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Research article

Periodic oscillation for a class of in-host MERS-CoV infection model with CTL immune response

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Abstract: The purpose of this paper is to give some sufficient conditions for the existence of periodic oscillation of a class of in-host MERS-Cov infection model with cytotoxic T lymphocyte (CTL) immune response. A new technique is developed to obtain a lower bound of the state variable characterizing CTL immune response in the model. Our results expand on some previous works.

Keywords: MERS-CoV; CTL immune response; periodic solutions; coincidence degree

1. Introduction

Middle East respiratory syndrome (MERS) is a viral respiratory disease caused by Middle East respiratory syndrome coronavirus (MERS-CoV). The intermediate host of MERS-CoV is probably the dromedary camel, a zoonotic virus [1]. Most MERS cases are acquired by human-to-human transmission. There is no vaccine or specific treatment available, and approximately 35% of patients with MERS-CoV infection have died [2]. There has been extensive works on infectious disease models and viral infection models associated with MERS that can help in disease control and provide strategies for potential drug treatments [3–8].

Dipeptidyl peptidase-4 (DPP4) plays an important role in viral infection [2]. Based on classic viral infection models developed in [9–11], a four-dimensional ordinary differential equation model is proposed and studied in [8]. The model in [8] describes the interaction mechanisms among uninfected cells, infected cells, DPP4 and MERS-CoV.

Recently, taking into account periodic factors such as diurnal temperature differences and periodic drug treatment, the model in [8] has been further extended a periodic case in [12], and then the existence of positive periodic solutions is studied by using the theorem in [13].

It is well-known that CTL immune responses play a very critical role in controlling viral load and the concentration of infected cells. Thus, many scholars have considered CTL immune responses in various viral infection models and have achieved many excellent research results [14–18]. CTL cells can kill virus-infected cells and are important for the control and clearance of MERS-CoV infections [19]. Inspired by the above research works, we consider the following periodic MERS-CoV infection model with CTL immune response:

$$\begin{cases} \dot{T}(t) = \lambda(t) - \beta(t)D(t)v(t)T(t) - d(t)T(t), \\ \dot{I}(t) = \beta(t)D(t)v(t)T(t) - d_1(t)I(t) - p(t)I(t)Z(t), \\ \dot{v}(t) = d_1(t)M(t)I(t) - c(t)v(t), \\ \dot{D}(t) = \lambda_1(t) - \beta_1(t)\beta(t)D(t)v(t)T(t) - \gamma(t)D(t), \\ \dot{Z}(t) = q(t)I(t)Z(t) - b(t)Z(t). \end{cases} \tag{1.1}$$

In model (1.1), $T(t)$, $I(t)$, $v(t)$, $D(t)$ and $Z(t)$ represent the concentrations of uninfected cells, infected cells, free virus, DPP4 on the surface of uninfected cells and CTL cells at time t, respectively. CTL cells increase at a rate bilinear rate $q(t)I(t)Z(t)$ by the viral antigen of the infected cells and decay at rate $b(t)Z(t)$; infected cells are killed by the CTL immune response at rate $p(t)I(t)Z(t)$. Except for $p(t)$, $q(t)$ and $b(t)$, all the remaining parameters of model (1.1) have the same biological meanings as in [12].

Throughout the paper, it is assumed that the functions $\lambda(t)$, $\beta(t)$, $d(t)$, $d_1(t)$, $p(t)$, $M(t)$, $c(t)$, $\lambda_1(t)$, $\gamma(t)$, $q(t)$ and $b(t)$ are positive, continuous and ω periodic ($\omega > 0$); the function $\beta_1(t)$ is non-negative, continuous and ω periodic.

From point of view in both biology and mathematics, it is one of the most significant topics to study the existence of periodic oscillations of a system (see, for example, [12, 20–26] and the references therein).

In the next section, some sufficient criteria are given for the existence of positive periodic oscillations of model (1.1). It should be mentioned here that, in the proofs of the main results in the following section, a new technique is developed to obtain a lower bound of the state variable $Z(t)$ characterizing CTL immune response in model (1.1).

2. Main results

For some function $f(t)$ which is continuous and ω-periodic on $\mathbb{R}$, let us define the following notations:

$$f^U = \max_{t\in[0,\omega]} f(t), \quad f^l = \min_{t\in[0,\omega]} f(t), \quad \widehat{f} = \frac{1}{\omega}\int_0^\omega f(t)dt.$$

Moreover, for convenience, let us give the following parameters:

$$R^* = \frac{\widehat{\lambda}\beta^l \exp\{L_3 + L_4\}}{\widehat{d_1}\exp\{M_2\}(\beta^l \exp\{L_3 + L_4\} + d^U)} > 1, \quad \omega^* = \frac{\widehat{b}}{2\widehat{\lambda}\widehat{q}}, \quad \delta^* = \frac{\widehat{d_1}}{2\widehat{p}}(R^* - 1),$$

$$M_1 = \ln(\frac{\lambda^U}{d^l}), \quad M_2 = \ln(\frac{\widehat{b}}{\widehat{q}} + 2\widehat{\lambda}\omega), \quad M_3 = \ln(\frac{\widehat{(d_1M)}}{\widehat{c}}) + M_2 + 2\widehat{c}\omega,$$

$$M_4 = \ln(\frac{\lambda_1^U}{\gamma^l}), \quad M_5 = \ln(\frac{\widehat{\beta}\exp\{M_1 + M_3 + M_4\}}{\widehat{p}\exp\{L_2\}}) + 2\widehat{b}\omega,$$

$$L_1 = \ln(\frac{\lambda^l}{\beta^U \exp\{M_3 + M_4\} + d^U}), \quad L_2 = \ln(\frac{\widehat{b}}{\widehat{q}} - 2\widehat{\lambda}\omega), \quad L_3 = \ln(\frac{\widehat{(d_1M)}}{\widehat{c}}) + L_2 - 2\widehat{c}\omega,$$

$$L_4 = \ln(\frac{\lambda_1^l}{(\beta_1\beta)^U \exp\{M_1 + M_3\} + \gamma^U}), \quad L_5 = \ln(\delta^*) - 2\widehat{b}\omega.$$

The following theorem is the main result of this paper.

Theorem 2.1. *If* $R^* > 1$ *and* $\omega < \omega^*$*, then model* (1.1) *has at least one positive* ω*-periodic solution.*

Proof. Making the change of variables $T(t) = \exp\{u_1(t)\}$, $I(t) = \exp\{u_2(t)\}$, $v(t) = \exp\{u_3(t)\}$, $D(t) = \exp\{u_4(t)\}$, $Z(t) = \exp\{u_5(t)\}$, then model (1.1) can be rewritten as

$$\begin{cases} \dot{u}_1(t) = \dfrac{\lambda(t)}{\exp\{u_1(t)\}} - \beta(t)\exp\{u_3(t) + u_4(t)\} - d(t), \\ \dot{u}_2(t) = \beta(t)\dfrac{\exp\{u_1(t) + u_3(t) + u_4(t)\}}{\exp\{u_2(t)\}} - d_1(t) - p(t)\exp\{u_5(t)\}, \\ \dot{u}_3(t) = d_1(t)M(t)\dfrac{\exp\{u_2(t)\}}{\exp\{u_3(t)\}} - c(t), \\ \dot{u}_4(t) = \dfrac{\lambda_1(t)}{\exp\{u_4(t)\}} - \beta_1(t)\beta(t)\exp\{u_1(t) + u_3(t)\} - \gamma(t), \\ \dot{u}_5(t) = q(t)\exp\{u_2(t)\} - b(t). \end{cases} \tag{2.1}$$

Thus, we only need to consider model (2.1).

Let us set

$$X = Y = \left\{u = (u_1(t), u_2(t), u_3(t), u_4(t), u_5(t))^T \in C(\mathbb{R}, \mathbb{R}^5) \mid u(t) = u(t + \omega)\right\}$$

with the norm

$$\|u\| = \max_{t\in[0,\omega]} |u_1(t)| + \max_{t\in[0,\omega]} |u_2(t)| + \max_{t\in[0,\omega]} |u_3(t)| + \max_{t\in[0,\omega]} |u_4(t)| + \max_{t\in[0,\omega]} |u_5(t)|.$$

It can be shown that X and Y are Banach spaces. Define

$$Nu = \begin{bmatrix} \frac{\lambda(t)}{\exp\{u_1(t)\}} - \beta(t)\exp\{u_3(t) + u_4(t)\} - d(t) \\ \beta(t)\frac{\exp\{u_1(t)+u_3(t)+u_4(t)\}}{\exp\{u_2(t)\}} - d_1(t) - p(t)\exp\{u_5(t)\} \\ d_1(t)M(t)\frac{\exp\{u_2(t)\}}{\exp\{u_3(t)\}} - c(t) \\ \frac{\lambda_1(t)}{\exp\{u_4(t)\}} - \beta_1(t)\beta(t)\exp\{u_1(t) + u_3(t)\} - \gamma(t) \\ q(t)\exp\{u_2(t)\} - b(t) \end{bmatrix} := \begin{bmatrix} N_1(t) \\ N_2(t) \\ N_3(t) \\ N_4(t) \\ N_5(t) \end{bmatrix} \ (u \in X),$$

$$Lu = \dot{u} \ (u \in \text{Dom } L), \quad Pu = \frac{1}{\omega}\int_0^\omega u(t)dt \ (u \in X), \quad Qu = \frac{1}{\omega}\int_0^\omega u(t)dt \ (u \in Y),$$

here $\text{Dom } L = \{u \in X, \ \dot{u} \in X\}$. It easily has that $\text{Ker } L = \{u \in X \mid u \in \mathbb{R}^5\}$ and $\text{Im } L = \{u \in Y \mid \int_0^\omega u(t)dt = 0\}$. Further, it is clear that $\text{Im } L$ is closed in Y and $\dim \text{Ker } L = \text{codim Im } L = 5$. Hence, L is a Fredholm mapping with index zero.

For $\mu \in (0,1)$, let us consider the equation $Lu = \mu Nu$, i.e.,

$$\begin{cases} \dot{u}_1(t) =\mu \left[\dfrac{\lambda(t)}{\exp\{u_1(t)\}} - \beta(t)\exp\{u_3(t)+u_4(t)\} - d(t)\right], \\ \dot{u}_2(t) =\mu \left[\beta(t)\dfrac{\exp\{u_1(t)+u_3(t)+u_4(t)\}}{\exp\{u_2(t)\}} - d_1(t) - p(t)\exp\{u_5(t)\}\right], \\ \dot{u}_3(t) =\mu \left[d_1(t)M(t)\dfrac{\exp\{u_2(t)\}}{\exp\{u_3(t)\}} - c(t)\right], \\ \dot{u}_4(t) =\mu \left[\dfrac{\lambda_1(t)}{\exp\{u_4(t)\}} - \beta_1(t)\beta(t)\exp\{u_1(t)+u_3(t)\} - \gamma(t)\right], \\ \dot{u}_5(t) =\mu \left[q(t)\exp\{u_2(t)\} - b(t)\right]. \end{cases} \tag{2.2}$$

For any solution $u = (u_1(t), u_2(t), u_3(t), u_4(t), u_5(t))^T \in X$ of (2.2), it has

$$\begin{cases} \displaystyle\int_0^\omega \left[\dfrac{\lambda(t)}{\exp\{u_1(t)\}} - \beta(t)\exp\{u_3(t)+u_4(t)\} - d(t)\right] dt = 0, \\ \displaystyle\int_0^\omega \left[\beta(t)\dfrac{\exp\{u_1(t)+u_3(t)+u_4(t)\}}{\exp\{u_2(t)\}} - d_1(t) - p(t)\exp\{u_5(t)\}\right] dt = 0, \\ \displaystyle\int_0^\omega \left[d_1(t)M(t)\dfrac{\exp\{u_2(t)\}}{\exp\{u_3(t)\}} - c(t)\right] dt = 0, \\ \displaystyle\int_0^\omega \left[\dfrac{\lambda_1(t)}{\exp\{u_4(t)\}} - \beta_1(t)\beta(t)\exp\{u_1(t)+u_3(t)\} - \gamma(t)\right] dt = 0, \\ \displaystyle\int_0^\omega \left[q(t)\exp\{u_2(t)\} - b(t)\right] dt = 0. \end{cases} \tag{2.3}$$

From the first two equations in (2.2), it has

$$\dot{u}_1(t)\exp\{u_1(t)\} = \mu\left[\lambda(t) - \beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\} - d(t)\exp\{u_1(t)\}\right],$$

and

$$\dot{u}_2(t)\exp\{u_2(t)\} = \mu\left[\beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\} - d_1(t)\exp\{u_2(t)\} - p(t)\exp\{u_2(t)+u_5(t)\}\right].$$

Hence, by integrating the above two equations on $[0,\omega]$, it has

$$\int_0^\omega \left[\lambda(t) - \beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\} - d(t)\exp\{u_1(t)\}\right] dt = 0 \tag{2.4}$$

and

$$\int_0^\omega \left[\beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\} - d_1(t)\exp\{u_2(t)\} - p(t)\exp\{u_2(t)+u_5(t)\}\right] dt = 0. \tag{2.5}$$

Note that $I(t) := \exp\{u_2(t)\}$ satisfies

$$\dot{I}(t) = \dot{u}_2(t)\exp\{u_2(t)\} = \mu\left[\beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\} - d_1(t) - p(t)\exp\{u_2(t)+u_5(t)\}\right].$$

Then, from (2.4) and (2.5), it has

$$\begin{aligned}\int_0^{\omega} |\dot{I}(t)|dt \leq& \mu \int_0^{\omega} [\beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\} + d_1(t) + p(t)\exp\{u_2(t)+u_5(t)\}]dt \\ \leq& 2\int_0^{\omega} \beta(t)\exp\{u_1(t)+u_3(t)+u_4(t)\}dt \\ \leq& 2\widehat{\lambda}\omega.\end{aligned} \tag{2.6}$$

From the third and the fifth equations of (2.2), it has

$$\begin{aligned}&\int_0^{\omega} |\dot{u}_3(t)|dt \leq \mu\left[\int_0^{\omega} d_1(t)M(t)\frac{\exp\{u_2(t)\}}{\exp\{u_3(t)\}}dt + \int_0^{\omega} c(t)dt\right] < 2\widehat{c}\omega,\\ &\int_0^{\omega} |\dot{u}_5(t)|dt \leq \mu\left[\int_0^{\omega} q(t)\exp\{u_2(t)\}dt + \int_0^{\omega} b(t)dt\right] < 2\widehat{b}\omega.\end{aligned} \tag{2.7}$$

Note that $u \in X$, there exist $\xi_i,\ \eta_i \in [0,\omega]$ $(i = 1,2,3,4,5)$, such that

$$u_i(\xi_i) = \min_{t\in[0,\omega]} u_i(t),\quad u_i(\eta_i) = \max_{t\in[0,\omega]} u_i(t)\ (i = 1,2,3,4,5).$$

From (2.2), $\dot{u}_1(\eta_1) = 0$ and $\dot{u}_4(\eta_4) = 0$, it has

$$\begin{aligned}&\frac{\lambda(\eta_1)}{\exp\{u_1(\eta_1)\}} - \beta(\eta_1)\exp\{u_3(\eta_1)+u_4(\eta_1)\} - d(\eta_1) = 0,\\ &\frac{\lambda_1(\eta_4)}{\exp\{u_4(\eta_4)\}} - \beta_1(\eta_4)\beta(\eta_4)\exp\{u_1(\eta_4)+u_3(\eta_4)\} - \gamma(\eta_4) = 0,\end{aligned}$$

which imply that

$$\begin{aligned}&u_1(t) \leq u_1(\eta_1) \leq \ln\left(\frac{\lambda(\eta_1)}{d(\eta_1)}\right) \leq \ln\left(\frac{\lambda^U}{d^l}\right) = M_1,\\ &u_4(t) \leq u_4(\eta_4) \leq \ln\left(\frac{\lambda_1(\eta_4)}{\gamma(\eta_4)}\right) \leq \ln\left(\frac{\lambda_1^U}{\gamma^l}\right) = M_4.\end{aligned} \tag{2.8}$$

From the last equation of (2.3), it has

$$\int_0^{\omega} q(t)\exp\{u_2(\xi_2)\}dt \leq \widehat{b}\omega \leq \int_0^{\omega} q(t)\exp\{u_2(\eta_2)\}dt,$$

which implies that

$$I(\xi_2) = \exp\{u_2(\xi_2)\} \leq \frac{\widehat{b}}{\widehat{q}} \leq \exp\{u_2(\eta_2)\} = I(\eta_2).$$

Then, from (2.6) and $\omega < \omega^*$, it has

$$\begin{aligned}&I(t) \leq I(\xi_2) + \int_0^{\omega} |\dot{I}(t)|dt \leq \frac{\widehat{b}}{\widehat{q}} + 2\widehat{\lambda}\omega,\\ &I(t) \geq I(\eta_2) - \int_0^{\omega} |\dot{I}(t)|dt \geq \frac{\widehat{b}}{\widehat{q}} - 2\widehat{\lambda}\omega = 2\widehat{\lambda}\,(\omega^* - \omega) > 0.\end{aligned}$$

Thus, it has

$$u_2(t) \le \ln\left(\frac{\widehat{b}}{\widehat{q}} + 2\widehat{\lambda}\omega\right) = M_2, \quad u_2(t) \ge \ln\left(\frac{\widehat{b}}{\widehat{q}} - 2\widehat{\lambda}\omega\right) = L_2. \tag{2.9}$$

From the third equation of (2.3), it has

$$\int_0^\omega d_1(t)M(t)\frac{\exp\{M_2\}}{\exp\{u_3(\xi_3)\}}dt \ge \widehat{c}\omega \ge \int_0^\omega d_1(t)M(t)\frac{\exp\{L_2\}}{\exp\{u_3(\eta_3)\}}dt,$$

which implies that

$$u_3(\xi_3) \le \ln\left(\frac{\widehat{(d_1M)}}{\widehat{c}}\right) + M_2, \quad u_3(\eta_3) \ge \ln\left(\frac{\widehat{(d_1M)}}{\widehat{c}}\right) + L_2.$$

Then, from (2.7), it has

$$\begin{aligned} u_3(t) &\le u_3(\xi_3) + \int_0^\omega |\dot{u}_3(t)|dt \le \ln\left(\frac{\widehat{(d_1M)}}{\widehat{c}}\right) + M_2 + 2\widehat{c}\omega = M_3, \\ u_3(t) &\ge u_3(\eta_3) - \int_0^\omega |\dot{u}_3(t)|dt \ge \ln\left(\frac{\widehat{(d_1M)}}{\widehat{c}}\right) + L_2 - 2\widehat{c}\omega = L_3. \end{aligned} \tag{2.10}$$

From the second equation of (2.3), it has

$$\widehat{p}\exp\{u_5(\xi_5)\}\omega \le \int_0^\omega \left[\beta(t)\frac{\exp\{M_1 + M_3 + M_4\}}{\exp\{L_2\}} - d_1(t)\right]dt \le \frac{\exp\{M_1 + M_3 + M_4\}}{\exp\{L_2\}}\widehat{\beta}\omega,$$

which implies that

$$u_5(\xi_5) \le \ln\left(\frac{\widehat{\beta}\exp\{M_1 + M_3 + M_4\}}{\widehat{p}\exp\{L_2\}}\right) := l_5.$$

Then, from (2.7), it has

$$u_5(t) \le u_5(\xi_5) + \int_0^\omega |\dot{u}_5(t)|dt \le l_5 + 2\widehat{b}\omega = M_5.$$

From $\dot{u}_1(\xi_1) = 0$, $\dot{u}_4(\xi_4) = 0$, (2.8) and (2.10), it has

$$\begin{aligned} \exp\{u_1(\xi_1)\} &= \frac{\lambda(\xi_1)}{\beta(\xi_1)\exp\{u_3(\xi_1) + u_4(\xi_1)\} + d(\xi_1)} \ge \frac{\lambda^l}{\beta^U\exp\{M_3 + M_4\} + d^U}, \\ \exp\{u_4(\xi_4)\} &= \frac{\lambda_1(\xi_4)}{\beta_1(\xi_4)\beta(\xi_4)\exp\{u_1(\xi_4) + u_3(\xi_4)\} + \gamma(\xi_4)} \ge \frac{\lambda_1^l}{(\beta_1\beta)^U\exp\{M_1 + M_3\} + \gamma^U}. \end{aligned}$$

Thus, it has

$$\begin{aligned} u_1(t) &\ge u_1(\xi_1) \ge \ln\left(\frac{\lambda^l}{\beta^U\exp\{M_3 + M_4\} + d^U}\right) = L_1, \\ u_4(t) &\ge u_4(\xi_4) = \ln\left(\frac{\lambda_1^l}{(\beta_1\beta)^U\exp\{M_1 + M_3\} + \gamma^U}\right) = L_4. \end{aligned} \tag{2.11}$$

Let us give an estimate of the lower bound of the state variable $u_5(t)$ related to CTL immune response. It should be mentioned here that a completely different method from that in [12] has been used.

Claim A If $R^* > 1$ and $\omega < \omega^*$, then

$$\exp\{u_5(\eta_5)\} \geq \delta^*.$$

If **Claim A** is not true, then it has that, for any t, $\exp\{u_5(t)\} \leq \exp\{u_5(\eta_5)\} < \delta^*$. Hence, it has from (2.3), (2.9)–(2.11) that

$$\begin{aligned}
0 =& \int_0^\omega \left[\beta(t)\frac{\exp\{u_1(t)+u_3(t)+u_4(t)\}}{\exp\{u_2(t)\}} - d_1(t) - p(t)\exp\{u_5(t)\}\right]dt\\
\geq& \int_0^\omega \left[\beta(t)\frac{\exp\{u_1(t)+L_3+L_4\}}{\exp\{M_2\}} - d_1(t) - p(t)\exp\{u_5(\eta_5)\}\right]dt\\
\geq& \frac{\beta^l\exp\{L_3+L_4\}}{\exp\{M_2\}}\int_0^\omega \exp\{u_1(t)\}dt - (\widehat{d_1}+\widehat{p}\delta^*)\omega,
\end{aligned}$$

which implies that

$$\int_0^\omega d(t)\exp\{u_1(t)\}dt \leq d^U\int_0^\omega \exp\{u_1(t)\}dt \leq \frac{d^U(\widehat{d_1}+\widehat{p}\delta^*)\exp\{M_2\}}{\beta^l\exp\{L_3+L_4\}}\omega := \Psi\omega. \tag{2.12}$$

Adding (2.4) and (2.5) together, it has

$$\begin{aligned}
\int_0^\omega [\lambda(t) - d(t)\exp\{u_1(t)\}]dt =& \int_0^\omega [d_1(t)\exp\{u_2(t)\} + p(t)\exp\{u_2(t)+u_5(t)\}]dt\\
\leq& \int_0^\omega \exp\{M_2\}[d_1(t) + p(t)\exp\{u_5(\eta_5)\}]dt\\
\leq& \exp\{M_2\}(\widehat{d_1}+\widehat{p}\delta^*)\omega,
\end{aligned}$$

which implies that

$$\begin{aligned}
\int_0^\omega d(t)\exp\{u_1(t)\}dt \geq& \left[\widehat{\lambda} - \exp\{M_2\}(\widehat{d_1}+\widehat{p}\delta^*)\right]\omega\\
=& \Psi\omega + \left[\widehat{\lambda} - \Psi - \exp\{M_2\}(\widehat{d_1}+\widehat{p}\delta^*)\right]\omega\\
=& \Psi\omega + \left[\widehat{\lambda} - \exp\{M_2\}\left(1+\frac{d^U}{\beta^l\exp\{L_3+L_4\}}\right)(\widehat{d_1}+\widehat{p}\delta^*)\right]\omega\\
=& \Psi\omega + \widehat{d_1}\exp\{M_2\}\left(1+\frac{d^U}{\beta^l\exp\{L_3+L_4\}}\right)\left(R^* - 1 - \frac{\widehat{p}}{\widehat{d_1}}\delta^*\right)\omega\\
=& \Psi\omega + \frac{\widehat{d_1}}{2}\exp\{M_2\}\left(1+\frac{d^U}{\beta^l\exp\{L_3+L_4\}}\right)(R^*-1)\omega\\
>& \Psi\omega,
\end{aligned}$$

which is a contradiction to (2.12). Thus, the claim holds.

From **Claim A** and (2.7), it has

$$u_5(t) \geq u_5(\eta_5) - \int_0^\omega |\dot{u}_5(t)|dt \geq \ln(\delta^*) - 2\widehat{b}\omega = L_5. \tag{2.13}$$

Now, for convenience, let us define

$$\overline{R^*} = \left(\widehat{\lambda} - \frac{\widehat{d_1 b}}{\widehat{q}}\right)\frac{\widehat{\beta}\widehat{(d_1 M)}}{\widehat{d}\widehat{d_1}\widehat{c}}\frac{\widehat{\lambda_1}}{\widehat{(\beta_1\beta)}\frac{\widehat{\lambda}\widehat{(d_1 M)}\widehat{b}}{\widehat{d}\widehat{c}\widehat{q}} + \widehat{\gamma}}, \quad Z_{max} = \frac{\widehat{q}}{\widehat{p}\widehat{b}}\left(\widehat{\lambda} - \frac{\widehat{d_1 b}}{\widehat{q}}\right).$$

Note that if $R^* > 1$, then it has

$$\widetilde{R^*} := \left(\widehat{\lambda} - \widehat{d_1}\exp\{M_2\}\right)\frac{\beta^l \exp\{L_3 + L_4\}}{d^U \widehat{d_1}\exp\{M_2\}} > 1,$$

which implies that

$$\begin{aligned} Z_{max} >& \frac{\widehat{q}}{\widehat{p}\widehat{b}}\left[\widehat{\lambda} - \widehat{d_1}\left(\frac{\widehat{b}}{\widehat{q}} + 2\widehat{\lambda}\omega\right)\right] = \frac{\widehat{q}}{\widehat{p}\widehat{b}}\left(\widehat{\lambda} - \widehat{d_1}\exp\{M_2\}\right) > 0, \\ \overline{R^*} \geq& \left(\widehat{\lambda} - \frac{\widehat{d_1 b}}{\widehat{q}}\right)\frac{\widehat{\beta}\widehat{(d_1 M)}}{\widehat{d}\widehat{d_1}\widehat{c}}\frac{\lambda_1^l}{(\beta_1\beta)^U \exp\{M_3 + M_1\} + \gamma^U} \geq \widetilde{R^*} > 1. \end{aligned}$$

Let $(u_1, u_2, u_3, u_4, u_5)^T \in \mathbb{R}^5$ be the solution of the following equations:

$$\begin{cases} \dfrac{\widehat{\lambda}}{\exp\{u_1\}} - \widehat{\beta}\exp\{u_3 + u_4\} - \widehat{d} = 0, \\ \dfrac{\widehat{\beta}\exp\{u_1 + u_3 + u_4\}}{\exp\{u_2\}} - \widehat{d_1} - \widehat{p}\exp\{u_5\} = 0, \\ \widehat{(d_1 M)}\dfrac{\exp\{u_2\}}{\exp\{u_3\}} - \widehat{c} = 0, \\ \dfrac{\widehat{\lambda_1}}{\exp\{u_4\}} - \widehat{(\beta_1\beta)}\exp\{u_1 + u_3\} - \widehat{\gamma} = 0, \\ \widehat{q}\exp\{u_2\} - \widehat{b} = 0. \end{cases} \quad (2.14)$$

Define $\Gamma : [0, Z_{max}] \to \mathbb{R}$, via

$$\Gamma(x) = \frac{\widehat{\beta}\widehat{(d_1 M)}}{\widehat{c}}\frac{\widehat{\lambda_1}\Gamma_1(x)}{\widehat{(\beta_1\beta)}\Gamma_1(x)\frac{\widehat{(d_1 M)}\widehat{b}}{\widehat{q}\widehat{c}} + \widehat{\gamma}} - \widehat{d_1} - \widehat{p}x,$$

where

$$\Gamma_1(x) = \frac{\widehat{\lambda}}{\widehat{d}} - \frac{\widehat{d_1 b}}{\widehat{d}\widehat{q}} - \frac{\widehat{p}\widehat{b}}{\widehat{d}\widehat{q}}x = \frac{\widehat{p}\widehat{b}}{\widehat{d}\widehat{q}}(Z_{max} - x).$$

Equation (2.14) can be rewritten as

$$\begin{aligned} &\exp\{u_2\} = \frac{\widehat{b}}{\widehat{q}}, \quad \exp\{u_3\} = \frac{\widehat{(d_1 M)}}{\widehat{c}}\exp\{u_2\} = \frac{\widehat{(d_1 M)}\widehat{b}}{\widehat{q}\widehat{c}}, \\ &\exp\{u_1\} = \frac{\widehat{\lambda}}{\widehat{d}} - \frac{\widehat{d_1}\exp\{u_2\}}{\widehat{d}} - \frac{\widehat{p}\exp\{u_2\}}{\widehat{d}}\exp\{u_5\} = \Gamma_1(\exp\{u_5\}), \end{aligned}$$

$$\exp\{u_4\} = \frac{\widehat{\lambda_1}}{\widehat{(\beta_1\beta)}\exp\{u_1+u_3\}+\widehat{\gamma}} = \frac{\widehat{\lambda_1}}{\widehat{(\beta_1\beta)}\Gamma_1(\exp\{u_5\})^{\frac{\widehat{(d_1M)}\widehat{b}}{\widehat{qc}}}+\widehat{\gamma}},$$
$$\frac{\widehat{\beta}\widehat{(d_1M)}}{\widehat{c}}\exp\{u_1+u_4\}-\widehat{d_1}-\widehat{p}\exp\{u_5\} = \Gamma(\exp\{u_5\}) = 0.$$

It is obvious that if there is a solution $(u_1, u_2, u_3, u_4, u_5)^T \in \mathbb{R}^5$ for (2.14), it must have $0 < \exp\{u_5\} < Z_{max}$. In addition, note that $\Gamma(x)$ is monotonically decreasing with respect to x on $[0, Z_{max}]$. It has from $\Gamma(Z_{max}) = -\widehat{d_1} - \widehat{p}Z_{max} < 0$ and

$$\Gamma(0) = \frac{\widehat{\beta}\widehat{(d_1M)}}{\widehat{c}}\frac{\widehat{\lambda_1}\Gamma_1(0)}{\widehat{(\beta_1\beta)}\Gamma_1(0)^{\frac{\widehat{(d_1M)}\widehat{b}}{\widehat{qc}}}+\widehat{\gamma}} - \widehat{d_1} > \frac{\widehat{\beta}\widehat{(d_1M)}}{\widehat{c}}\frac{\widehat{\lambda_1}(\frac{\widehat{\lambda}}{\widehat{d}}-\frac{\widehat{d_1b}}{\widehat{dq}})}{\widehat{(\beta_1\beta)}\frac{\widehat{\lambda}}{\widehat{d}}^{\frac{\widehat{(d_1M)}\widehat{b}}{\widehat{qc}}}+\widehat{\gamma}} - \widehat{d_1} = \widehat{d_1}(\overline{R^*}-1) > 0$$

that there exists a unique positive constant $x = Z^* \in (0, Z_{max})$ such that $\Gamma(Z^*) = 0$.

The above discussions show that, if $R^* > 1$, (2.14) has a unique solution $(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*)^T$, here $u_i^* = \ln(e_i)$ $(i = 1, 2, 3, 4, 5)$,

$$e_1 = \Gamma_1(Z^*) > 0,\ \ e_2 = \frac{\widehat{b}}{\widehat{q}} > 0,\ \ e_3 = \frac{\widehat{(d_1M)}\widehat{b}}{\widehat{qc}} > 0,\ \ e_4 = \frac{\widehat{\lambda_1}}{\widehat{(\beta_1\beta)}\Gamma_1(Z^*)^{\frac{\widehat{(d_1M)}\widehat{b}}{\widehat{qc}}}+\widehat{\gamma}} > 0,\ \ e_5 = Z^* > 0.$$

Let us define the following set

$$\Omega = \{u \in X \mid \|u\| < U_1 = 1 + \sum_{i=1}^{5}(\max\{|M_i|, |L_i|\} + |u_i^*|)\} \subset X.$$

Moreover, by similar arguments as in [12], it has that N is L-compact on $\overline{\Omega}$.

Now, let us compute the Leray-Schauder degree $\deg\left\{QN, \partial\Omega \cap Ker\,L, (0,0,0,0,0)^T\right\} := \Delta$ as follows,

$$\begin{aligned}\Delta =& \text{sign}\begin{vmatrix} -\frac{\widehat{\lambda}}{e_1} & 0 & -\widehat{\beta}e_3e_4 & -\widehat{\beta}e_3e_4 & 0 \\ \widehat{\beta}\frac{e_1e_3e_4}{e_2} & -\widehat{\beta}\frac{e_1e_3e_4}{e_2} & \widehat{\beta}\frac{e_1e_3e_4}{e_2} & \widehat{\beta}\frac{e_1e_3e_4}{e_2} & -\widehat{p}e_5 \\ 0 & \widehat{(d_1M)}\frac{e_2}{e_3} & -\widehat{(d_1M)}\frac{e_2}{e_3} & 0 & 0 \\ -\widehat{(\beta_1\beta)}e_1e_3 & 0 & -\widehat{(\beta_1\beta)}e_1e_3 & -\frac{\widehat{\lambda_1}}{e_4} & 0 \\ 0 & \widehat{q}e_2 & 0 & 0 & 0 \end{vmatrix}\\ =& \text{sign}\left\{-\widehat{(d_1M)}\widehat{p}\widehat{q}\frac{e_2^2e_5}{e_3}\left(\frac{\widehat{\lambda\lambda_1}}{e_1e_4} - \widehat{\beta}\widehat{(\beta_1\beta)}e_1e_3^2e_4\right)\right\}\\ =& \text{sign}\left\{-\widehat{(d_1M)}\widehat{p}\widehat{q}\frac{e_2^2e_5}{e_3e_1e_4}\left[\widehat{d}e_1\left(\widehat{(\beta_1\beta)}e_1e_3e_4 + \widehat{\gamma}e_4\right) + \widehat{\beta}\widehat{\gamma}e_1e_3e_4^2\right]\right\}\\ =& -1 \neq 0,\end{aligned}$$

where $\widehat{\lambda} = \widehat{\beta}e_1e_3e_4 + \widehat{d}e_1$ and $\widehat{\lambda_1} = \widehat{(\beta_1\beta)}e_1e_3e_4 + \widehat{\gamma}e_4$ are used.

Finally, it has those all the conditions of the continuation theorem in [13] (also see, for example, Lemma 2.1 in [12]) are satisfied. This proves that, if $\omega < \omega^*$ and $R^* > 1$, model (2.1) has at least one ω-periodic solution. □

Let us consider the following classical viral infection dynamic model [9] with CTL immune response:

$$\begin{cases}\dot{T}(t) = \lambda(t) - \beta(t)v(t)T(t) - d(t)T(t),\\ \dot{I}(t) = \beta(t)v(t)T(t) - d_1(t)I(t) - p(t)I(t)Z(t),\\ \dot{v}(t) = d_1(t)M(t)I(t) - c(t)v(t),\\ \dot{Z}(t) = q(t)I(t)Z(t) - b(t)Z(t),\end{cases} \tag{A}$$

where, all the coefficients are the same with that in model (1.1).

Define $R_1 : [0, \omega^*] \to \mathbb{R}$, via

$$R_1(x) = \frac{\widehat{\lambda}\beta^l\left[\frac{\widehat{(d_1M)}}{\widehat{c}}\exp\{-2\widehat{c}x\}\left(\frac{\widehat{b}}{\widehat{q}} - 2\widehat{\lambda}x\right)\right]}{\widehat{d_1}\left(\frac{\widehat{b}}{\widehat{q}} + 2\widehat{\lambda}x\right)\left\{d^U + \beta^l\left[\frac{\widehat{(d_1M)}}{\widehat{c}}\exp\{-2\widehat{c}x\}\left(\frac{\widehat{b}}{\widehat{q}} - 2\widehat{\lambda}x\right)\right]\right\}}.$$

Obviously, $R_1(x)$ is monotonically decreasing on $[0, \omega^*]$ and

$$R_1(0) = \frac{\widehat{\lambda}\beta^l(\widehat{d_1M})\widehat{q}}{\widehat{d_1}(d^U\widehat{c}\widehat{q} + \beta^l(\widehat{d_1M})\widehat{b})}, \quad R_1(\omega^*) = 0.$$

Therefore, if $R_1(0) > 1$, then there exists a unique constant $\omega^{**} \in (0, \omega^*)$ such that $R_1(\omega^{**}) = 1$, $R_1(x) > 1$ for $0 \le x < \omega^{**}$ and $R_1(x) < 1$ for $\omega^{**} < x \le \omega^*$.

For model (A), it is not difficult to derive the following result.

Theorem 2.2. *If $R_1(\omega) > 1$ and $\omega < \omega^*$ (i.e. $R_1(0) > 1$ and $\omega < \omega^{**} < \omega^*$), then model (A) has at least one positive ω-periodic solution.*

Remark 2.1. *If all the coefficients in model (A) take constants values, i.e., $\lambda(t) \equiv \lambda > 0$, $\beta(t) \equiv \beta > 0$, $d(t) \equiv d > 0$, $d_1(t) \equiv d_1 > 0$, $p(t) \equiv p > 0$, $M(t) \equiv M > 0$, $c(t) \equiv c > 0$, $q(t) \equiv q > 0$ and $b(t) \equiv b > 0$, then model (A) becomes the classical model which is first proposed by Nowak and Bangham in [9]. the condition $\omega < \omega^{**}$ in Theorem 2.2 is naturally satisfied. Furthermore, it has $R_1(0) = (\lambda\beta Mq)/(dcq + \beta d_1 Mb) := R_1$. From* [9], *it has that the condition $R_1 > 1$ implies the existence of a unique positive equilibrium. This shows that the conditions and conclusion in Theorem 2.2 are reasonable.*

3. Conclusions and simulations

In summary, Theorem 2.1 in the paper successfully extends the main result in [12]) to a MERS-CoV viral infection model with CTL immune response. In the proof of Theorem 2.1, we use a very different method from that in [9] to obtain the lower bound $(\ln(\delta^*) - 2\widehat{b}\omega)$ of the state variable $u_5(t)$. Furthermore, as a special case, Theorem 2.2 gives sufficient conditions for the existence of positive periodic solution of model (A). Model (A) is a natural extension of the classical model in [9]. As the end of the paper, let us give a example to summarize the applications of Theorem 2.1. Let us choose the coefficients in model (1.1) as follows (for the values of some parameters, please refer to [7, 27] for the case of some autonomous models), $\lambda(t) = 45(1 + 0.1\sin(4\pi t))$, $\beta(t) = 1.4 \times 10^{-8}(1 + 0.1\cos(4\pi t))$, $d(t) = 0.001(1 + 0.5\cos(4\pi t))$, $d_1(t) = 0.056(1 + 0.5\cos(4\pi t))$, $p(t) = 0.00092(1 + 0.5\cos(4\pi t))$, $M(t) = 100000$,

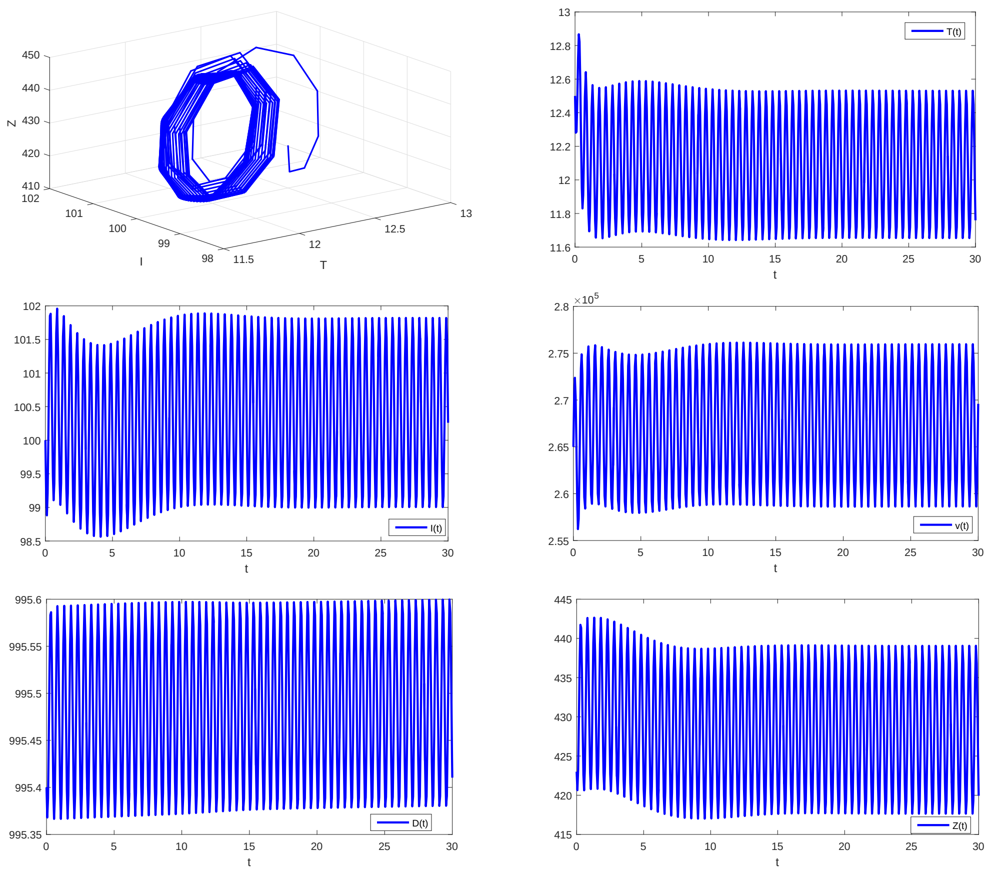

Figure 1. With the increasing of the time t, the evolution form of the solution of model (1.1).

$c(t) = 2.1(1 + 0.3\cos(4\pi t))$, $\lambda_1(t) = 10(1 + 0.1\sin(4\pi t))$, $\beta_1(t) = 0.001$, $\gamma(t) = 0.01(1 + 0.1\cos(4\pi t))$, $q(t) = 0.005(1 + 0.5\sin(4\pi t))$, $b(t) = 0.5(1 + 0.4\cos(4\pi t))$. Then, with the help of Maple mathematical software, it has $\omega = 0.5 < \omega^* \approx 1.111111$, $M_1 \approx 11.502875$, $M_2 \approx 4.976734$, $M_3 \approx 14.965318$, $M_4 \approx 7.108426$, $M_5 \approx 18.976215$, $L_1 \approx -0.383569$, $L_2 = 4.007333$, $L_3 \approx 9.795917$, $L_4 \approx 0.623402$, $L_5 \approx 1.387881$, $R^* \approx 1.2170332 > 1$. From Theorem 2.1, it follows that model (1.1) has at least one positive ω ($\omega = 0.5$)-periodic solution. Figure 1 gives the corresponding numerical simulation, and the initial value is chosen as $(T(0), I(0), v(0), D(0), Z(0))^T = (12.5, 100, 265000, 995.4, 423)^T$.

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Conflict of interest

The authors declare there is no conflict of interest.

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