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Research article

Global stability analysis of a viral infection model in a critical case

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Abstract: Recently, it has been proved that for the diffusive viral infection model with cell-to-cell infection, the virus-free steady state E_0 is globally attractive when the basic reproduction number $R_0 < 1$, and the virus is uniformly persistent if $R_0 > 1$. However, the global stability analysis in the critical case of $R_0 = 1$ is not given due to a technical difficulty. For the diffusive viral infection model including a single equation with diffusion term, global stability analysis in the critical case has been performed by constructing Lyapunov functions. Unfortunately, this method is not applicable for two or more equations with diffusion terms, which was left it as an open problem. The present study is devoted to solving this open problem and shows that E_0 is globally asymptotically stable when $R_0 = 1$ for three equations with diffusion terms by means of Gronwall's inequality, comparison theorem and the properties of semigroup.

Keywords: reaction-diffusion equation model; global attractor; globally attractive; asymptotical stability

1. Introduction

HIV spreads through either cell-free viral infection or direct transmission from infected to healthy cells (cell-to-cell infection) [1]. It is reported that more than 50% of viral infection is caused by the cell-to-cell infection [2]. Cell-to-cell infection can occur when infected cells encounter healthy cells and form viral synapse [3]. Recently, applying reaction-diffusion equations to model viral dynamics with cell-to-cell infection have been received attentions (see, e.g., [4–6]). Ren et al. [5] proposed the following reaction-diffusion equation model with cell-to-cell infection:

$$\begin{aligned}
\frac{\partial T(t,\,x)}{\partial t} &= \nabla\cdot(d_1(x)\nabla T)+\lambda(x)-\beta_1(x)TT^*-\beta_2(x)TV-d(x)T,\ t>0,\ x\in\Omega,\\
\frac{\partial T^*(t,\,x)}{\partial t} &= \nabla\cdot(d_2(x)\nabla T^*)+\beta_1(x)TT^*+\beta_2(x)TV-r(x)T^*,\ t>0,\ x\in\Omega,\\
\frac{\partial V(t,\,x)}{\partial t} &= \nabla\cdot(d_3(x)\nabla V)+N(x)T^*-e(x)V,\ t>0,\ x\in\Omega,\\
T(0,\,x) &= T^0(x)>0,\ T^*(0,\,x)=T_0^*(x)\geq 0,\ V(0,\,x)=V_0(x)\geq 0,\ x\in\Omega.
\end{aligned} \tag{1.1}$$

In the model (1.1), $T(t,\,x)$, $T^*(t,\,x)$ and $V(t,\,x)$ denote densities of healthy cells, infected cells and virus at time t and location x, respectively. The detailed biological meanings of parameters for the model (1.1) can be found in [5]. The well-posedness of the classical solutions for the model (1.1) have been studied. The model (1.1) admits a basic reproduction number R_0, which is defined by the spectral radius of the next generation operator [5]. The model (1.1) defines a solution semiflow $\Psi(t)$, which has a global attractor. The model (1.1) admits a unique virus-free steady state $E_0=(T_0(x),\,0,\,0)$, which is globally attractive if $R_0<1$. If $R_0>1$, the model (1.1) admits at least one infection steady state and virus is uniformly persistent [5].

It is a challenging problem to consider the global stability of E_0 in the critical case of $R_0=1$. In [6], Wang et al. studied global stability analysis in the critical case by establishing Lyapunov functions. Unfortunately, the method can not be applied for the model consisting of two or more equations with diffusion terms, which was left it as an open problem.

Adopting the idea in [7–9], the present study is devoted to solving this open problem and shows that E_0 is globally asymptotically stable when $R_0=1$ for the model (1.2). For simplicity, in the following, we assume that the diffusion rates $d_1(x)$, $d_2(x)$ and $d_3(x)$ are positive constants. That is ,we consider the following model

$$\begin{aligned}
\frac{\partial T(t,\,x)}{\partial t} &= d_1\Delta T+\lambda(x)-\beta_1(x)TT^*-\beta_2(x)TV-d(x)T,\ t>0,\ x\in\Omega,\\
\frac{\partial T^*(t,\,x)}{\partial t} &= d_2\Delta T^*+\beta_1(x)TT^*+\beta_2(x)TV-r(x)T^*,\ t>0,\ x\in\Omega,\\
\frac{\partial V(t,\,x)}{\partial t} &= d_3\Delta V+N(x)T^*-e(x)V,\ t>0,\ x\in\Omega,\\
T(0,\,x) &= T^0(x)>0,\ T^*(0,\,x)=T_0^*(x)\geq 0,\ V(0,\,x)=V_0(x)\geq 0,\ x\in\Omega,
\end{aligned} \tag{1.2}$$

with the boundary conditions:

$$\frac{\partial T(t,\,x)}{\partial \nu}=\frac{\partial T^*(t,\,x)}{\partial \nu}=\frac{\partial V(t,\,x)}{\partial \nu}=0,\ t>0,\ x\in\partial\Omega, \tag{1.3}$$

where Ω is the spatial domain and ν is the outward normal to $\partial\Omega$. We assume that all the location-dependent parameters are continuous, strictly positive and uniformly bounded functions on $\overline{\Omega}$.

2. Main result

Let $\mathbb{Y} = C\left(\overline{\Omega}, \mathbb{R}^3\right)$ with the supremum norm $\|\cdot\|_{\mathbb{Y}}$, $\mathbb{Y}^+ = C\left(\overline{\Omega}, \mathbb{R}^3_+\right)$. Then $(\mathbb{Y}, \mathbb{Y}^+)$ is an ordered Banach space. Let $\mathcal{T}$ be the semigroup for the system:

$$\begin{aligned}\frac{\partial T^*(t, x)}{\partial t} &= d_2\Delta T^* + \beta_1(x)T_0(x)T^* + \beta_2(x)T_0(x)V - r(x)T^*,\\ \frac{\partial V(t, x)}{\partial t} &= d_3\Delta V + N(x)T^* - e(x)V,\end{aligned}$$

where $T_0(x)$ is the solution of the elliptic problem $d_1\Delta T + \lambda(x) - d(x)T = 0$ under the boundary conditions (1.3). Then $\mathcal{T}$ has the generator

$$\widetilde{A} = \begin{pmatrix} d_2\Delta + \beta_1(x)T_0(x) - r(x) & \beta_2(x)T_0(x) \\ N(x) & d_3\Delta - e(x) \end{pmatrix}.$$

Let us define the exponential growth bound of $\mathcal{T}$ as

$$\overline{\omega} = \overline{\omega}(\mathcal{T}) := \lim_{t\to+\infty} \frac{\ln \|\mathcal{T}\|}{t},$$

and define the spectral bound of $\widetilde{A}$ by

$$s\left(\widetilde{A}\right) := \sup\left\{Re\lambda,\ \lambda \in \sigma\left(\widetilde{A}\right)\right\}.$$

Theorem 2.1. *If $R_0 = 1$, E_0 of the model* (1.2) *is globally asymptotically stable.*

Proof. We first show the local asymptotic stability of E_0 of the model (1.2). Suppose $\zeta > 0$ and let $v_0 = (T^0, T^*_0, V_0)$ with $\|v_0 - E_0\| \le \zeta$. Define $m_1(t, x) = \frac{T(t,x)}{T_0(x)} - 1$ and $p(t) = \max_{x\in\overline{\Omega}} \{m_1(t, x), 0\}$. According to $d_1\Delta T_0(x) + \lambda(x) - d(x)T_0(x) = 0$, we have

$$\frac{\partial m_1}{\partial t} - d_1\Delta m_1 - 2d_1\frac{\nabla T_0(x)\nabla m_1}{T_0(x)} + \frac{\lambda(x)}{T_0(x)}m_1 = -\frac{\beta_1(x)TT^*}{T_0(x)} - \frac{\beta_2(x)TV}{T_0(x)}.$$

Let $\widetilde{T}_1(t)$ be the positive semigroup generated by

$$d_1\Delta + 2d_1\frac{\nabla T_0(x)\nabla}{T_0(x)} - \frac{\lambda(x)}{T_0(x)}$$

associated with (1.3) (see Theorem 4.4.3 in [10]). From Theorem 4.4.3 in [10], we can find $q > 0$ such that $\left\|\widetilde{T}_1(t)\right\| \le M_1e^{-qt}$ for some $M_1 > 0$. Hence, one gets

$$m_1(\cdot, t) = \widetilde{T}_1(t)m_{10} - \int_0^\infty \widetilde{T}_1(t-s)\left[\frac{\beta_1(\cdot)T(\cdot, s)T^*(\cdot, s)}{T_0(\cdot)} + \frac{\beta_2(\cdot)T(\cdot, s)V(\cdot, s)}{T_0(\cdot)}\right]ds,$$

where $m_{10} = \frac{T^0}{T_0(x)} - 1$. In view of the positivity of $\widetilde{T}_1(t)$, it follows that

$$\begin{aligned} p(t) &= \max_{x\in\overline{\Omega}} \{\omega_1(t, x), 0\} \\ &= \max_{x\in\overline{\Omega}} \left\{ \widetilde{T}_1(t)m_{10} - \int_0^\infty \widetilde{T}_1(t-s)\left[\frac{\beta_1(\cdot)T(\cdot, s)T^*(\cdot, s)}{T_0(\cdot)} + \frac{\beta_2(\cdot)T(\cdot, s)V(\cdot, s)}{T_0(\cdot)}\right]ds, 0\right\} \\ &\le \max_{x\in\overline{\Omega}} \left\{\widetilde{T}_1(t)m_{10}, 0\right\} \\ &\le \left\|\widetilde{T}_1(t)m_{10}\right\| \\ &\le M_1 e^{-qt}\left\|\frac{T^0}{T_0(x)} - 1\right\| \\ &\le \frac{\zeta M_1 e^{-qt}}{T_m}, \end{aligned}$$

where $T_m = \min_{x\in\overline{\Omega}}\{T_0(x)\}$. Note that (T^*, V) satisfies

$$\begin{aligned} \frac{\partial T^*(t, x)}{\partial t} &= d_2\Delta T^* + \beta_1(x)T_0(x)T^* + \beta_2(x)T_0(x)V - r(x)T^* \\ &\quad + \beta_1(x)T_0(x)\left(\frac{T}{T_0(x)} - 1\right)T^* + \beta_2(x)T_0(x)\left(\frac{T}{T_0(x)} - 1\right)V, \\ \frac{\partial V(t, x)}{\partial t} &= d_3\Delta V + N(x)T^* - e(x)V. \end{aligned}$$

It then follows that

$$\begin{pmatrix} T^*(\cdot, t) \\ V(\cdot, t) \end{pmatrix} = \mathcal{T}(t)\begin{pmatrix} T_0^* \\ V_0 \end{pmatrix}$$

$$+ \int_0^\infty \mathcal{T}(t-s)\begin{pmatrix} \beta_1(\cdot)T_0(\cdot)\left(\frac{T(\cdot, s)}{T_0(\cdot)} - 1\right)T^*(\cdot, s) + \beta_2(\cdot)T_0(\cdot)\left(\frac{T(\cdot, s)}{T_0(\cdot)} - 1\right)V(\cdot, s) \\ 0 \end{pmatrix}ds.$$

From Theorem 3.5 in [11], we have that $s\left(\widetilde{A}\right) = \sup\left\{Re\lambda, \lambda \in \sigma\left(\widetilde{A}\right)\right\}$ has the same sign as $R_0 - 1$. If $R_0 = 1$, then $s\left(\widetilde{A}\right) = 0$. Then we easily verify all the conditions of Proposition 4.15 in [12]. It follows from $R_0 = 1$ and Proposition 4.15 in [12] that we can find $M_1 > 0$ such that $\|\mathcal{T}(t)\| \le M_1$ for $t \ge 0$, where M_1 can be chosen as large as needed in the sequel. Since $p(s) \le \frac{\zeta M_1 e^{-qs}}{T_m}$, one gets

$$\begin{aligned} \max\{\|T^*(\cdot, t)\|, \|V(\cdot, t)\|\} &\le M_1 \max\{\|T_0^*\|, \|V_0\|\} \\ &\quad + M_1(\|\beta_1\| + \|\beta_2\|)\|T_0\|\int_0^\infty p(s)\max\{\|T^*(s)\|, \|V(s)\|\}ds \\ &\le M_1\zeta + M_2\zeta\int_0^\infty e^{-qs}\max\{\|T^*(s)\|, \|V(s)\|\}ds, \end{aligned}$$

where

$$M_2 = \frac{M_1^2(\|\beta_1\| + \|\beta_2\|)\|T_0\|}{T_m}.$$

By using Gronwall's inequality, we get

$$\max\{\|T^*(\cdot,\,t)\|,\,\|V(\cdot,\,t)\|\} \leq M_1\zeta e^{\int_0^\infty \zeta M_2 e^{-qs}ds} \leq M_1\zeta e^{\frac{\zeta M_2}{q}}.$$

Then $\frac{\partial T}{\partial t} - d_1\Delta T > \lambda(x) - d(x)T - M_1\zeta e^{\frac{\zeta M_2}{q}}\left(\beta_1(x)+\beta_2(x)\right)T$. Let $\widehat{u_1}$ be the solution of the system:

$$\begin{aligned}
&\frac{\partial \widehat{u_1}(t,\,x)}{\partial t} = d_1\Delta\widehat{u_1} + \lambda(x) - d(x)\widehat{u_1} - M_1\zeta e^{\frac{\zeta M_2}{q}}\left(\beta_1(x)+\beta_2(x)\right)\widehat{u_1},\ x\in\Omega,\ t>0,\\
&\frac{\partial \widehat{u_1}(t,\,x)}{\partial \nu} = 0,\ x\in\partial\Omega,\ t>0,\\
&\widehat{u_1}(x,\,0) = T^0,\ x\in\overline{\Omega}.
\end{aligned} \tag{2.1}$$

Then $T(t,\,x)\geq \widehat{u_1}(t,\,x)$ for $x\in\overline{\Omega}$ and $t\geq 0$. Let $T_\zeta(x)$ be the positive steady state of the model (2.1) and $\widehat{m}(t,\,x)=\widehat{u_1}(t,\,x)-T_\zeta(x)$. Then $\widehat{m}(t,\,x)$ satisfies

$$\begin{aligned}
&\frac{\partial \widehat{m}(t,\,x)}{\partial t} = d_1\Delta\widehat{m} - \left[d(x) + M_1\zeta e^{\frac{\zeta M_2}{q}}(\beta_1(x)+\beta_2(x))\right]\widehat{m},\ x\in\Omega,\ t>0,\\
&\frac{\partial \widehat{m}(t,\,x)}{\partial \nu} = 0,\ x\in\partial\Omega,\ t>0,\\
&\widehat{m}(x,\,0) = T^0 - T_\zeta(x),\ x\in\overline{\Omega}.
\end{aligned}$$

For sufficiently large M_1, from Theorem 4.4.3 in [10], we have $\|F_1(t)\|\leq M_1e^{\overline{\alpha}_0 t}$, where $\overline{\alpha}_0<0$ is a constant and $F_1(t):\ C\left(\overline{\Omega},\,\mathbb{R}\right)\to C\left(\overline{\Omega},\,\mathbb{R}\right)$ is the C_0 semigroup of $d_1\Delta - d(\cdot)$ subject to (1.3) [5]. Hence, we have

$$\begin{aligned}
&\widehat{m}(\cdot,\,t) = F_1(t)\left(T^0 - T_\zeta(x)\right) - \int_0^\infty F_1(t-s)M_1\zeta e^{\frac{\zeta M_2}{q}}\left(\beta_1(\cdot)+\beta_2(\cdot)\right)\widehat{m}(\cdot,\,s)ds,\\
&\left\|\widehat{m}(\cdot,\,t)\right\| \leq M_1\left\|T^0 - T_\zeta(x)\right\|e^{\overline{\alpha}_0 t} + \int_0^\infty M_1^2 e^{\overline{\alpha}_0(t-s)}\zeta e^{\frac{\zeta M_2}{q}}\left(\|\beta_1(\cdot)\|+\|\beta_2(\cdot)\|\right)\left\|\widehat{m}(\cdot,\,s)\right\|ds.
\end{aligned}$$

Let $\mathbf{K} = M_1^2\zeta e^{\frac{\zeta M_2}{q}}\left(\|\beta_1\|+\|\beta_2\|\right)$. By employing Gronwall's inequality, one gets

$$\left\|\widehat{u_1}(\cdot,\,t) - T_\zeta(x)\right\| = \left\|\widehat{m}(\cdot,\,t)\right\| \leq M_1\left\|T^0 - T_\zeta(x)\right\|e^{\mathbf{K}t+\overline{\alpha}_0 t}.$$

Choosing $\zeta>0$ sufficiently small such that $\mathbf{K} < -\frac{\overline{\alpha}_0}{2}$, then

$$\left\|\widehat{u_1}(\cdot,\,t) - T_\zeta(x)\right\| \leq M_1\left\|T^0 - T_\zeta(x)\right\|e^{\overline{\alpha}_0 t/2},$$

and

$$\begin{aligned}
T(\cdot,\,t) - T_0(x) &\geq \widehat{u_1}(\cdot,\,t) - \widehat{U}(x)\\
&= \widehat{u_1}(\cdot,\,t) - U_\pi(x) + U_\pi(x) - \widehat{U}(x)\\
&\geq -\zeta M_1 - (M_1+1)\|T_\zeta(x) - T_0(x)\|.
\end{aligned}$$

Since $p(t)\leq \frac{\zeta M_1}{T_m}$, one gets $T(\cdot,\,t) - T_0(x) \leq \zeta M_1\frac{\|T_0(x)\|}{T_m}$, and hence

$$\|T(\cdot,\,t) - T_0(x)\| = \max\left\{\zeta M_1 + (M_1+1)\|T_\zeta(x) - T_0(x)\|,\ \zeta M_1\frac{\|T_0(x)\|}{T_m}\right\}.$$

From

$$\lim_{\zeta\to 0} T_\zeta(x) = T_0(x),$$

by choosing ζ small enough, for $t > 0$, there holds $\|T(\cdot, t) - T_0(x)\|$, $\|T^*(\cdot, t)\|$, $\|V(\cdot, t)\| \le \varepsilon$, which implies the local asymptotic stability of E_0.

By Theorem 1 in [5], the solution semiflow $\Psi(t) : \mathbb{Y}^+ \to \mathbb{Y}^+$ of the model (1.2) has a global attractor Π. In the following, we prove the global attractivity of E_0. Define

$$\partial\mathbb{Y}_1 = \left\{\left(\widetilde{T}, \widetilde{T^*}, \widetilde{V}\right) \in \mathbb{Y}^+ : \widetilde{T^*} = \widetilde{V} = 0\right\}.$$

Claim 1. For $v_0 = (T^0, T^*_0, V_0) \in \Pi$, the omega limit set $\omega(v_0) \subset \partial\mathbb{Y}_1$.

Since $\frac{\partial T}{\partial t} \le d_1\Delta T + \lambda(x) - d(x)T$, T is a subsolution of the problem

$$\begin{aligned}
&\frac{\partial \widehat{T}(t, x)}{\partial t} = d_1\Delta\widehat{T} + \lambda(x) - d(x)\widehat{T},\ x \in \Omega,\ t > 0,\\
&\frac{\partial \widehat{T}(t, x)}{\partial \nu} = 0,\ x \in \partial\Omega,\ t > 0,\\
&\widehat{T}(x, 0) = T^0(x),\ x \in \overline{\Omega}.
\end{aligned} \tag{2.2}$$

It is well known that model (2.2) has a unique positive steady state $T_0(x)$, which is globally attractive. This together with the comparison theorem implies that

$$\limsup_{t\to+\infty} T(t, x) \le \limsup_{t\to+\infty} \widehat{T}(t, x) = T_0(x),$$

uniformly for $x \in \Omega$. Since $v_0 = (T^0, T^*_0, V_0) \in \Pi$, we know $T^0 \le T_0$. If $T^*_0 = V_0 = 0$, the claim easily holds. We assume that either $T^*_0 \ne 0$ or $V_0 \ne 0$. Thus one gets $T^*(t, x) > 0$ and $V(t, x) > 0$ for $x \in \overline{\Omega}$ and $t > 0$. Then $T(t, x)$ satisfies

$$\begin{aligned}
&\frac{\partial T(t, x)}{\partial t} < d_1\Delta T + \lambda(x) - d(x)T(t, x),\ x \in \Omega,\ t > 0,\\
&\frac{\partial T(t, x)}{\partial \nu} = 0,\ x \in \partial\Omega,\ t > 0,\\
&T(x, 0) \le T_0(x),\ x \in \Omega.
\end{aligned}$$

The comparison principle yields $T(t, x) < T_0(x)$ for $x \in \overline{\Omega}$ and $t > 0$. Following [7], we introduce

$$h(t, v_0) := \inf\left\{\widetilde{h} \in \mathbb{R} : T^*(\cdot, t) \le \widetilde{h}\phi_2,\ V(\cdot, t) \le \widetilde{h}\phi_3\right\}.$$

Then $h(t, v_0) > 0$ for $t > 0$. We show that $h(t, v_0)$ is strictly decreasing. To this end, we fix $t_0 > 0$, and let $\overline{T^*}(\cdot, t) = h(t_0, v_0)\phi_2$ and $\overline{V}(\cdot, t) = h(t_0, v_0)\phi_3$ for $t \ge t_0$. Due to $T(\cdot, t) < T_0(x)$, one gets

$$\begin{aligned}
&\frac{\partial \overline{T^*}(t, x)}{\partial t} > d_2\Delta\overline{T^*} + \beta_1(x)T\overline{T^*} + \beta_2(x)T\overline{V} - r(x)\overline{T^*},\\
&\frac{\partial \overline{V}(t, x)}{\partial t} = d_3\Delta\overline{V} + N(x)\overline{T^*} - e(x)\overline{V},\\
&\overline{T^*}(x, t_0) \ge T^*(x, t_0),\ \overline{V}(x, t_0) \ge V(x, t_0),\ x \in \Omega.
\end{aligned} \tag{2.3}$$

Hence $\left(\overline{T^*}(t, x), \overline{V}(t, x)\right) \geq (T^*(t, x), V(t, x))$ for $x \in \overline{\Omega}$ and $t \geq t_0$. From the model (2.3), one gets $h(t_0, v_0)\phi_2(x) = \overline{T^*}(t, x) > T^*(t, x)$ for $x \in \overline{\Omega}$ and $t > t_0$. Similarly, we get $h(t_0, v_0)\phi_3(x) = \overline{V}(t, x) > V(t, x)$ for $x \in \overline{\Omega}$ and $t > t_0$. Since $t_0 > 0$ is arbitrary, $h(t, v_0)$ is strictly decreasing. Let $h_* = \lim_{t\to+\infty} h(t, v_0)$. Then we have $h_* = 0$. Let $Q = (Q_1, Q_2, Q_3) \in \omega(v_0)$. Then there is $\{t_k\}$ with $t_k \to +\infty$ such that $\Psi(t_k)v_0 \to Q$. We get $h(t, Q) = h_*$ for $t \geq 0$ due to $\lim_{t\to+\infty} \Psi(t + t_k)v_0 = \Psi(t) \lim_{t\to+\infty} \Psi(t_k)v_0 = \Psi(t)Q$. If $Q_2 \neq 0$ and $Q_3 \neq 0$, we repeat the above discussions to illustrate that $h(t, Q)$ is strictly decreasing, which contradicts to $h(t, Q) = h_*$. Thus, we have $Q_2 = Q_3 = 0$.

Claim 2. $\Pi = \{E_0\}$.

Since $\{E_0\}$ is globally attractive in $\partial\mathbb{Y}_1$, $\{E_0\}$ is the only compact invariant subset of the model (1.2). From the invariance of $\omega(v_0)$ and $\omega(v_0) \subset \partial\mathbb{Y}_1$, one gets $\omega(v_0) = \{E_0\}$. By Lemma 3.11 in [9], we get $\Pi = \{E_0\}$.

The local asymptotic stability and global attractivity yield the global asymptotic stability of E_0. □

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Conflict of interest

The authors decare no conflicts of interest.

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