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Dynamics of an HIV model with cytotoxic T-lymphocyte memory

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Abstract

We consider a four-dimensional HIV model that includes healthy cells, infected cells, primary cytotoxic T-lymphocyte response (CTLp), and secondary cytotoxic T-lymphocyte response (CTLe). The CTL memory generation depends on CD4⁺ T-cell help, and infection of CD4⁺ T cells results in impaired T-cell help. We show that the system has up to five equilibria. By the Routh–Hurwitz theorem and central manifold theorem we obtain some sufficient conditions for the local stability, globally stability of the equilibria, and the bifurcations. We still discover the bistability case where in the system there may coexist two stable equilibria or a stable equilibrium together with a stable limit cycle. Several numerical analyses are carried out to illustrate the validity of our theoretical results.

Keywords: HIV model; Routh–Hurwitz theorem; Central manifold; Bistability; Hopf bifurcation

1 Introduction

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) have become global health problems; there were estimated 38.0 million people living with HIV at the end of 2019 [1]. HIV can be transmitted via the exchange of a variety of body fluids from infected people, such as blood, breast milk, or semen and vaginal secretions, but it is known that current antiretroviral drugs cannot enucleate HIV from the body. Mathematical models have been formulated for various epidemiological diseases like novel coronavirus (COVID-19) [2–4] or malaria [5]. Models of HIV as a chronic infectious disease have been investigated in many papers. Some models focus on the size of infection, starting from the population models [6–8], whereas other focus on cell infection, starting from the virus models, which have become an important tool in both understanding HIV-1 infection in host and providing valuable insight into HIV pathogenesis. A well-known model for HIV infection is the following system [9, 10]:

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xy, \\ \frac{dy}{dt} = \beta xy - ay, \\ \frac{dv}{dt} = ky - uv, \end{cases} \quad (1.1)$$

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where variables x , y , and v represent the densities of the healthy cells, the infected cells, and the virus at time t , respectively. Here a mass action infection mechanism is adopted. The parameters β and λ stand for the infection and constant growth rates of the healthy cell, respectively. System (1.1) and its variations have been investigated in many papers [11–16]. Stephen et al. [17] recently added the term $\frac{\rho TV}{C+v}$ incorporating the homeostatic proliferation of T-cells, which leads to interesting dynamic results, such as bistability and Hopf bifurcation.

It is well-known that it takes a long period for an HIV to become an AIDS, and in the medical literature [18], it was pointed out that the latent reservoir (i.e., latent infection) was the main obstacle to eradicate the virus. Therefore the four-dimensional mathematical model including the latent infection seems more reasonable [19, 20]. In recent years, latent cells were considered in many models, such as Beddington–DeAngelis function response with delay [20], Crowley–Martin function response [21], and general infection function with CTC and VTC transmission [22].

To recover from a viral infection, the cytotoxic T lymphocyte (CTL), which can clear away the infected cells to prevent further viral replications, plays a particularly important role. In 1996, Nowak and Bangham [9] proposed the well-known model with immune response:

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xy, \\ \frac{dy}{dt} = \beta xy - ay - pyz, \\ \frac{dv}{dt} = ky - uv, \\ \frac{dz}{dt} = cyz - bz, \end{cases}$$

where the variable z represents the concentration of CTLs. Many authors have studied the infective models with different immune responses, such as lytic and nonlytic immune responses [23, 24], cell-mediated immune mechanism or humoral immune mechanism [25–27], delayed immune response with drug therapies [28], and general CTL immune response with silent infected cell-to-cell spread [29].

However, after a viral infection, the CTLs that are responsible for clearing away the infected cells become cytotoxic T-lymphocyte precursors (CTLp) and have receptors for detecting the virus from the previous infection [30]. Upon contacting with the virus during a subsequent infection, the precursors differentiate and become cytotoxic T-lymphocyte effectors (CTLe), and these cells are again responsible for clearing away the invading virus. Considering this infective mechanism, Wodarz et al. [31, 32] provided the following model with CTL response:

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xy, \\ \frac{dy}{dt} = \beta xy - ay - pyz, \\ \frac{dw}{dt} = cyw - cqyw - bw, \\ \frac{dz}{dt} = cqyw - hz, \end{cases} \tag{1.2}$$

where the healthy cells x and the infected cells y are described similarly as in system (1.1). Instead of just one class of CTL response, the CTLp and CTLe are introduced. The CTLp

and CTL_e are represented by w and z . These precursors emerge at rate cyw and may become effectors at rate $cqyw$ or cleared away naturally at rate bw . Similarly, the effectors are created at rate $cqyw$ and cleared at rate hz .

In model (1.2), there is no virus term whose population is assumed at a quasi-steady state, which is proportional to infected cells. Model (1.2) is completely analyzed by Bernard et al. [33], who have found that the system transforms from one equilibrium to the next as the basic reproductive number R_0 increases. When R_0 increases further, they show that periodic solutions may arise from the third equilibrium via Hopf bifurcation.

In fact, another model with cytotoxic T-lymphocyte memory proposed in [31, 32] is given by

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xy, \\ \frac{dy}{dt} = \beta xy - ay - pyz, \\ \frac{dw}{dt} = cxyw - cqyw - bw, \\ \frac{dz}{dt} = cqyw - hz. \end{cases} \tag{1.3}$$

This model assumes that the target cells are CD4⁺ T cells; moreover, it includes the additional feature that expansion of the CTL_p population is proportional to both antigen and the number of uninfected CD4⁺ T-cells capable of delivering T-cell help. The memory generation depends on CD4⁺ T-cell help, and infection of CD4⁺ T-cells results in impaired T-cell help. We also assume that differentiation into effector functions is independent of CD4⁺ T-cell help [31]. A detailed explanation of the model can be found in [31]. All the parameters are positive.

Dynamics of system (1.3) is numerically analyzed in [31, 32]. In this paper, we provide a rigorous analytical method of system (1.3), and the basic framework is as follows. In Sect. 2, we establish the well-posedness of the model including nonnegativity and boundedness of the solutions, the existence of equilibria, and local stability of the boundary equilibria. The local stability analysis of the positive equilibria and their bifurcations are presented in Sect. 3. Numerical illustrations are given in Sect. 4. Finally, we discuss both mathematical and biological perspectives of the findings in Sect. 5.

2 The equilibrium and stability of boundary equilibrium

For mathematical simplicity, we do some rescallings in system (1.3). Let $x = \sqrt{\frac{\lambda}{\beta}}\bar{x}$, $y = \sqrt{\frac{\lambda}{\beta}}\bar{y}$, $w = \frac{\beta}{pcq}\sqrt{\lambda\beta}\bar{w}$, $z = \frac{1}{p}\sqrt{\lambda\beta}\bar{z}$, $t = \frac{1}{\sqrt{\lambda\beta}}\tau$, $\bar{d} = \frac{d}{\sqrt{\lambda\beta}}$, $\bar{a} = \frac{a}{\sqrt{\lambda\beta}}$, $\bar{c} = \frac{c}{\beta}\sqrt{\frac{\lambda}{\beta}}$, $\bar{q} = \frac{cq}{\beta}$, $\bar{b} = \frac{b}{\sqrt{\lambda\beta}}$, and $\bar{h} = \frac{h}{\sqrt{\lambda\beta}}$. After changing back to the origin variables x, y, w, z, t , the scaled system is given by

$$\begin{cases} \frac{dx}{dt} = 1 - dx - xy, \\ \frac{dy}{dt} = xy - ay - yz, \\ \frac{dw}{dt} = cxyw - qyw - bw, \\ \frac{dz}{dt} = yw - hz, \end{cases} \tag{2.1}$$

where the horizontal lines on the heads of these parameters are removed, and the parameters $\bar{d}, \bar{a}, \bar{c}, \bar{q}, \bar{b}, \bar{h}$ are replaced by d, a, c, q, b, h . Obviously, all the parameters are

positive. The basic reproductive number of model (1.3) is $R_{00} = \frac{\lambda\beta}{ad}$, and for system (2.1), R_{00} becomes $R_0 = \frac{1}{ad}$.

Theorem 2.1 *All solutions $(x(t), y(t), w(t), z(t))$ of system (2.1) are nonnegative for $t > 0$. Moreover, if $x(0) \geq 0, y(0) \geq 0, w(0) \geq 0$, and $z(0) \geq 0$, then all solutions of system (2.1) are ultimately bounded.*

Proof By variation of constants we find the following solutions of (2.1):

$$\begin{cases} x(t) = x(0)e^{-\int_0^t (d+y(s)) ds} + \int_0^t e^{-\int_s^t (d+y(u)) du} ds, \\ y(t) = y(0)e^{\int_0^t (x(s)-a-z(s)) ds}, \\ w(t) = w(0)e^{\int_0^t (x(s)y(s)-qy(s)-b) ds}, \\ z(t) = e^{-ht}(z(0) + \int_0^t y(s)w(s)e^{hs} ds), \end{cases} \tag{2.2}$$

which proves the nonnegativity of solutions of system (2.1).

Note that the first equation of (2.1) implies $\frac{dx}{dt} \leq 1 - dx$. The solution is given by $x(t) \leq x(0)e^{-dt} + \frac{1}{d}$, which yields $\limsup_{t \rightarrow \infty} x(t) \leq \frac{1}{d}$. Adding the first two equations of (2.1), we obtain

$$\frac{d(x+y)}{dt} = \frac{dx}{dt} + \frac{dy}{dt} = 1 - dx - ay - yz \leq 1 - dx - ay \leq 1 - d_1(x+y),$$

where $d_1 = \min\{d, a\}$. It has the solution $x + y \leq (x(0) + y(0))e^{-d_1 t} + \frac{1}{d_1}$, which implies $\limsup_{t \rightarrow \infty} (x(t) + y(t)) \leq \frac{1}{d_1}$, and thus $x(t)$ and $y(t)$ are bounded.

Supposing that z is unbounded, by the second equation of (2.1) we have $\lim_{t \rightarrow \infty} y(t) = 0$, which implies $\lim_{t \rightarrow \infty} w(t) = 0$ from the third equation of (2.1). Then we get $\lim_{t \rightarrow \infty} z(t) = 0$ from the fourth equation of (2.1), which contradicts with the unboundedness of z . Thus z must be bounded. Lastly, assume that w is unbounded. Based on the boundedness of z and the fourth equation of (2.1), we obtain $\lim_{t \rightarrow \infty} y(t) = 0$, and from the third equation of (2.1) it follows that $\lim_{t \rightarrow \infty} w(t) = 0$, which causes a contradiction. Hence w is bounded. The proof is complete. □

Theorem 2.1 shows that there exists a bounded positive invariant region $\Gamma \subset R_+^4$ for the system. Thus we concentrate on Γ to discuss the dynamics. In fact, the infection-free equilibrium $E_0 = (\frac{1}{d}, 0, 0, 0)$ always exists, and there exists an infectious equilibrium without CTL, $E_1 = (a, d(R_0 - 1), 0, 0)$ if $R_0 > 1$. To find the infectious equilibrium with CTL, it suffices to solve the system

$$\begin{cases} 1 - dx - xy = 0, \\ y = \frac{b}{cx-q}, \\ w = \frac{hz}{y}, \\ z = x - a. \end{cases} \tag{2.3}$$

After submitting y, w, z into the first equation of (2.3), we get the equation

$$f(x) := cdx^2 + (b - c - dq)x + q = 0. \tag{2.4}$$

If x_1, x_2 are solutions of (2.4), then $x_1x_2 = \frac{q}{cd} > 0$ and $x_1 + x_2 = -\frac{b-c-dq}{cd}$. Hence, to ensure the existence of a positive solution, we have $b < c + dq$.

The determinant of (2.4) is

$$\Delta = (b - c - dq)^2 - 4cdq.$$

Then $\Delta = 0$ if and only if

$$b = c + dq \pm 2\sqrt{cdq}.$$

Note that $c + dq - 2\sqrt{cdq} \geq 0$. Combining this with the condition $b < c + dq$, we get that $\Delta \geq 0$ only if $0 < b \leq c + dq - 2\sqrt{cdq}$, and $y > 0$ and $z > 0$ imply $x > \frac{q}{c}$ and $x > a$ by (2.3).

Set

$$R_1 = 1 + \frac{b}{d(ca - q)}. \tag{2.5}$$

Noting that $f(\frac{q}{c}) = \frac{bq}{c} > 0$, we obtain

$$f(a) = a d(ca - q) \left[1 + \frac{b}{d(ca - q)} - R_0 \right] = \frac{ab}{R_1 - 1} (R_1 - R_0). \tag{2.6}$$

Notations $x_{2\pm} = \frac{(c+dq-b) \pm \sqrt{(b-c-dq)^2 - 4cdq}}{2cd}$, $y_{2\pm} = \frac{b}{cx_{2\pm} - q}$, $w_{2\pm} = \frac{hz_{2\pm}}{y_{2\pm}}$, $z_{2\pm} = x_{2\pm} - a$, $x_{20} = \frac{c+dq-b}{2cd}$, $y_{20} = \frac{2bd}{c-b-dq}$, $w_{20} = \frac{h(c+dq-b-2acd)(c-b-dq)}{4bcd^2}$, $z_{20} = \frac{c+dq-b-2acd}{2cd}$.

The positive equilibria of model (2.1) are classified by the sign of Δ . Let us consider three cases.

Case I $\Delta > 0$, which is equivalent to $0 < b < c + dq - 2\sqrt{cdq}$. Here we consider three cases by the sign of $f(a)$.

1. $f(a) < 0$. In this case, $\Delta > 0$ is obviously satisfied, and $a > \frac{q}{c}$ is equivalent to $R_1 > 1$, and thus $R_1 < R_0$ by (2.6). Combining this with $R_1 > 1$, we get that model (2.1) admits a unique positive equilibrium $E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+})$ if $1 < R_1 < R_0$.

2. $f(a) = 0$. In this case, $R_0 = R_1$, which indicates that a is a solution of $f(x) = 0$, and the other root is $x_* = \frac{q}{acd}$. To get a positive equilibrium of model (2.1), $x_* = \frac{q}{acd} > a$ and $a > \frac{q}{c}$ are required, which yields $q > a^2cd$ and $ac > q$. Combining this with $\Delta > 0$ (if and only if $0 < b < c + dq - 2\sqrt{cdq}$), model (2.1) admits a unique positive equilibrium $E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+})$ if $R_1 = R_0 > 1$ and $a^2cd < q < ac$.

3. $f(a) > 0$. Let us consider two cases.

(1) $\frac{q}{c} \geq a$, which is equivalent to $R_1 \leq 1$. To ensure the positive equilibrium of model (2.1), the following conditions are required:

$$\begin{cases} f(\frac{q}{c}) > 0, \\ \Delta > 0, \\ -\frac{b-c-dq}{2cd} > \frac{q}{c}, \\ \frac{q}{c} \geq a. \end{cases} \tag{2.7}$$

Note that $f(\frac{q}{c}) > 0$ always holds, and $\Delta > 0$ if and only if $0 < b < c + dq - 2\sqrt{cdq}$, whereas $-\frac{b-c-dq}{2cd} > \frac{q}{c}$ if $0 < b < c - dq$. Intersecting these two inequalities we have $c + dq - 2\sqrt{cdq} < c - dq$ if $c > dq$, which is required to ensure that $b > 0$. Note that $c \leq \frac{q}{a}$, Combining this with $c > dq$, we have $ad < 1$ to ensure that the intersection is nonempty, and hence model (2.1) admits two positive equilibria $E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+})$ and $E_{2-} = (x_{2-}, y_{2-}, w_{2-}, z_{2-})$ if $R_0 > 1 \geq R_1$, $dq < c$, and $0 < b < c + dq - 2\sqrt{cdq}$.

(2) $\frac{q}{c} < a$, which is equivalent to $R_1 > 1$. Model (2.1) admits two positive equilibria if the following conditions are satisfied:

$$\begin{cases} f(a) > 0, \\ \Delta > 0, \\ -\frac{b-c-dq}{2cd} > a, \\ \frac{q}{c} < a. \end{cases} \tag{2.8}$$

Note that $f(a) > 0$ if and only if $R_1 > R_0$ by (2.6) and $R_1 > 1$, and $-\frac{b-c-dq}{2cd} > a$ is equivalent to $0 < b < c + dq - 2acd$; $\Delta > 0$ if and only if $0 < b < c + dq - 2\sqrt{cdq}$. Note that $c + dq - 2\sqrt{cdq} \leq c + dq - 2acd$ if and only if $q \geq a^2cd$, whereas $c + dq - 2\sqrt{cdq} > c + dq - 2acd$ if and only if $q < a^2cd$, and hence model (2.1) admits two positive equilibria if one of the following conditions holds: (i) $R_1 > 1$, $R_1 > R_0$, $q \geq a^2cd$, and $0 < b < c + dq - 2\sqrt{cdq}$; (ii) $R_1 > 1$, $R_1 > R_0$, $q < a^2cd$, and $0 < b < c + dq - 2acd$.

Case II $\Delta = 0$ if and only if $b = c + dq - 2\sqrt{cdq}$, and model (2.1) admits a unique positive equilibrium if

$$\begin{cases} \Delta = 0, \\ -\frac{b-c-dq}{2cd} > a, \\ -\frac{b-c-dq}{2cd} > \frac{q}{c}. \end{cases} \tag{2.9}$$

Note that $-\frac{b-c-dq}{2cd} > a$ if $0 < b < c + dq - 2acd$, whereas $-\frac{b-c-dq}{2cd} > \frac{q}{c}$ yields $0 < b < c - dq$. Combining these two conditions with $\Delta = 0$ which is equivalent to $b = c + dq - 2\sqrt{cdq}$, the following results are obtained: $c + dq - 2\sqrt{cdq} < c + dq - 2acd$ if $q > a^2cd$, while $c + dq - 2\sqrt{cdq} < c - dq$ if $c > dq$, therefore model (2.1) admits a unique positive equilibrium if $b = c + dq - 2\sqrt{cdq}$, $q > a^2cd$, and $c > dq$.

Case III If $\Delta < 0$, then there is no positive equilibrium, because $f(x) = 0$ has no real root. The following theorem summarizes all positive equilibria of system (2.1).

Theorem 2.2 (1) Model (2.1) admits a unique positive equilibrium $E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+})$ if one of the following conditions is satisfied: (i) $1 < R_1 < R_0$; (ii) $R_1 = R_0 > 1$ and $a^2cd < q < ac$.

(2) Model (2.1) admits two positive equilibria $E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+})$ and $E_{2-} = (x_{2-}, y_{2-}, w_{2-}, z_{2-})$ if one of the following conditions is satisfied: (i) $R_0 > 1 \geq R_1$, $dq < c$, and $0 < b < c + dq - 2\sqrt{cdq}$; (ii) $R_1 > 1$, $R_1 > R_0$, $q \geq a^2cd$, and $0 < b < c + dq - 2\sqrt{cdq}$; (iii) $R_1 > 1$, $R_1 > R_0$, $q < a^2cd$, and $0 < b < c + dq - 2acd$.

(3) Model (2.1) admits a unique positive equilibrium $E_{20} = (x_{20}, y_{20}, w_{20}, z_{20})$ if $b = c + dq - 2\sqrt{cdq}$, $q > a^2cd$, and $c > dq$.

Next, we discuss the local stability and global stability of the boundary equilibria. The stability of the equilibria is based on the Jacobian matrix of model (2.1):

$$J(x, y, w, z) = \begin{pmatrix} -d - y & -x & 0 & 0 \\ y & x - a - z & 0 & -y \\ cyw & cxw - qw & cxy - qy - b & 0 \\ 0 & w & y & -h \end{pmatrix}. \tag{2.10}$$

The characteristic roots at the equilibrium E_0 are given by

$$s_1 = -d < 0, \quad s_2 = -b < 0, \quad s_3 = -h < 0, \quad s_4 = \frac{1 - da}{d},$$

and $s_4 = \frac{1 - da}{d} = a(R_0 - 1) < 0$ is equivalent to $R_0 < 1$. Hence the local stability of equilibrium E_0 is given by the following theorem.

Theorem 2.3 *The infection-free equilibrium E_0 is asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.*

Theorem 2.4 *If $R_0 < 1$, then the infection-free equilibrium E_0 is globally asymptotically stable.*

Proof To show the global stability of equilibrium E_0 , we use the method of fluctuation lemma employed by Hirsch et al. [34–36]. We introduce some notations. For a continuous bounded function $g : [0, \infty] \rightarrow R$, let

$$g^\infty = \limsup_{t \rightarrow \infty} g(t), \quad g_\infty = \liminf_{t \rightarrow \infty} g(t),$$

By Theorem 2.1 the solutions $x(t), y(t), w(t)$, and $z(t)$ are always nonnegative and bounded for any nonnegative initial conditions, and the limits $\limsup_{t \rightarrow \infty}$ and $\liminf_{t \rightarrow \infty}$ always exist for each of these solutions. By the fluctuation lemma there exists a sequence t_n such that

$$\lim_{n \rightarrow \infty} x(t_n) = x^\infty, \quad \lim_{n \rightarrow \infty} \dot{x}(t_n) = 0.$$

Set $t = t_n$. Then the first equation of model (2.1) gives $\dot{x}(t_n) + dx(t_n) + x(t_n)y(t_n) = 1$. Letting $n \rightarrow \infty$, it follows that

$$d \lim_{n \rightarrow \infty} x(t_n) + \lim_{n \rightarrow \infty} x(t_n) \lim_{n \rightarrow \infty} y(t_n) = 1,$$

which yields

$$dx^\infty \leq dx^\infty + dx^\infty y_\infty = dx^\infty(1 + y_\infty) \leq dx^\infty(1 + y^\infty) = 1. \tag{2.11}$$

By a similar argument, for the remaining three equations in model (2.1), we get

$$ay^\infty \leq y^\infty(a + z_\infty) \leq x^\infty y^\infty, \tag{2.12}$$

$$bw^\infty \leq w^\infty(b + qy_\infty) \leq cx^\infty y^\infty w^\infty, \tag{2.13}$$

$$hz^\infty \leq y^\infty w^\infty. \tag{2.14}$$

We claim that $y^\infty = 0$. Otherwise, $y^\infty > 0$; then it follows from (2.11) and (2.12) that $ay^\infty \leq x^\infty y^\infty \leq \frac{y^\infty}{a}$, that is, $(a - \frac{1}{a})y^\infty = a(1 - R_0)y^\infty \leq 0$. Therefore $R_0 \geq 1$, which contradicts the condition $R_0 < 1$, and thus $y^\infty = 0$. And from equations (2.13) and (2.14) we get that $w^\infty = 0$ and $z^\infty = 0$. The conditions $y^\infty = 0$, $w^\infty = 0$, and $z^\infty = 0$ imply that $y(t) \rightarrow 0$, $w(t) \rightarrow 0$, and $z(t) \rightarrow 0$ as $t \rightarrow \infty$, respectively. Thus from the first equation of model (2.1) we have the asymptotic differential equation $\dot{x} = 1 - dx$. By simple calculation we get the solution $x(t) = x(0)e^{-dt} + \frac{1}{d}$, which clearly shows that the solution $x(t) \rightarrow \frac{1}{d}$ as $t \rightarrow \infty$ by the theory of asymptotically autonomous systems. The proof is complete. \square

The characteristic equation of model (2.1) at E_1 is

$$[(s + d + y_1)(s - x_1 + a) + x_1 y_1](s - cx_1 y_1 + qy_1 + b)(s + h) = 0. \tag{2.15}$$

Letting $(s + d + y_1)(s - x_1 + a) + x_1 y_1 = 0$, we have $s^2 + (d + y_1)s + ay_1 = 0$. Note that $s_1 + s_2 = -(d + y_1) < 0$ and $s_1 s_2 = ay_1 > 0$, which imply that s_1 and s_2 have negative real parts. Obviously, $s_3 = -h$ has a negative real part. In order for all the roots of equation (2.15) to have negative real parts, it is required that

$$s_4 = cx_1 y_1 - qy_1 - b = d(R_0 - 1)(ca - q) - b = \frac{b(R_0 - R_1)}{R_1 - 1} < 0,$$

which implies $R_1 > R_0 > 1$ or $R_0 > 1 > R_1$.

Theorem 2.5 *Equilibrium E_1 is locally asymptotically stable for $1 < R_0 < R_1$ or $R_0 > 1 > R_1$ and is unstable for $1 < R_1 < R_0$.*

Remark Note that $f(a) = \frac{ab}{(R_1 - 1)}(R_1 - R_0) = -as_4$, from which it follows that E_1 is locally asymptotically stable, whereas system (2.1) may have positive equilibrium under certain conditions by Theorem 2.2 (case I.3). Moreover, system (2.1) may have both stable positive equilibrium and stable boundary equilibrium E_1 .

3 Stability of positive equilibria and their bifurcations

By an easy calculation the characteristic equation of the positive equilibrium follows:

$$s^4 + \alpha_1 s^3 + \alpha_2 s^2 + \alpha_3 s + \alpha_4 = 0, \tag{3.1}$$

where

$$\begin{cases} \alpha_1 = h + \frac{1}{x}, \\ \alpha_2 = xy + \frac{h}{x} + yw, \\ \alpha_3 = hxy + \frac{yw}{x} + byw, \\ \alpha_4 = \frac{byw}{x} - cwx y^3. \end{cases} \tag{3.2}$$

Here x, y, w, z are the coordinates of the positive equilibria. Obviously, $\alpha_1 > 0, \alpha_2 > 0,$ and $\alpha_3 > 0,$ and we only need to judge the sign of $\alpha_4.$

Firstly, we focus on the positive equilibrium $E_{20}.$ By calculation we have

$$\alpha_4 = \frac{by_{20}w_{20}}{x_{20}} - cw_{20}x_{20}y_{20}^3 = \frac{w_{20}y_{20}(b - cx_{20}^2y_{20}^2)}{x_{20}}.$$

Note that $1 - dx_{20} - x_{20}y_{20} = 0,$ and it follows that

$$b - cx_{20}^2y_{20}^2 = -cd^2x_{20}^2 + 2cdx_{20} + b - c = \frac{4dcq - (c + dq - b)^2}{4c} = -\frac{\Delta}{4c} = 0, \tag{3.3}$$

which indicates that $\alpha_4 = 0,$ and the characteristic equation of equilibrium E_{20} becomes

$$s(s^3 + \alpha_1s^2 + \alpha_2s + \alpha_3) = 0.$$

It has a characteristic root $s_1 = 0,$ and s_2, s_3, s_4 are determined by the equation

$$s^3 + \alpha_1s^2 + \alpha_2s + \alpha_3 = 0, \tag{3.4}$$

where

$$\begin{cases} \alpha_1 = h + \frac{1}{x_{20}} > 0, \\ \alpha_2 = x_{20}y_{20} + \frac{h}{x_{20}} + y_{20}w_{20} > 0, \\ \alpha_3 = hx_{20}y_{20} + \frac{y_{20}w_{20}}{x_{20}} + by_{20}w_{20} > 0. \end{cases} \tag{3.5}$$

Note that $\alpha_i > 0, i = 1, 2, 3,$ and according to the Routh–Hurwitz criterion, $s_2, s_3,$ and s_4 have negative real parts only if $\Delta_{20} = \alpha_1\alpha_2 - \alpha_3 = \frac{h^2}{x_{20}} + y_{20} + \frac{h}{x_{20}} + (h - b)y_{20}w_{20} > 0.$

Next, we focus on $s_1 = 0.$ Transforming the equilibrium E_{20} to the origin by $\bar{x} = x - x_{20}, \bar{y} = y - y_{20}, \bar{w} = w - w_{20}, \bar{z} = z - z_{20},$ system (2.1) becomes

$$\begin{cases} \frac{dx}{dt} = -\frac{1}{x_{20}}x - x_{20}y - xy, \\ \frac{dy}{dt} = y_{20}x - y_{20}z + xy - yz, \\ \frac{dw}{dt} = cx_{20}yw + cw_{20}xy + cy_{20}xw + cy_{20}w_{20}x + \frac{byw}{y_{20}} + \frac{bw_{20}y}{y_{20}}, \\ \frac{dz}{dt} = y_{20}w + w_{20}y - hz + yw, \end{cases} \tag{3.6}$$

where the horizontal lines on the heads of these letters are removed, and we still denote $\bar{x}, \bar{y}, \bar{w}, \bar{z}$ by $x, y, w, z.$ Set

$$u = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ \frac{bw_{20}}{x_{20}y_{20}} & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

Under the transformations $(\bar{x}, \bar{y}, \bar{w}, \bar{z})^T = u(x, y, w, z)^T$, model (3.6) becomes

$$\begin{cases} \frac{dx}{dt} = -\frac{1}{x_{20}}x - x_{20}y - xy, \\ \frac{dy}{dt} = y_{20}x - y_{20}z + xy - yz, \\ \frac{dw}{dt} = -\frac{bcw_{20}}{x_{20}}x^2 + \left(\frac{qw_{20}}{x_{20}} - \frac{b^2w_{20}}{x_{20}y_{20}^2}\right)xy + cy_{20}xw + \frac{b}{y_{20}}yw + cxyw - \frac{bcw_{20}}{x_{20}y_{20}}x^2y, \\ \frac{dz}{dt} = y_{20}w + w_{20}y - hz + yw - \frac{bw_{20}}{x_{20}}x - \frac{bw_{20}}{x_{20}y_{20}}xy, \end{cases} \tag{3.7}$$

where the horizontal lines on the heads of these letters are removed, and we still denote $\bar{x}, \bar{y}, \bar{w}, \bar{z}$ by x, y, w, z . The third equation of model (3.7) has no linear term, and then the center manifold is a curve tangent to the w -axis.

To obtain an approximative expression of the center manifold, we set

$$\begin{cases} x = m_1w + m_2w^2 + o(w^2), \\ y = n_1w + n_2w^2 + o(w^2), \\ z = p_1w + p_2w^2 + o(w^2), \end{cases} \tag{3.8}$$

where $m_1, n_1, p_1, m_2, n_2, p_2$ are undetermined coefficients. It follows that

$$\begin{cases} \frac{dx}{dt} = m_1 \frac{dw}{dt} + [2m_2w + o(w)] \frac{dw}{dt}, \\ \frac{dy}{dt} = n_1 \frac{dw}{dt} + [2n_2w + o(w)] \frac{dw}{dt}, \\ \frac{dz}{dt} = p_1 \frac{dw}{dt} + [2p_2w + o(w)] \frac{dw}{dt}. \end{cases} \tag{3.9}$$

To find the unknown coefficients $m_1, m_2, n_1, n_2, p_1, p_2$, we substitute (3.7) and (3.8) into (3.9), compare the coefficients at w and w^2 , and obtain

$$\begin{cases} \frac{1}{x_{20}}m_1 + n_1x_{20} = 0, \\ -\left(\frac{m_2}{x_{20}} + n_2x_{20} + m_1n_1\right) \\ = \left[-\frac{bcm_1^2w_{20}}{x_{20}} + \left(\frac{qw_{20}}{x_{20}} - \frac{b^2w_{20}}{x_{20}y_{20}^2}\right)m_1n_1 + cm_1y_{20} + \frac{b}{y_{20}}n_1\right]m_1, \\ y_{20}m_1 - y_{20}p_1 = 0, \\ y_{20}m_2 - y_{20}p_2 + m_1n_1 - n_1p_1 \\ = n_1\left[-\frac{bcm_1^2w_{20}}{x_{20}} + \left(\frac{qw_{20}}{x_{20}} - \frac{b^2w_{20}}{x_{20}y_{20}^2}\right)m_1n_1 + cm_1y_{20} + \frac{b}{y_{20}}n_1\right], \\ y_{20} + n_1w_{20} - hp_1 - \frac{bw_{20}}{x_{20}}m_1 = 0, \\ n_2w_{20} - hp_2 + n_1 - \frac{bw_{20}m_2}{x_{20}} - \frac{bw_{20}m_1n_1}{x_{20}y_{20}} \\ = p_1\left[-\frac{bcm_1^2w_{20}}{x_{20}} + \left(\frac{qw_{20}}{x_{20}} - \frac{b^2w_{20}}{x_{20}y_{20}^2}\right)m_1n_1 + cm_1y_{20} + \frac{b}{y_{20}}n_1\right]. \end{cases} \tag{3.10}$$

According to (3.8) and (3.9), we have

$$\frac{dw}{dt} = \left[-\frac{bcm_1^2w_{20}}{x_{20}} + \left(\frac{qw_{20}}{x_{20}} - \frac{b^2w_{20}}{x_{20}y_{20}^2}\right)m_1n_1 + cm_1y_{20} + \frac{b}{y_{20}}n_1\right]w^2 + o(w^2). \tag{3.11}$$

Note that $\frac{dw}{dt}$ is only related to m_1, n_1 , and p_1 , and it follows that (by (3.10))

$$m_1 = \frac{y_{20}x_{20}^2}{hx_{20}^2 + w_{20} + bw_{20}x_{20}}, \quad p_1 = \frac{y_{20}x_{20}^2}{hx_{20}^2 + w_{20} + bw_{20}x_{20}},$$

$$n_1 = -\frac{y_{20}}{hx_{20}^2 + w_{20} + bw_{20}x_{20}}.$$

Substituting $m_1, p_1,$ and n_1 into (3.11) and noting that $b - cx_{20}^2y_{20}^2 = 0,$ we have

$$\begin{aligned} \frac{dw}{dt} &= \left(\frac{bw_{20}x_{20}(b - cx_{20}^2y_{20}^2) - qw_{20}x_{20}y_{20}^2}{(w_{20} + hx_{20}^2 + bw_{20}x_{20})^2} + \frac{cx_{20}^2y_{20}^2 - b}{w_{20} + hx_{20}^2 + bw_{20}x_{20}} \right) w^2 + o(w^2) \\ &= -\frac{qw_{20}x_{20}y_{20}^2}{(w_{20} + hx_{20}^2 + bw_{20}x_{20})^2} w^2 + o(w^2). \end{aligned}$$

The coefficient of w^2 is $-\frac{qw_{20}x_{20}y_{20}^2}{(w_{20} + hx_{20}^2 + bw_{20}x_{20})^2} < 0.$ Hence the equilibrium E_{20} is a saddle-node.

Theorem 3.1 *If $\frac{h^2}{x_{20}} + y_{20} + \frac{h}{x_{20}^2} + (h - b)y_{20}w_{20} > 0,$ then the infectious equilibrium E_{20} is a saddle-node.*

For the equilibria E_{2-} and $E_{2+},$ we have the following properties.

Proposition 3.1 *When the equilibria E_{2-} and E_{2+} exist, then $\det(J(E_{2-})) < 0$ and $\det(J(E_{2+})) > 0.$*

Proof Similarly to the analysis of equilibrium $E_{20},$ we obtain $\alpha_4 = \frac{byw}{x} - cwx y^3 = \frac{yw}{x}(b - cx^2y^2).$ Set

$$g(x) \doteq b - cx^2y^2 = -cd^2x^2 + 2cdx + b - c,$$

which is strictly increasing in $(-\infty, \frac{1}{d}).$ Suppose $x_{2+} < \frac{1}{d}.$ Submitting x_{2+} into this inequality and simplifying it, we have $c + b - dq > \sqrt{\Delta}.$ Note that $c + b - dq > 0.$ Squaring both sides and simplifying, we obtain $4bc > 0,$ which implies $x_{2-} < \frac{c+dq-b}{2cd} < x_{2+} < \frac{1}{d}.$

An easy calculation shows that $g(\frac{c+dq-b}{2cd}) = -\frac{\Delta}{4c}$ by (3.3). Then $g(\frac{c+dq-b}{2cd}) < 0$ when $\Delta > 0.$ It follows that $g(x_{2-}) < g(\frac{c+dq-b}{2cd}) < 0,$ which yields $\det(J(E_{2-})) = \alpha_4 = \frac{y_{2-}w_{2-}}{x_{2-}}g(x_{2-}) < 0.$

Solving $g(x) = 0,$ we obtain the roots $x_+ = \frac{c+\sqrt{bc}}{cd}, x_- = \frac{c-\sqrt{bc}}{cd}.$ In fact, $x_- < \frac{1}{d} < x_+.$ Suppose $x_- < x_{2+},$ that is, $\frac{c+dq-b+\sqrt{\Delta}}{2cd} > \frac{c-\sqrt{bc}}{cd}.$ By direct calculation we have $\sqrt{\Delta} > c + b - dq - 2\sqrt{bc}.$ If $c + b - dq - 2\sqrt{bc} \leq 0,$ then it holds. If $c + b - dq - 2\sqrt{bc} > 0,$ after squaring both sides and simplifying, we obtain $(b - c - dq)^2 - (c + b - dq)^2 > 4dcq + 4bc - 4\sqrt{bc}(c + b - dq),$ which gives $b + c - dq - 2\sqrt{bc} > 0.$ It follows that $\frac{1}{d} > x_{2+} > x_-,$ and hence $g(x_{2+}) > g(x_-) = 0,$ which in turn yields $\det(J(E_{2+})) = \alpha_4 = \frac{y_{2+}w_{2+}}{x_{2+}}g(x_{2+}) > 0.$ This completes the proof. \square

Theorem 3.2 *The infectious equilibrium E_{2-} is unstable once it exists.*

Proof Since the determinant $\det(E_{2-}) < 0,$ there is at least one characteristic root that has no negative real part. Therefore E_{2-} is unstable. \square

Next, we discuss the stability of equilibria $E_{2+}.$ By (3.2) the characteristic equation at E_{2+} is given by

$$s^4 + \alpha_1s^3 + \alpha_2s^2 + \alpha_3s + \alpha_4 = 0,$$

where

$$\begin{cases} \alpha_1 = h + \frac{1}{x_{2+}}, \\ \alpha_2 = x_{2+}y_{2+} + \frac{h}{x_{2+}} + y_{2+}w_{2+}, \\ \alpha_3 = hx_{2+}y_{2+} + \frac{y_{2+}w_{2+}}{x_{2+}} + by_{2+}w_{2+}, \\ \alpha_4 = \frac{by_{2+}w_{2+}}{x_{2+}} - cw_{2+}x_{2+}y_{2+}^3. \end{cases}$$

Note that $\alpha_1 > 0$, $\alpha_2 > 0$, and $\alpha_3 > 0$, and according to the proof of Propositiony 3.1, we know that $\alpha_4 > 0$. The relevant Routh–Hurwitz determinants are

$$\begin{cases} \Delta_1 = \alpha_1, \\ \Delta_2 = \alpha_1\alpha_2 - \alpha_3, \\ \Delta_3 = \alpha_3\Delta_2 - \alpha_1^2\alpha_4, \\ \Delta_4 = \alpha_4\Delta_3. \end{cases} \tag{3.12}$$

Note that $\Delta_1 > 0$ and the sign of Δ_4 is the same as Δ_3 . By the formulas of x_{2+} , y_{2+} , and z_{2+} , Δ_2 and Δ_3 can be written more explicitly as

$$\begin{cases} \Delta_2 = A_2h^2 + B_2h + C_2, \\ \Delta_3 = \frac{h}{x_{2+}^2}[A_3h^2 + B_3h + C_3], \end{cases} \tag{3.13}$$

where

$$\begin{cases} A_2 = \frac{1}{x_{2+}} + z_{2+}, \\ B_2 = \frac{1}{x_{2+}^2} - bz_{2+}, \\ C_2 = y_{2+}, \\ A_3 = x_{2+}^3y_{2+} + x_{2+}z_{2+} + x_{2+}^4y_{2+}z_{2+} + x_{2+}^2z_{2+}^2 + bz_{2+}^2x_{2+}^3 + cz_{2+}x_{2+}^4y_{2+}^2, \\ B_3 = x_{2+}^2y_{2+} + z_{2+} + 2cx_{2+}^3z_{2+}y_{2+}^2 - bx_{2+}^4y_{2+}z_{2+} - bx_{2+}^2z_{2+}^2 - b^2z_{2+}^2x_{2+}^3 - bz_{2+}x_{2+}, \\ C_3 = x_{2+}^4y_{2+}^2 + x_{2+}^2y_{2+}z_{2+} + bx_{2+}^3y_{2+}z_{2+} + cx_{2+}^2z_{2+}y_{2+}^2 - bz_{2+}. \end{cases}$$

Next, we give the following lemma to show that if both Δ_2 and Δ_3 can become zero, then Δ_3 will cross zero before Δ_2 does.

Lemma 3.1 *If E_{2+} exists, then Δ_2 is positive when Δ_3 crosses zero for some change in parameters.*

Remark The proof is similar to that in [33], so here we omit it.

Thus, to consider the stability of the positive equilibrium E_{2+} , we only need to consider the possibility of $\Delta_3 = 0$ (see [33]). Note that x, y, z do not contain h and $\Delta_3 = 0$ is just a

quadratic equation in terms of h . Let

$$\begin{cases} \Delta_4 = B_3^2 - 4A_3C_3, \\ h_2^* = \frac{-B_3 + \sqrt{\Delta_4}}{2A_3}, \\ h_1^* = \frac{-B_3 - \sqrt{\Delta_4}}{2A_3}, \\ h^* = -\frac{B_3}{2A_3}. \end{cases} \tag{3.14}$$

Obviously, $h_1^* < h^* < h_2^*$, and thus we have the following theorem.

Theorem 3.3 *Suppose the infectious equilibrium E_{2+} exists.*

(1) *If $C_3 < 0$, then E_{2+} is locally asymptotically stable when $h \in (h_2^*, +\infty)$ and is unstable when $h \in (0, h_2^*)$.*

(2) *If $C_3 > 0$, then*

(i) *E_{2+} is always locally asymptotically stable when $B_3 \geq 0$, and*

(ii) *if $B_3 < 0$, then E_{2+} is always locally asymptotically stable when $\Delta_4 < 0$. Moreover, if $\Delta_4 = 0$, then E_{2+} is locally asymptotically stable when $h \neq h^*$; if $\Delta_4 > 0$, then E_{2+} is locally asymptotically stable when $h \in (0, h_1^*) \cup (h_2^*, +\infty)$ and unstable when $h \in (h_1^*, h_2^*)$.*

(3) *If $C_3 = 0$, then E_{2+} is always locally asymptotically stable when $B_3 \geq 0$, and if $B_3 < 0$, then E_{2+} is locally asymptotically stable when $h \in (-\frac{B_3}{A_3}, +\infty)$ and unstable when $h \in (0, -\frac{B_3}{A_3})$.*

Remarks 1. The proof is straightforward by considering the sign of the quadratic polynomial $A_3h^2 + B_3h + C_3$, and the detailed proof is contained in Theorem 3.4, so we omit it.

2. If we use the computing method of paper [33], then Δ_2 and Δ_3 can be written more explicitly as

$$\begin{cases} \Delta_2 = A_{22}(h - b)^2 + B_{22}(h - b) + C_{22}, \\ \Delta_3 = A_{33}(h - b)^2 + B_{33}(h - b) + C_{33}, \end{cases} \tag{3.15}$$

where

$$\begin{cases} A_{22} = \frac{1}{x_{2+}} + z_{2+}, \\ B_{22} = \frac{2b}{x_{2+}} + bz_{2+} + \frac{1}{x_{2+}^2}, \\ C_{22} = \frac{b^2}{x_{2+}} + \frac{b}{x_{2+}} + y_{2+}, \\ A_{33} = \frac{1}{x_{2+}}(x_{2+}y_{2+} + \frac{z_{2+}}{x_{2+}}) + z_{2+}(x_{2+}y_{2+} + \frac{z_{2+}}{x_{2+}} + bz_{2+}) + \frac{cz_{2+}x_{2+}^2y_{2+}^2}{x_{2+}}, \\ B_{33} = 2by_{2+} + (\frac{1}{x_{2+} + bz_{2+}})(x_{2+}y_{2+} + \frac{z_{2+}}{x_{2+}} + bz_{2+}) + 2bcz_{2+}x_{2+}y_{2+}^2 + 2cz_{2+}y_{2+}^2, \\ C_{33} = b^2y_{2+} + \frac{by_{2+}}{x_{2+}} + y_{2+}(x_{2+}y_{2+} + \frac{z_{2+}}{x_{2+}} + bz_{2+}) + cx_{2+}^2y_{2+}^2(\frac{b^2z_{2+}}{x_{2+}} + \frac{2bz_{2+}}{x_{2+}^2} + \frac{z_{2+}}{x_{2+}^3}). \end{cases}$$

Obviously, $A_{22} > 0$, $B_{22} > 0$, $C_{22} > 0$, $A_{33} > 0$, $B_{33} > 0$, and $C_{33} > 0$, which indicates that $\Delta_{22} > 0$ and $\Delta_{33} > 0$ as long as $h > b$. As in [33], the infectious equilibrium E_{2+} with CTL response is always stable if the death rate of the CTLe is higher than that of the CTLp.

Theorem 3.4 *Consider the infectious equilibrium E_{2+} (here E_{2+} exists).*

- (1) If $C_3 < 0$, then a Hopf bifurcation occurs at $h = h_2^*$.
- (2) If $C_3 > 0$, $B_3 < 0$, and $\Delta_4 > 0$, then two Hopf bifurcations occur at $h = h_1^*$ and $h = h_2^*$.
- (3) If $C_3 = 0$ and $B_3 < 0$, then a Hopf bifurcation occurs at $h = -\frac{B_3}{A_3}$.

Proof As in [37], a four-dimensional model has a Hopf bifurcation if $\Delta_1 > 0$, $\Delta_2 > 0$, and $\Delta_3 = 0$. Obviously, $\Delta_1 > 0$ always holds by (3.12), and according to Lemma 3.1, $\Delta_2 > 0$ as Δ_3 crosses zero for some change of parameters. Therefore a Hopf bifurcation occurs as $\Delta_3 = 0$, which is equivalent to finding the roots of the quadratic polynomial equation $A_3h^2 + B_3h + C_3 = 0$, where A_3, B_3, C_3 are independent of h by (3.13) and (3.14). Hence $A_3h^2 + B_3h + C_3 = 0$ is a quadratic equation of h . Note that if $C_3 < 0$, then a positive root $h_2^* = \frac{-B_3 + \sqrt{\Delta_3}}{2A_3}$ exists, which indicates that E_{2+} is stable for $h \in (0, h_2^*)$ and E_{2+} is unstable for $h \in (h_2^*, +\infty)$, whereas $\Delta_3 = 0$ if $h = h_2^*$. Hence by [37] a Hopf bifurcation occurs at $h = h_2^*$.

However, if $C_3 > 0$ and $B_3 < 0$, then $\Delta_3 > 0$ as $h \in (0, h_1^*) \cup (h_2^*, +\infty)$, which implies that E_{2+} is stable, whereas $\Delta_3 < 0$ as $h \in (h_1^*, h_2^*)$, which ensures that E_{2+} is unstable, and $\Delta_3 = 0$ as $h = h_2^*$ or $h = h_1^*$. Hence by [37] two Hopf bifurcations occur at $h = h_2^*$ and $h = h_1^*$.

If $C_3 = 0$ and $B_3 < 0$, then $\Delta_3 > 0$ as $h \in (-\frac{B_3}{A_3}, +\infty)$, which implies that E_{2+} is stable, whereas $\Delta_3 < 0$ as $h \in (0, -\frac{B_3}{A_3})$, which ensures that E_{2+} is unstable, and $\Delta_3 = 0$ as $h = -\frac{B_3}{A_3}$. Thus by [37] a Hopf bifurcation occurs at $h = -\frac{B_3}{A_3}$. □

Remark Since the expressions of x, y, w, z are very complicated, it is too complicated to directly discuss the sign of $\Delta_4 = B_3^2 - 4A_3C_3$. In the next section, by numerical calculations we will demonstrate that the three cases $\Delta_4 > 0$, $\Delta_4 = 0$, and $\Delta_4 < 0$ are possible.

4 Numerical illustrations

In this section, we demonstrate the theoretical results by numerical simulations. For convenience, we will work on the scaled model (2.1) instead of the original model (1.3).

The values of λ used for simulations in [32] are $\lambda = 1$ and $\lambda = 10$, and as a bifurcation in [33], this indicates that the values of λ have a fairly large variation; therefore we take $\lambda = 0.5657$. Note that $\beta = 0.5$ and $\beta = 0.001$ were used in [32], whereas $\beta = \frac{3}{400}$ was used in [33], and hence choosing $\beta = 0.0707$ is reasonable. The parameter $q \in [0, 1]$ represents the decomposition rate; here we choose $q = 0.7071$. The same parameter values as in [32] are taken, and appropriate value for h is chosen:

$$d = 0.1, \quad p = 1, \quad c = 0.1, \quad b = 0.1, \quad h = 0.06.$$

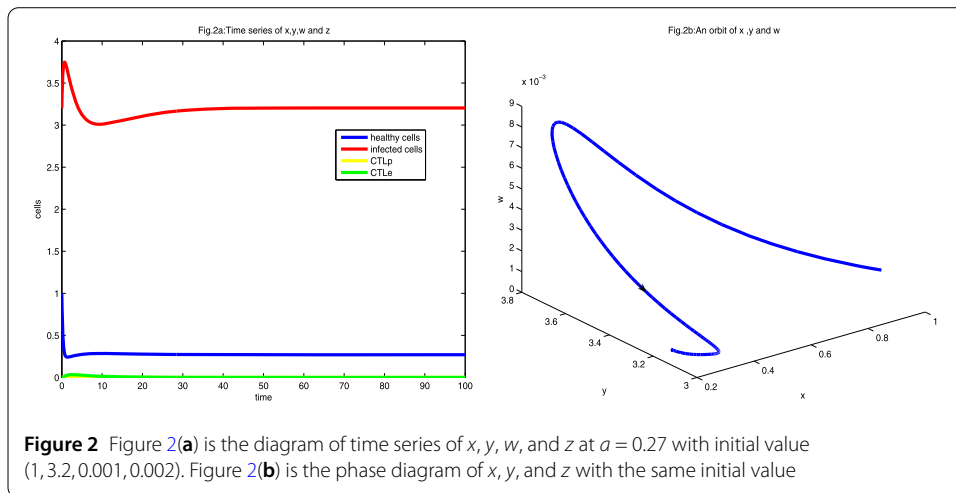
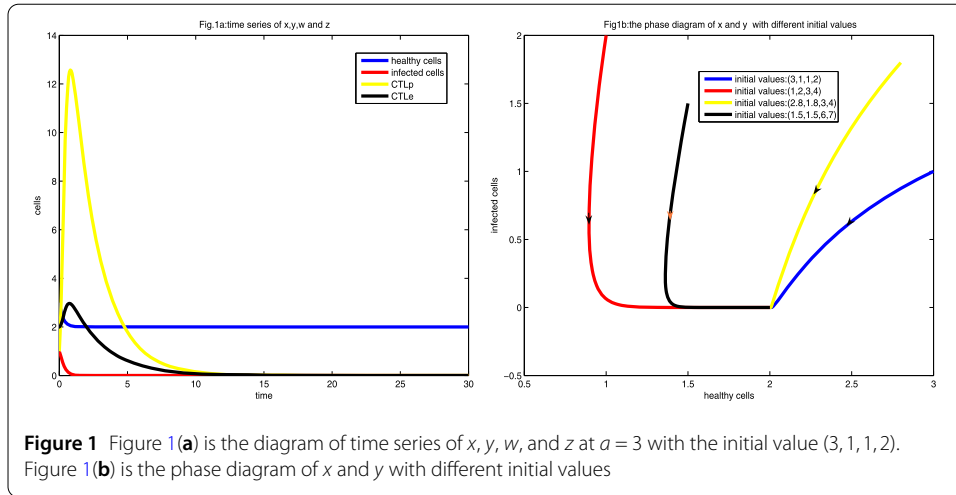
According to the relationship between the parameters of the original model (1.3) and the scaled model (2.1), the parameter values in the scaled model (2.1) are chosen as follows:

$$c = 4, \quad b = 0.5, \quad q = 1, \quad h = 0.3, \quad d = 0.5.$$

Choose a as the bifurcation parameter. With these parameter values, we obtain

$$R_0 = \frac{1}{ad} = \frac{1}{0.5a} = \frac{2}{a}, \quad R_1 = 1 + \frac{b}{d(ca - q)} = 1 + \frac{0.5}{0.5(4a - 1)} = 1 + \frac{1}{4a - 1}.$$

To get $R_0 < 1$, $a > 2$ is required, which in turn yields that the infection-free equilibrium $E_0 = (\frac{1}{a}, 0, 0) = (2, 0, 0)$ is globally stable by Theorem 2.4. For $a = 3$, system (2.1) has a globally stable infection-free equilibrium E_0 , which is shown in Fig. 1.



As shown in Fig. 1, the healthy and infected cells decrease and converge to the equilibrium E_0 directly, whereas CTLe and CTLp firstly increase, then decrease, and finally converge to zero, which reveals that the infected cells CTLp and CTLe die out directly after a brief fluctuation.

As a decreases to the critical value $a_1^c \doteq 2$, R_0 increases and passes the threshold 1, which reveals that E_0 becomes unstable. However, the infectious equilibrium $E_1 = (a, d(R_0 - 1), 0, 0) = (a, 0.5(\frac{2}{a} - 1), 0, 0)$ without CTL appears. As stated in Theorem 2.5, E_1 is stable if $1 < R_0 < R_1$ or $R_0 > 1 > R_1$. By direct calculation we have $R_0 < R_1$ if $2a^2 - 4a + 1 = (a - \frac{2+\sqrt{2}}{2})(a - \frac{2-\sqrt{2}}{2}) > 0$, which implies that $1 < R_0 < R_1$ is equivalent to $1.707 \approx \frac{2+\sqrt{2}}{2} < a < 2$ or $\frac{1}{4} < a < \frac{2-\sqrt{2}}{2} \approx 0.2930$, whereas $R_0 > 1 > R_1$ is equivalent to $0 < a < \frac{1}{4}$. Adding the second case together, we conclude that E_1 is stable if $a \in (0, \frac{1}{4}) \cup (\frac{1}{4}, \frac{2-\sqrt{2}}{2}) \cup (\frac{2+\sqrt{2}}{2}, 2)$.

Let $a = 0.27$. Obviously, $E_1 = (a, d(R_0 - 1), 0, 0) = (0.27, \frac{173}{54}, 0, 0)$ is stable, as shown in Fig. 2.

As shown in Figs. 2(a) and 2(b), all cells converge to the equilibrium E_1 after a short time.

According to Theorem 2.2, system (2.1) admits a unique positive equilibrium

$$E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+}) = \left(1 + \frac{1}{2}\sqrt{2}, \frac{3}{2} - \sqrt{2}, -\frac{3}{10}(3 + 2\sqrt{2})(-2 - \sqrt{2} + 2a), 1 + \frac{1}{2}\sqrt{2} - a \right)$$

if $\frac{2-\sqrt{2}}{2} < a < \frac{2+\sqrt{2}}{2}$ (Theorem 2.2 (1)(i)). If $a \in (0, \frac{1}{4}) \cup (\frac{1}{4}, \frac{2-\sqrt{2}}{2})$ (Theorem 2.2 (2)(i),2(ii)), then system (2.1) admits two positive equilibria $E_{2+} = (x_{2+}, y_{2+}, w_{2+}, z_{2+})$ and

$$E_{2-} = \left(1 - \frac{1}{2}\sqrt{2}, \frac{3}{2} + \sqrt{2}, \frac{3}{10}(-3 + 2\sqrt{2})(-2 + \sqrt{2} + 2a), 1 - \frac{1}{2}\sqrt{2} - a \right),$$

which is unstable once it exists.

Next, we will prove Theorem 3.3 numerically. By direct calculation the characteristic equation at E_{2+} in term of a is (here $h = 0.3$ is a constant)

$$P(s) = s^4 + \alpha_1 s^3 + \alpha_2 s^2 + \alpha_3 s + \alpha_4 = 0,$$

where

$$\begin{cases} \alpha_1 = \frac{23}{10} - \sqrt{2}, \\ \alpha_2 = \frac{7}{5} - \frac{2}{5}\sqrt{2} - \frac{3}{10}a, \\ \alpha_3 = \frac{3}{340}(-5 + 2\sqrt{2})(-20 + 17a - 8\sqrt{2}), \\ \alpha_4 = -\frac{3}{20}(-4 + 3\sqrt{2})(-2 - \sqrt{2} + 2a). \end{cases} \tag{4.1}$$

It follows that the existence conditions of positive equilibrium E_{2+} ($a \in (0, \frac{1}{4}) \cup (\frac{1}{4}, \frac{2-\sqrt{2}}{2})$ or $a \in (\frac{2-\sqrt{2}}{2}, \frac{2+\sqrt{2}}{2})$) directly guarantee that $\alpha_i > 0, i = 1, 2, 3, 4$.

According to formulas (3.13), we obtain the Routh–Hurwitz determinants:

$$\begin{cases} \Delta_2(a) = \frac{171}{50} - \frac{58}{25}\sqrt{2} + \frac{3}{50}a, \\ \Delta_3(a) = \frac{3}{17,000}(-5 + 2\sqrt{2})(a - a_-)(a - a_+), \end{cases} \tag{4.2}$$

where $a_{\pm} = \frac{3593}{34}\sqrt{2} - \frac{15,119}{102} \pm \frac{1}{102}\sqrt{461,988,655 - 326,669,598\sqrt{2}}$. Note that $\Delta_2(a) > 0$ for all $a > 0$ by (4.2), whereas if $a < a_-$, or $a > a_+$, then we have $\Delta_3(a) > 0$. Thus E_{2+} is locally stable by the Routh–Hurwitz theorem if $a_- < a < \frac{2+\sqrt{2}}{2}$. Let $a = 1$. By simple calculation we obtain $E_{2+} = (1 + \frac{1}{2}\sqrt{2}, \frac{3}{2} - \sqrt{2}, \frac{3}{10}\sqrt{2}(3 + 2\sqrt{2}), \frac{1}{2}\sqrt{2})$ and $\alpha_{1E_{2+}} \approx 0.8858, \alpha_{2E_{2+}} \approx 0.5343, \alpha_{3E_{2+}} \approx 0.2743, \alpha_{4E_{2+}} \approx 0.0515, \Delta_{2E_{2+}} \approx 0.1990, \Delta_{3E_{2+}} \approx 0.0142$ by (4.1) and (4.2). Therefore it is locally stable, as shown in Fig. 3.

As can be seen in Fig. 3(a) and Fig. 3(b), each cell first shocks and then settles to equilibrium E_{2+} .

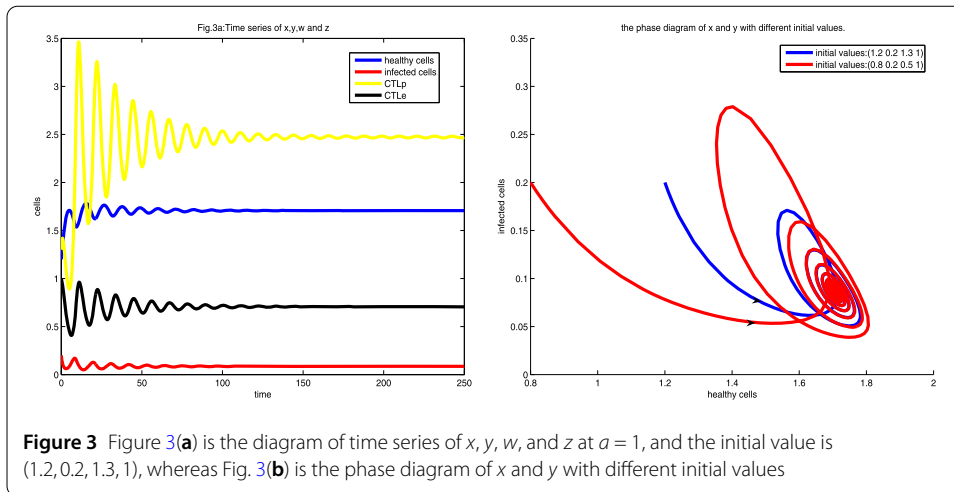


Figure 3 Figure 3(a) is the diagram of time series of $x, y, w,$ and z at $a = 1$, and the initial value is $(1.2, 0.2, 1.3, 1)$, whereas Fig. 3(b) is the phase diagram of x and y with different initial values

Now we verify the Hopf bifurcation by Theorem 3.4. The formulas given by (3.14) are

$$\begin{cases} A_2 = 3 - \frac{1}{2}\sqrt{2} - a, \\ B_2 = \frac{11}{2} - \frac{17}{4}\sqrt{2} + \frac{1}{2}a, \\ C_2 = \frac{3}{2} - \sqrt{2}, \\ A_3 = -\frac{87}{8}a + \frac{21}{2} + \frac{29}{4}\sqrt{2} - \frac{29}{4}\sqrt{2}a + \frac{11}{4}a^2 + \frac{15}{8}\sqrt{2}a^2, \\ B_3 = -\frac{1}{544}(15\sqrt{2} + 22)[a - (-\frac{407}{34} + \frac{657}{68}\sqrt{2} - \frac{1}{68}\sqrt{1,566,150 - 1,107,132\sqrt{2}})] \\ \quad \times [a - (-\frac{407}{34} + \frac{657}{68}\sqrt{2} + \frac{1}{68}\sqrt{1,566,150 - 1,107,132\sqrt{2}})], \\ C_3 = -\frac{1}{272}(-22 + 15\sqrt{2})(16\sqrt{2} + 28 - 17a). \end{cases} \tag{4.3}$$

It follows that the existence conditions of positive equilibrium E_{2+} ($a \in (0, \frac{1}{4}) \cup (\frac{1}{4}, \frac{2-\sqrt{2}}{2})$ or $a \in (\frac{2-\sqrt{2}}{2}, \frac{2+\sqrt{2}}{2})$) also directly guarantee that $A_3 > 0$ and $C_3 > 0$ (Theorem 3.4 (2)).

Since $B_3 < 0$ (Theorem 3.4 (2)), we have

$$a > -\frac{407}{34} + \frac{657}{68}\sqrt{2} + \frac{1}{68}\sqrt{1,566,150 - 1,107,132\sqrt{2}} \approx 2.155$$

or

$$0 < a < -\frac{407}{34} + \frac{657}{68}\sqrt{2} - \frac{1}{68}\sqrt{1,566,150 - 1,107,132\sqrt{2}} \approx 1.225.$$

Moreover, according to (3.14), we obtain

$$\begin{aligned} \Delta_4 &= \frac{1}{36,992}(467 + 330\sqrt{2})(-20 + 17a - 8\sqrt{2})^2 \\ &\quad \times \left[a - \left(-135 + \frac{193}{2}\sqrt{2} + 2\sqrt{9184 - 6494\sqrt{2}} \right) \right] \\ &\quad \times \left[a - \left(-135 + \frac{193}{2}\sqrt{2} - 2\sqrt{9184 - 6494\sqrt{2}} \right) \right], \end{aligned} \tag{4.4}$$

whereas $\Delta_4 = 0$ yields

$$a = -135 + \frac{193}{2}\sqrt{2} \pm 2\sqrt{9184 - 6494\sqrt{2}}, \frac{8\sqrt{2} + 20}{17}, \frac{8\sqrt{2} + 20}{17}$$

$$\approx 2.0949, 0.8483, 1.8420, 1.8420.$$

Denote $a^* = -135 + \frac{193}{2}\sqrt{2} - 2\sqrt{9184 - 6494\sqrt{2}} \approx 0.8483 \in (\frac{2-\sqrt{2}}{2}, \frac{2+\sqrt{2}}{2})$. Intersecting with the existence condition of equilibrium E_{2+} and $B_3 < 0$, we obtain $\Delta_4 < 0$ for $a \in (a^*, \frac{2+\sqrt{2}}{2})$ and $\Delta_4 = 0$ for $a = a^*$, whereas $\Delta_4 > 0$ for $a \in (0, \frac{1}{4}) \cup (\frac{1}{4}, \frac{2-\sqrt{2}}{2}) \cup (\frac{2-\sqrt{2}}{2}, a^*)$, which implies that the two roots of $\Delta_3 = 0$ are (by (3.13))

$$h_1^* = \frac{-B_3 - \sqrt{\Delta_4}}{2A_3}, \quad h_2^* = \frac{-B_3 + \sqrt{\Delta_4}}{2A_3}, \tag{4.5}$$

where A_3 and B_3 are given in (4.3), and Δ_4 is given in (4.4). By Theorem 3.3, E_{2+} is stable if $h \in (0, h_1^*) \cup (h_2^*, +\infty)$. Submitting $a = 0.5$ into (4.5), we get $h_1^* \approx 0.03872$ and $h_2^* \approx 0.2728$, and therefore E_{2+} is stable if $h = 0.3$ (given number) $> h_2^*$. For $a = 0.31$, we have $h_1^* \approx 0.029245$ and $h_2^* \approx 0.304727$, which implies that $h = 0.3$ (given number) $\in (h_1^*, h_2^*)$, and thus E_2 is unstable.

Fix $a = 0.31$ and take h as the bifurcation parameter. By Theorem 3.4 there are two Hopf bifurcations at $h = h_1^* \approx 0.029245$ and $h = h_2^* \approx 0.304727$, which implies that two limit cycles occur. With the help of Matcont [38], we obtain that the first Lyapunov coefficient is -0.07004781 as $h = h_1^* \approx 0.029245$, whereas another first Lyapunov coefficient is -0.001386494 as $h = h_2^* \approx 0.304727$, and thus the two Hopf bifurcations are supercritical, and the limit cycles are stable. The phase diagrams of system are shown in Fig. 4.

As can be seen in Figs. 4(a), 4(b), and 4(c), a stable limit cycle appears, and stable periodic solutions bifurcate from it.

We must point out that when $a \in (0, \frac{1}{4}) \cup (\frac{1}{4}, \frac{2-\sqrt{2}}{2})$, the infectious equilibrium E_1 without CTL is stable, whereas the infectious equilibrium E_{2+} with CTL exists. To display this case, let $a = 0.27$ and $h = 0.4$, which indicates that both E_1 and E_{2+} are stable. By direct calculation we obtain $E_1 \approx (0.27, 3.2037, 0, 0)$ and $E_{2+} \approx (1.7071, 0.0858, 1.4371, 6.7009)$, and we draw the diagrams with different initial values.

As shown in Figs. 5(a) and 5(b), there are two stable equilibria E_1 and E_{2+} , that is, bistability occurs, and the infected cells converge to one of them depending on the initial values.

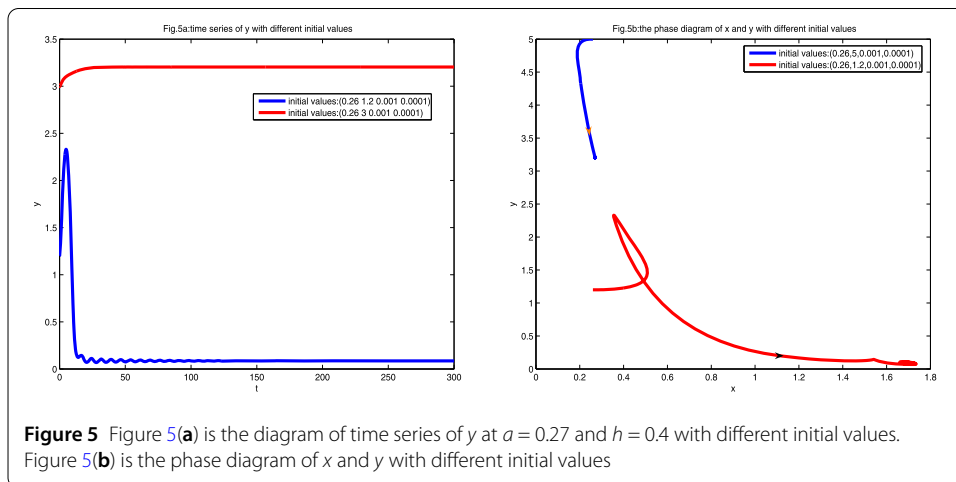
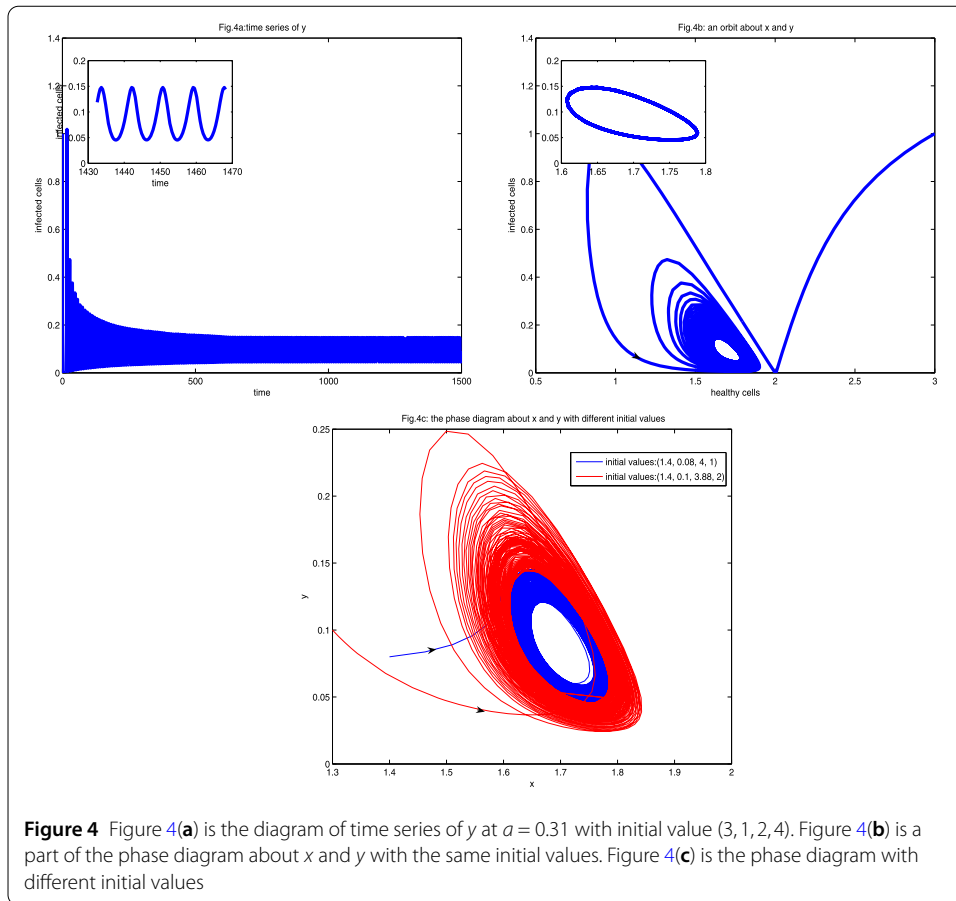
Besides, when equilibrium E_{2+} is unstable, then a stable limit cycle occurs, and E_1 is still stable. To display this phenomenon directly, letting $a = 0.1$ and $h = 0.3$, we draw the diagrams with different initial values.

As shown in Figs. 6(a) and 6(b), a stable equilibrium E_1 , an unstable equilibrium E_{2+} , and a stable limit cycle, which is bifurcated from E_{2+} , appear, and the infected cells converge to one of them depending on the initial values.

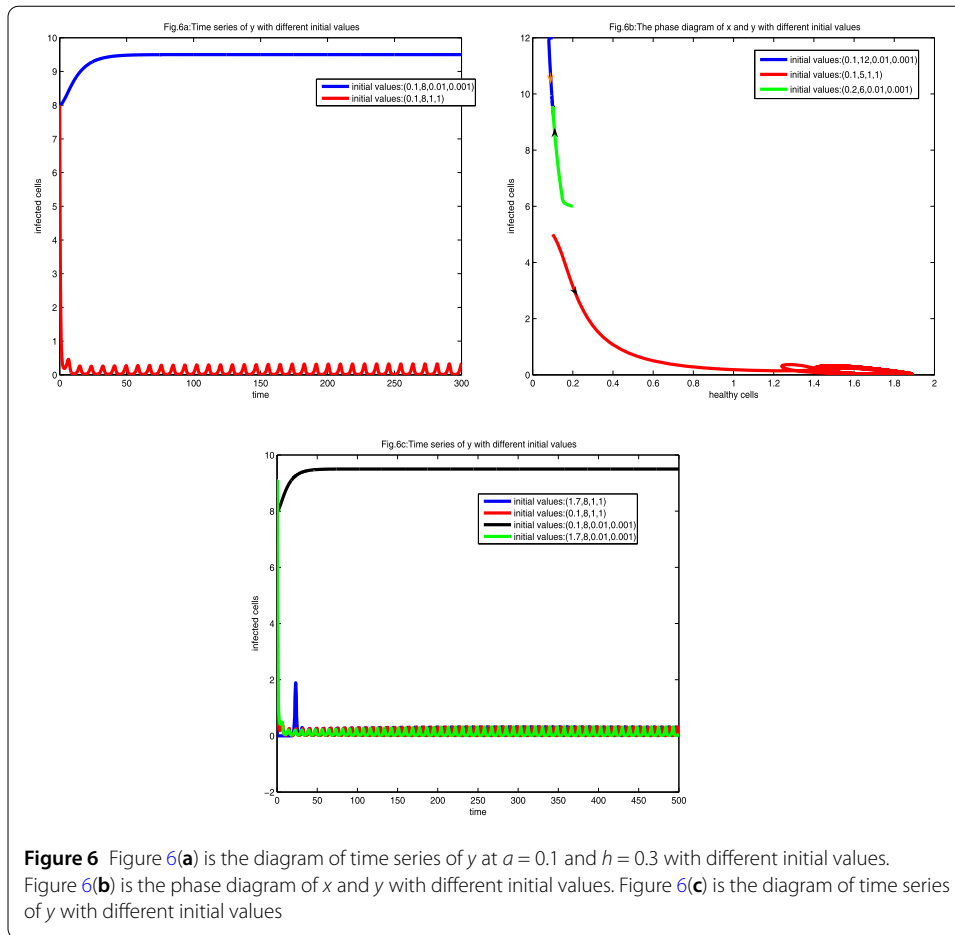
For the case of $C_3 < 0$, in Theorems 3.3 and 3.4, we give another set of parameters $d = 3.6 = b, q = 1, c = 28.8, h = 0.8$. We do not discuss it now.

5 Discussion

This paper studies an HIV model proposed by Wodarz et al. [31, 32] to describe the interaction between healthy cells and infected cells as well as primary and secondary immune



response. Compared with [33], in this model, we assume that the production of primary immune response is not only connected with infected cells but also with healthy cells. We also assume that virus at its steady state is proportional to infected cells. The structure of equilibria is analyzed in [31, 32]. But for a higher-dimensional system, stability and bifurcation analysis is important and complex for the full range of possibilities. Because of adding the healthy cells to the produced CTLp, the model shows rich dynamic behavior on stability and bifurcations.



It is interesting that this model displays the bistability phenomenon, that is, two stable equilibria E_1 and E_{2+} or a stable equilibrium E_1 and a stable limit cycle, which is bifurcated from the unstable equilibrium E_{2+} . Which one is stable not only depends on relationship of parameters but also depends on the initial values of cells. As shown in Figs. 5(a) and 5(b), high initial virus load close to E_1 leads to the convergence to E_1 , which means that CTL memory fails to establish. Low initial virus load close to E_{2+} leads to the convergence to E_{2+} , CTL memory successfully establishes, and the virus load first increases and then decreases to stay at a low level. Therefore we must increase dosage to inhibit the virus replication in a brief period and help the immune response establish. As shown in Fig. 6(a), if the initial healthy cells and virus load are the same, and high initial CTL account means that the CTL response establishes, virus load may decrease at primary process, which was considered as the CTL clear away some virus, but over time, it oscillates and cannot be completely eradicated. This phenomenon can be viewed as an individual having a chronic disease that may flare up from time to time, and it is a long struggle between virus and immune response. Initial values with little CTL lead to high virus load. As can be seen in Fig. 6(c), high or low initial healthy cells do not change the development of disease. However, high initial healthy cells first lead to decreasing the virus load to a very low state, which is almost clear away the virus, which means that the healthy cells play an important role in clearing away the virus under certain circumstances.

The interaction of virus and the host immune system is a complicated and long process as HIV has a long latent period, and the disease cannot cure completely. We have shown rich dynamic patterns, but the model considered here is just a simple one. It is easy to improve and expand the model. For example, we can add the virus equation in model (1.3) (see a more detailed description in [32]), we may consider delay in this model as in [39], drug treatment [13], or latent cells [40] mentioned in the introduction. Such modifications should more precisely react the reality and give us more advice in understanding the infection process, which leads to a more challenging mathematical analysis.

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Availability of data and materials

Data sharing not applicable to this paper as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CL found the model and carried out the numerical simulation, and CL and LK did the mathematical analysis and wrote the paper together. All authors read and approved the final manuscript.

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