

is asymptotically stable. Applying Theorem 4.3 to model (1.2), we can prove the following result.

Proposition 4.1. *Any non-constant periodic solution to model (1.2), if one exists, is asymptotically orbitally stable with asymptotic phase.*

Proof. Using the matrix $J^{[2]} p(t)$, we can write the second additive compound model (4.1) for model (1.2) with respect to a solution $(x(t), y(t), v(t))$ as

$$\begin{aligned} w'_1 &= (-d-a-\rho-\beta v-\beta_1 y+\beta_1 x) w_1 + \beta x w_2 + \beta x w_3, \\ w'_2 &= k w_1 + (-d-u-\beta v-\beta_1 y) w_2 + (-\beta_1 x+\rho) w_3, \\ w'_3 &= (\beta v+\beta_1 y) w_2 + (\beta_1 x-a-\rho-u) w_3. \end{aligned} \tag{4.2}$$

Let

$$V(w_1(t), w_2(t), w_3(t) x(t), y(t), v(t)) = \sup\left\{|w_1(t)|, \tfrac{y}{v}|w_2(t)+w_3(t)|\right\}. \tag{4.3}$$

Take $\sigma = \left\{\underline{y}, \underline{v}\right\}$, $y(t) \geq \sigma, v(t) \geq \sigma$. From the result of Lemma 3.2, we have $v(t) \leq M$. Thus it follows

$$\begin{aligned} &V(w_1(t), w_2(t), w_3(t), x(t), y(t), v(t)) \\ &\quad = \sup\left\{|w_1(t)|, \tfrac{y}{v}|w_2(t)+w_3(t)|\right\} \\ &\quad \geq \tfrac{\sigma}{M} \sup\{|w_1(t)|, |w_2(t)+w_3(t)|\}. \end{aligned} \tag{4.4}$$

The right-hand derivative of $V(t)$ exists and its calculation is described in [22]. Direct calculations lead to the following differential inequalities

$$\begin{aligned} D_+|w_1(t)| &\leq (-d-a-\rho-\beta v-\beta_1 y+\beta_1 x)|w_1| + \beta x|w_2| + \beta x|w_3|, \\ D_+|w_2(t)| &\leq k w_1 + (-d-u-\beta v-\beta_1 y)|w_2| + (-\beta_1 x+\rho)|w_3|, \\ D_+|w_3(t)| &\leq (\beta v+\beta_1 y)|w_2| + (\beta_1 x-a-\rho-u)|w_3|. \end{aligned} \tag{4.5}$$

Then we have

$$D_+\left[\frac{y}{v}(|w_2(t)|+|w_3(t)|)\right] \leq k\frac{y}{v}|w_1| + \left(\frac{y'}{y} - \frac{v'}{v} - G\right)\frac{y}{v}(|w_2(t)|+|w_3(t)|), \tag{4.6}$$

where $G = \min\{d+u, a+u\}$, thus

$$D_+V(t) \leq \sup\{h_1(t), h_2(t)\} V(t), \tag{4.7}$$

where

$$\begin{aligned} h_1(t) &= \tfrac{y'}{y} - d - \beta v - \beta_1 y, \\ h_2(t) &= \tfrac{y'}{y} - u - G. \end{aligned} \tag{4.8}$$

Case 1. If $d > a$, that means $-d < -a$. Then $G = a+u$, it follows

$$\begin{aligned} &h_2(t) = \tfrac{y'}{y} - a > h_1(t), \\ &D_+V(t) \leq h_2(t) V(t) = \left(-a + \tfrac{y'}{y}\right) V(t). \end{aligned} \tag{4.9}$$

Case 2. If $d < a$, that means $-d > -a$. Then $G = d+u$, it follows

$$\begin{aligned} &h_2(t) = \tfrac{y'}{y} - d > h_1(t), \\ &D_+V(t) \leq h_2(t) V(t) = \left(-d + \tfrac{y'}{y}\right) V(t). \end{aligned} \tag{4.10}$$

Let $\mu = \min\{a, d\}$, then we have

$$D_+V(t) \leq \left(-\mu + \frac{y'}{y}\right) V(t). \tag{4.11}$$

By Gronwall inequality we have the following results

$$D_+V(t) \leq V(0) y(t) e^{-\mu t} \leq V(0) M e^{-\mu t}.$$

Thus, $V(t) \to 0$, when $t \to +\infty$. Since we have (4.4), $(w_1(t), w_2(t), w_3(t)) \to 0$. Thus the periodic linear model (4.1) is asymptotically stable. The condition *iii* in Lemma 4.1 is satisfied. In Section 2, we have proved that E^* is locally asymptotically stable. Thus the proof of Theorem 4.2 is completed.

5. Discussion

In this paper, based on both cell-to-cell transmission and virus-to-cell infection mode, the global dynamics of HIV-1 model with cure rate was investigated by using Lyapunov function, LaSalles invariance principle and second additive compound matrix. The infection-free equilibrium is globally asymptotically stable if $R_0 < 1$ and $a > d$. The chronic-infection equilibrium

is globally asymptotically stable if $R_0 > 1$. In addition, when $R_0 > 1$, model (1.2) is permanent. And we showed the explicit expression of the reproduction number $R_0 = \frac{s(\beta k+\beta_1 u)}{du(a+\rho)}$. This indicated a higher spreading ratio of viral and a more precise viral dissemination threshold than the classical infection mode which only considered virus-to-cell infection [23-26]. In addition, the expression of the reproduction number also suggested that cure rate also played a important part in slowing down the viral dissemination, and the greater cure rate ρ was, the slower viral spread.

Conflict of Interests

The authors declare that there is no conflict of interests.

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