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Complex dynamic behavior in a viral model with state feedback control strategies

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Abstract With the consideration of mechanism of prevention and control for the spread of viral diseases, in this paper, we propose two novel virus dynamics models where state feedback control strategies are introduced. The first model incorporates the density of infected cells (or free virus) as control threshold value; we analytically show the existence and orbit stability of positive periodic solution. Theoretical results imply that the density of infected cells (or free virus) can be controlled within an adequate level. The other model determines the control strategies by monitoring the density of uninfected cells when it reaches a risk threshold value. We analytically prove the existence and orbit stability of semi-trivial periodic solution, which show that the viral disease dies out. Numerical simulations are carried out to illustrate the main results.

Keywords Virus dynamics model · State feedback control · Positive periodic solution · Semi-trivial periodic solution · Orbital stability

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1 Introduction

Viruses are the most abundant type of biological entities and are found in almost every ecosystem on Earth, which can infect all types of life forms, from animals and plants to bacteria and archaea. Many serious diseases, such as ebola, AIDS, avian influenza, and SARS, are caused by viruses. The control and hence eradication of diseases is one of the major concerns in the study of viral epidemiology. Since viral reproduction always involves host cells and uses the cellular machinery for the synthesis of their genome and other components, there have been two methodologies used to mimic these processes by mathematical models. Perhaps the earliest and simplest classical virus dynamics model was developed by Kermack et al. in [1] and Anderson et al. in [2,3] as follows

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \delta x - \beta xy, \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta xy - \mu y, \end{cases} \tag{1}$$

where x denotes the density of uninfected cells and y denotes the density of infected cells, λ is the rate of production of uninfected cells, δ is their per capita death rate, β is the rate of infection of uninfected cells, and μ is the rate of disappearance of infected cells. Model (1) is very important in viral epidemiology, which has been studied by many authors. A more detailed description of model (1) and its dynamic behaviors may be found in [1–3] and the references therein.

Not long after that many similar models which include the dynamics of free virus or immune response have been used to describe the short-term dynamics of virus load during drug treatment and have helped to estimate virus turnover rates in vivo. We refer to some of them in [4–13] and the references therein. However, Bartholdy et al. [14] and Wodarz et al. [15] found that the turnover of free virus is much faster than that of infected cells, which allowed them to make a quasi-steady state assumption—that is, the amount of free virus is simply proportional to the number of infected cells. Therefore, the density of infected cells y in model (1) also can be considered as a measure of the free virus load.

In recent years, many researchers studied the evolution of virus dynamics models from different perspectives. These include the existence of the threshold value, which is the index for the persistence and extinction of a viral disease; the local or global stability of virus-free equilibrium and the virus equilibrium; the existence and stability of periodic solutions, to name just a few (see, e.g., [16–25]). Particularly, Nakata [26] studied the global dynamics of a viral infection model with a latent period and nonlinear function which denotes the incidence rate of the virus infection in vivo. Wang and Zhao [27] considered the investigation of the effects of periodic drug treatment on a standard within-host virus model. Ball et al. [28] examined the dynamics of strain replacement in a simple model that includes a convex trade-off between rapid virus reproduction and long-term host cell survival. Lang and Li [29] investigated the consequences of a more general CTL response and show that a sigmoidal response function gives rise to complex behaviors previously unobserved.

It is well known that exploring an effective and easily implementable control measure to keep the level of spread of diseases is significant both theoretically and practically. For example, of many strategies, the efficient ways for elimination or control of malignant neoplasm are still chemotherapy, radiotherapy, and immunotherapy in clinical treatment in recent years. The clinical data show that the course of these treatments for some viral diseases is relatively short but the density of various cells in vivo changed radically, which in nature is submitted to short temporary effects that are negligible compared to the process duration. These short-time perturbations are often assumed to be in the form of impulses in the modeling process.

Very recently, many works have been focused on the analysis of mathematical models described by ordinary differential equations with control effects [30–33]. Particularly, the state-dependent impulsive control strategies are applied widely to the prevention of spread of infectious disease due to its economic, high efficiency, and feasibility nature. This idea can be found in many other areas like agricultural production and fishery industry; where the control measures, such as catching, poisoning, releasing the natural enemy, and harvesting, are taken only when the number of population reaches an economic threshold value. Following this idea, the dynamic behaviors of population, epidemic and language models with state-dependent impulsive effects are considered, and the existence and stability of positive periodic solution by the Poincaré map, properties of the Lambert W function, and analog of Poincaré criterion are obtained [34–38].

Motivated by the above works, we propose, in this paper, two novel virus dynamics models with state feedback control strategies. The main purpose is to investigate the state feedback control strategies which govern whether the viral disease dies out or not, and further to examine how the state feedback control strategies affect the prevention and control of viral disease.

This paper is organized as follows. In the next section, we introduce two novel virus dynamics models where the state feedback control strategies are considered, some basic definitions, and an important lemma. The density of infected cells (or free virus) as control threshold value, and some sufficient conditions are presented in Sect. 3 for the existence and orbital stability of positive periodic solutions. In Sect. 4, the existence and stability of semi-trivial periodic solution are obtained, where the density of uninfected cells is the control threshold value. The numerical simulations are carried out in Sect. 5 for illustration. Some concluding remarks are presented in Sect. 6.

2 Model formulation and preliminaries

The basic reproductive rate for model (1) is $R_0 = \frac{\lambda\beta}{\mu\delta}$, which is defined as the average number of secondary infected cells generated by a single infected cell placed in an uninfected cell (or free virus). It is clear that (i) if $R_0 < 1$, then model (1) admits only a global asymptotical stable virus-free equilibrium $(\frac{\lambda}{\delta}, 0)$; (ii) if $R_0 > 1$, then model (1) admits an unstable trivial equilibrium

$(\frac{\lambda}{\delta}, 0)$ and a unique globally asymptotically stable positive equilibrium (x^*, y^*), where

$$x^* = \frac{\mu}{\beta}, \qquad y^* = \frac{\lambda}{\mu}\left(1 - \frac{1}{R_0}\right). \tag{2}$$

Generally, the objective of treatment and control for viral disease is to reduce the density of free virus or infected cells in vivo. For all this, we propose, firstly, a novel virus dynamics model with state feedback control strategies, while regarding the density of free virus or infected cells as control threshold value. The control model is governed by the following state feedback impulsive differential equation:

$$\left\{\begin{array}{l} \left.\begin{array}{l} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \delta x - \beta xy \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta xy - \mu y \end{array}\right\} y \neq Y_c, \\ \left.\begin{array}{l} \triangle x(t) = x(t^+) - x(t) = -px(t) + \tau \\ \triangle y(t) = y(t^+) - y(t) = -qy(t) \end{array}\right\} y = Y_c. \end{array}\right. \tag{3}$$

The meaning of model (3) is as follows: when the density of infected cells (or free virus) y reaches the critical threshold value Y_c at time $t_i(Y_c)$ at the i-th time, control strategies (such as chemotherapy, radiotherapy, immunotherapy, etc.) are taken and the densities of uninfected cells x and infected cells (or free virus) y immediately become $(1-p)x(t_i(Y_c))+\tau$ and $(1-q)y(t_i(Y_c))$, respectively, where $p, q \in (0, 1)$, and $\tau > 0$.

Remark 1 It is clear that a priori time of control strategies depends on the density of infected cells (or free virus), which makes our control strategy a "state feedback control."

On the other hand, from the dependencies between the densities of uninfected cells and infected cells (or free virus) in model (1), it is obvious that if the density of uninfected cells is high then infected cells (or free virus) are growing fast. Therefore, regarding the density of uninfected cells as control threshold value, we propose another novel model simulating immune boosting and viral suppressing as state feedback control strategies, and investigate its dynamical behaviors. We suppose that, therefore, when the density of uninfected cells x reaches the risk threshold value X_r at time $t_i(X_r)$ at the i-th time, the control strategies are taken and the densities of uninfected cells x and infected cells (or free virus) y turn very suddenly to a great degree to $(1-p)x(t_i(X_r))+\tau$ and $(1-q)y(t_i(X_r))$, respectively, where $p, q \in (0, 1)$, $\tau > 0$, and $(1-p)X_r + \tau < X_r$.

Under the assumption aforementioned, we come to a control model that is governed by the following ordinary differential equation with state feedback control strategies:

$$\left\{\begin{array}{l} \left.\begin{array}{l} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \delta x - \beta xy \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta xy - \mu y \end{array}\right\} x \neq X_r, \\ \left.\begin{array}{l} \triangle x(t) = x(t^+) - x(t) = -px(t) + \tau \\ \triangle y(t) = y(t^+) - y(t) = -qy(t) \end{array}\right\} x = X_r. \end{array}\right. \tag{4}$$

We assume, throughout this paper, that $R_0 = \frac{\lambda\beta}{\mu\delta} > 1$. By the biological background, we only consider models (3) and (4) in the region $\mathbb{R}^2_+ = \{(x, y) : x > 0, y > 0\}$, where the biology makes sense. Obviously, $\mathbb{R}^2_+$ is divided into four domains with vertical isocline $\frac{\mathrm{d}x}{\mathrm{d}t} = 0$ and horizontal isocline $\frac{\mathrm{d}y}{\mathrm{d}t} = 0$, followed by

$$\begin{aligned} I &:= \left\{(x, y) \in R^2_+ : \frac{\mathrm{d}x}{\mathrm{d}t} < 0, \frac{\mathrm{d}y}{\mathrm{d}t} < 0\right\}, \\ II &:= \left\{(x, y) \in R^2_+ : \frac{\mathrm{d}x}{\mathrm{d}t} > 0, \frac{\mathrm{d}y}{\mathrm{d}t} < 0\right\}, \\ III &:= \left\{(x, y) \in R^2_+ : \frac{\mathrm{d}x}{\mathrm{d}t} > 0, \frac{\mathrm{d}y}{\mathrm{d}t} > 0\right\}, \\ IV &:= \left\{(x, y) \in R^2_+ : \frac{\mathrm{d}x}{\mathrm{d}t} < 0, \frac{\mathrm{d}y}{\mathrm{d}t} > 0\right\}. \end{aligned} \tag{5}$$

The global existence and uniqueness of solution for models (3) and (4) are guaranteed by the smoothness of the right-hand sides of models (3) and (4). For more details, we refer to [39].

Lemma 1 *Solutions of models* (3) *and* (4) *with the initial value in the interior of* $\mathbb{R}^2_+$ *at time* $t = t_0 \geq 0$ *are positive.*

The proof of Lemma 1 is obvious, hence we omit it here.

Let $\mathbb{S} \subset \mathbb{R}^2_+$ be a nonempty set and $P_0 \in \mathbb{R}^2_+$ be a point. The distance between P_0 and $\mathbb{S}$ is defined by $\rho(P_0, \mathbb{S}) = \inf_{P\in\mathbb{S}} |P - P_0|$. Let $z(t) = (x(t), y(t))$ be a solution of model (3) starting from initial point $z_0 \in \mathbb{R}^2_+$ at $t = t_0$. We define the positive orbit as follows:

$O^+(z_0, t_0) := \{z(t) = (x(t), y(t)) : t \geq t_0, z(t_0) = z_0\}$.

Definition 1 (*Orbital stability* [40]) A trajectory $O^+(z_0, t_0)$ is said to be orbitally stable if for any given $\varepsilon > 0$, there is a constant $\delta = \delta(\varepsilon) > 0$ such that for any other solution $z^*(t)$ of model (3), $\rho(z^*(t), O^+(z_0, t_0)) < \varepsilon$ for all $t > t_0$ when $\rho(z^*(t_0), O^+(z_0, t_0)) < \delta$.

Definition 2 (*Orbitally asymptotical stability* [40]) A trajectory $O^+(z_0, t_0)$ is said to be orbitally asymptotically stable if it is orbitally stable, and there exists a constant $\eta > 0$ such that for any other solution $z^*(t)$ of model (3), $\lim_{t\to\infty} \rho(z^*(t), O^+(z_0, t_0)) = 0$ when $\rho(z^*(t_0), O^+(z_0, t_0)) < \eta$.

Next, for model (3), let

$$\Gamma_1 := \{(x, y) : x > 0, y = (1 - q)Y_c\}$$

and

$$\Gamma_2 := \{(x, y) : x > 0, y = Y_c\}.$$

For any point $A_0(x_0, Y_c) \in \Gamma_2$, consider $O^+(A_0, t_0)$ starting from point A_0 at time t_0, then $O^+(A_0, t_0)$ jumps to point $A_0^+((1-p)x_0+\tau, (1-q)Y_c)$ on section Γ_1 at $t = t_0^+$ due to control effects $\triangle x(t) = -px(t)+\tau$ and $\triangle y(t) = -qY_c$. Then, trajectory $O^+(A_0, t_0)$ intersects section Γ_2 at point $A_1(x_1, Y_c)$ again. Therefore, we can define a Poincaré map on section Γ_2 as follows:

$$x_1 = F_1(x_0, p, q, \tau, Y_c) := F_1(x_0). \tag{6}$$

Furthermore, we can define $x_2 = F_1(x_1) = F_1^2(x_0)$, $\ldots, x_k = F_1(x_{k-1}) = F_1(F_1^{k-1}(x_0)) = F_1^k(x_0), \ldots$.

Definition 3 A trajectory $O^+(A_0, t_0)$ of model (3) is said to be order-k periodic if there exists a positive integer $k \geq 1$ such that k is the smallest integer for $F_1^k(x_0) = x_0$.

Similarly, we can define two sections to model (4) by

$$\Gamma_3 := \{(x, y) : x = (1 - p)X_r + \tau, y > 0\},$$
$$\Gamma_4 := \{(x, y) : x = X_r, y > 0\}$$

and a Poincaré map on section Γ_4

$$y_1 = F_2(y_0, p, q, \tau, X_r) := F_2(y_0). \tag{7}$$

Next, we consider the following autonomous system with pulse effects:

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = f(x, y), & \dfrac{\mathrm{d}y}{\mathrm{d}t} = g(x, y), & \varphi(x, y) \neq 0, \\ \triangle x = \xi(x, y), & \triangle y = \eta(x, y), & \varphi(x, y) = 0, \end{cases} \tag{8}$$

where f and g are continuous differentiable functions defined on $\mathbb{R}^2$ and φ is a sufficiently smooth function with $\mathrm{grad}\varphi \neq 0$. Let $(\mu(t), \nu(t))$ be a positive T-periodic solution of system (8). The following result comes from Corollary 2 of Theorem 1 of [41].

Lemma 2 (Analog of Poincaré criterion) *If the Floquet multiplier μ satisfies $|\mu| < 1$, where*

$$\mu = \prod_{j=1}^{n} \kappa_j \exp\left\{\int_0^T \left[\frac{\partial f}{\partial x}(\mu(t), \nu(t)) + \frac{\partial g}{\partial y}(\mu(t), \nu(t))\right] \mathrm{d}t\right\}$$

with

$$\kappa_j = \frac{1}{\frac{\partial \varphi}{\partial x} f + \frac{\partial \varphi}{\partial y} g}\left[\left(\frac{\partial \eta}{\partial y}\frac{\partial \varphi}{\partial x} - \frac{\partial \eta}{\partial x}\frac{\partial \varphi}{\partial y} + \frac{\partial \varphi}{\partial x}\right) f_+ + \left(\frac{\partial \xi}{\partial x}\frac{\partial \varphi}{\partial y} - \frac{\partial \xi}{\partial y}\frac{\partial \varphi}{\partial x} + \frac{\partial \varphi}{\partial y}\right) g_+\right] \tag{9}$$

and f, g, $\frac{\partial \xi}{\partial x}$, $\frac{\partial \xi}{\partial y}$, $\frac{\partial \eta}{\partial x}$, $\frac{\partial \eta}{\partial y}$, $\frac{\partial \varphi}{\partial x}$, and $\frac{\partial \varphi}{\partial y}$ have been calculated at the point $(\mu(\tau_j), \nu(\tau_j))$, $f_+ = f(\mu(\tau_j^+), \nu(\tau_j^+))$, $g_+ = g(\mu(\tau_j^+), \nu(\tau_j^+))$, and τ_j $(j \in N)$ is the time of the j-th jump, then (μ, ν) is orbitally asymptotically stable.

3 Analysis of the virus dynamics model (3)

Since virus equilibrium (x^*, y^*) is globally asymptotically stable for model (1), any solution of model (3) without state feedback control strategy will eventually tend to (x^*, y^*). If $Y_c \leq y^*$, we easily see that trajectory of model (3) with initial value $(x_0, y_0) \in \Gamma_1$ will intersect section Γ_2 infinitely many times, and when $Y_c > y^*$, then trajectory of model (3) starting from point $(x_0, y_0) \in \Gamma_1$ may intersect section Γ_2 finitely many times. Therefore, in this section, we give some sufficient conditions for the existence and stability of positive periodic solutions in two cases of $Y_c \leq y^*$ and $Y_c > y^*$, respectively.

3.1 Case $Y_c \le y^*$

The following result is on the existence of positive order-1 periodic solution.

Theorem 1 *For any $p, q \in (0,1)$, and $\tau > 0$, model (3) admits a positive order-1 periodic solution.*

Proof For point $A_0^+(x_0, (1-q)Y_c) \in \Gamma_1$ in domain *II* with $x_0 \le (1-p)\frac{\mu}{\beta}$, in view of the properties (5) of the phase space of model (3), trajectory $O^+(A_0^+, t_0)$ of model (3) will enter into domain *III* or in succession enter into domain *IV* and finally intersect Γ_2 at point $A_1(x_1, Y_c)$. Therefore, we have $x_1 > \frac{\mu}{\beta}$. At point A_1, trajectory $O^+(A_0^+, t_0)$ jumps to point $A_1^+((1-p)x_1+\tau, (1-q)Y_c)$ on section Γ_1 due to state feedback control strategies. Furthermore, trajectory $O^+(A_0^+, t_0)$ intersects section Γ_2 at point $A_2(x_2, Y_c)$.

From the facts $x_0 \le (1-p)\frac{\mu}{\beta}$ and $x_1 > \frac{\mu}{\beta}$, then $x_0 < (1-p)x_1 + \tau$. It follows that point A_0^+ is left point A_1^+. We claim that point A_1 is right point A_2. In fact, if point A_1 is left point A_2 or the two points coincide, then orbits $\overset{\frown}{A_0^+A_1}$ and $\overset{\frown}{A_1^+A_2}$ must intersect at a point (x^0, y^0). This shows that there are two different solutions which start from this point. It contradicts with the uniqueness of solution for model (3). Therefore, by Poincaré map (6), it follows that

$$x_2 - x_1 = F_1(x_0) - x_1 < 0. \tag{10}$$

On the other hand, for the intersection $B_0^+(\frac{\mu}{\beta}, (1-q)Y_c)$ of line $L_1 : \beta x - \mu = 0$ and section Γ_1, trajectory $O^+(B_0^+, t_0)$ intersects section Γ_2 at point $B_1(\hat{x}_1, Y_c)$ and then jumps to point $B_1^+((1-p)\hat{x}_1+\tau, (1-q)Y_c)$ on section Γ_1 and finally reaches point $B_2(\hat{x}_2, Y_c)$ on section Γ_2 again. If there is a positive constant τ^* such that $(1-p)\hat{x}_1 + \tau^* = \frac{\mu}{\beta}$, then B_1^+ coincides with point B_0^+ for $\tau = \tau^*$; that is, point B_1 coincides with point B_2. Otherwise, point B_1^+ is left point B_0^+ due to $(1-p)\hat{x}_1+\tau < \frac{\mu}{\beta}$ for $\tau \in (0, \tau^*)$ and is right point B_0^+ due to $(1-p)\hat{x}_1 + \tau > \frac{\mu}{\beta}$ for $\tau > \tau^*$. Further, from the properties (5) of phase space of model (3), point B_2 is right point B_1 for any $\tau \in (0, \tau^*) \cup (\tau^*, +\infty)$. Namely, $\hat{x}_2 > \hat{x}_1$ for this case.

Thus, from the above discussion, we get that

(i) if $\hat{x}_1 = \hat{x}_2$, then model (3) has a positive order-1 periodic solution;
(ii) if $\hat{x}_2 > \hat{x}_1$, then

$$\hat{x}_2 - \hat{x}_1 = F_1(\hat{x}_1) - \hat{x}_1 > 0. \tag{11}$$

By (10) and (11), it follows that Poincaré map (6) has a fixed point. This amounts to saying that model (3) has a positive order-1 periodic solution. This completes the proof.

Let $(\phi(t), \psi(t))$ be a positive order-1 periodic solution of model (3) with period T. On the orbital stability of solution $(\phi(t), \psi(t))$ of model (3), we have the following Theorem 2.

Theorem 2 *If*

$$\kappa = \left|(1-p)\frac{\beta[(1-p)\phi(T)+\tau]-\mu}{\beta\phi(T)-\mu}\right| \times \exp\left\{-\int_0^T [\delta + \beta\psi(t)]\,\mathrm{d}t\right\} < 1, \tag{12}$$

then $(\phi(t), \psi(t))$ is orbitally asymptotically stable.

Proof Suppose that $(\phi(t), \psi(t))$ intersects the sections Γ_1 and Γ_2 at points $C^+((1-p)\phi(T)+\tau, (1-q)Y_c)$ and $C(\phi(T), Y_c)$, respectively. Comparing with system (8), we have

$$f(x,y) = \lambda - \delta x - \beta xy, \quad g(x,y) = \beta xy - \mu y,$$

$\xi(x,y) = -px+\tau, \eta(x,y) = -qy, \varphi(x,y) = y - Y_c$, $(\phi(T), \psi(T)) = (\phi(T), Y_c)$, and $(\phi(T^+), \psi(T^+)) = ((1-p)\phi(T)+\tau, (1-q)Y_c)$. Thus,

$$\frac{\partial f}{\partial x} = -\delta - \beta y, \quad \frac{\partial g}{\partial y} = \beta x - \mu, \quad \frac{\partial \xi}{\partial x} = -p, \tag{13}$$

and

$$\frac{\partial \eta}{\partial y} = -q, \quad \frac{\partial \varphi}{\partial y} = 1, \quad \frac{\partial \xi}{\partial y} = \frac{\partial \eta}{\partial x} = \frac{\partial \varphi}{\partial x} = 0. \tag{14}$$

Furthermore, it follows from (13), (14), and (9) that

$$\kappa = \frac{(1-p)g(\phi(T^+), \psi(T^+))}{g(\phi(T), \psi(T))} = (1-p)(1-q)\frac{\beta[(1-p)\phi(T)+\tau]-\mu}{\beta\phi(T)-\mu} \tag{15}$$

and

$$\mu = \kappa \exp\left\{\int_0^T [-\delta - \beta\psi(t) + (\beta\phi(t) - \mu)]\,\mathrm{d}t\right\}. \tag{16}$$

On the other hand, integrating both sides of the second equation of model (3) along the orbit $\widetilde{C^+C}$ gives

$$\ln\frac{1}{1-q}=\int_{(1-q)Y_c}^{Y_c}\frac{\mathrm{d}y}{y}=\int_0^T(\beta x-\mu)\,\mathrm{d}t$$
$$=\int_0^T[\beta\phi(t)-\mu]\,\mathrm{d}t. \tag{17}$$

From (15)–(17), we obtain

$$|\mu|=\left|(1-p)(1-q)\frac{\beta[(1-p)\phi(T)+\tau]-\mu}{\beta\phi(T)-\mu}\right|$$
$$\times\frac{1}{1-q}\exp\left\{-\int_0^T[\delta+\beta\psi(t)]\,\mathrm{d}t\right\}$$
$$=\left|(1-p)\frac{\beta[(1-p)\phi(T)+\tau]-\mu}{\beta\phi(T)-\mu}\right|$$
$$\times\exp\left\{-\int_0^T[\delta+\beta\psi(t)]\,\mathrm{d}t\right\}.$$

By condition (12), we know that model (3) satisfies all conditions of Lemma 2. It then follows from Lemma 2 that the order-1 periodic solution $(\phi(t),\psi(t))$ of model (3) is orbitally asymptotically stable. This completes the proof.

Remark 2 Generally, the condition (12) of Theorem 2 is not easy to test since the expression of periodic solution $(\phi(t),\psi(t))$ is unknown. We note that, however, it is also weaker since the exponent term of condition (12) is less than 1.

The following corollary is a direct consequence of Theorem 2.

Corollary 1 *Let $(\phi(t),\psi(t))$ be a positive order-1 periodic solution of model (3) with periodic T. If*

$$\left|(1-p)\frac{\beta[(1-p)\phi(T)+\tau]-\mu}{\beta\phi(T)-\mu}\right|\exp\{-\delta T\}<1,$$

then $(\phi(t),\psi(t))$ is orbitally asymptotically stable.

3.2 Case $Y_c > y^*$

As already mentioned above, this case $Y_c > y^*$ is complex since the virus equilibrium (x^*, y^*) of model (1) is globally asymptotically stable. Additionally, since control measures are aimed at reducing the density of infected cells (or free virus) y, we suppose that $(1-q)Y_c < y^*$. We now have the following result on the existence and orbital stability of positive order-k periodic solution of model (3) with $Y_c > y^*$.

Theorem 3 *For any $p, q \in (0,1)$, and $\tau > 0$, one of the following statements is valid.*

(a) If there is a positive constant $\hat{x} = \hat{x}(Y_c) \in (0, x^*]$ such that trajectory $O^+(E_0, t_0)$ of model (3) starting from point $E_0(\hat{x}, (1-q)Y_c)$ is tangent to line $L: y = Y_c$ at point $(\frac{\mu}{\beta}, Y_c)$ and $(1-p)\frac{\lambda}{\delta}+\tau < \hat{x}$, then model (3) has a positive order-1 or order-2 periodic solution, which is orbitally asymptotically stable.

(b) Suppose that for any $x \in (0, x^*]$, trajectory $O^+(A_0, t_0)$ of model (3) starting from the initial point $A_0(x_0, (1-q)Y_c)$ cuts line $L: y = Y_c$ at point $B(\hat{x}_0, Y_c)$, where $\hat{x}_0 \geq x^*$. Further, if $(1-p)\frac{\lambda}{\delta}+\tau < x^*$, then model (3) has a positive order-1 or order-2 periodic solution, which is orbitally asymptotically stable.

(c) Suppose that for any $x \in (0, x^*]$, trajectory $O^+(F, t_0)$ of model (3) starting from point $F(x, (1-q)Y_c)$ does not intersect with line $L: y = Y_c$. Further, if $(1-p)\frac{\lambda}{\delta}+\tau < x^*$, then model (3) has no positive order-k ($k \geq 1$) periodic solution and the virus equilibrium (x^*, y^*) is globally asymptotically stable.

Proof We first prove conclusion (a). Suppose that there is a positive constant $\hat{x} = \hat{x}(Y_c) \in (0, x^*]$ such that trajectory $O^+(E_0, t_0)$ of model (3) starting from point $E_0(\hat{x}, (1-q)Y_c)$ crosses section Γ_1 at point $E_{0p}(\hat{x}_1, (1-q)Y_c)$ and is tangent to line $y = Y_c$ at point $E_1(\frac{\mu}{\beta}, Y_c)$. Then trajectory starting from point $(x, (1-q)Y_c)$ with $x \in (\hat{x}, x^*)$ will tend to virus equilibrium (x^*, y^*) and not intersect with section Γ_2. Moreover, since $(1-p)\frac{\lambda}{\delta}+\tau < \hat{x}$, then $(1-p)x+\tau < \hat{x}$ for any point $(x, Y_c) \in \Gamma_2$ and $x < \frac{\lambda}{\delta}$. Therefore, for any $E(x, Y_c) \in \Gamma_2$ and $x < \frac{\lambda}{\delta}$, trajectory $O^+(E, t_0)$ starting from point $E(x, Y_c)$ will intersect with Γ_2 infinitely many times due to state feedback control strategies $\triangle x = -px(t)+\tau$ and $\triangle y(t) = -qY_c$.

Considering any two points $D_i(x_i, Y_c)$ and $D_j(x_j, Y_c)$ on section Γ_2, where $x_i, x_j \in (0, \frac{\delta}{\lambda})$, and $x_i < x_j$, it is obviously that point $D_i^+((1-p)x_i+\tau, (1-q)Y_c)$ is left point $D_j^+((1-p)x_j+\tau, (1-q)Y_c)$ in view of control strategies $(1-p)x_i+\tau < (1-p)x_j+\tau <$

$\hat{x}$. Further, trajectories $O^+(D_i, t_0)$ and $O^+(D_j, t_0))$ intersect section Γ_2 at points $D_{i+1}(x_{i+1}, Y_c)$ and $D_{j+1}(x_{j+1}, Y_c)$, respectively. We claim that

$$x_{j+1} < x_{i+1}. \tag{18}$$

In fact, if (18) is false, that is $x_{j+1} \geq x_{i+1}$, then point $D_{j+1}(x_{j+1}, Y_c)$ is right point $D_{i+1}(x_{i+1}, Y_c)$, or the two points coincide. So it follows that trajectories $O^+(D_i, t_0)$ and $O^+(D_j, t_0)$ intersect at a point $(\hat{x}, \hat{y})$. This implies that there are two different solutions which start from the point $(\hat{x}, \hat{y})$, which contradicts the uniqueness of solution. Inequality (18) is thus valid.

Suppose that trajectory $O^+(C_0, t_0)$ of model (3) starting from point $C_0(x_0, Y_c)$ $(x_0 < \frac{\lambda}{\delta})$ on section Γ_2 jumps to point $C_0^+((1-p)x_0+\tau, (1-q)Y_c)$ on section Γ_1, and reaches section Γ_2 at point $C_1(x_1, Y_c)$ again due to the fact $(1-p)\frac{\lambda}{\delta} + \tau < \tilde{x}$, where $x_1 \in (x^*, \frac{\lambda}{\delta})$ and then jumps to point $C_1^+((1-p)x_1 + \tau, Y_c)$ at section Γ_1. At state C_1^+, trajectory $O^+(C_0, t_0)$ intersects section Γ_2 at point $C_2(x_2, Y_c)$, where $x_2 \in (x^*, \frac{\lambda}{\delta})$. By the Poincaré map (6) of section Γ_2, it follows that $x_1 = F_1(x_0)$ and $x_2 = F_1^2(x_0)$. Repeating the above process, we have $x_{n+1} = F_1^n(x_0)$ $(n = 0, 1, \ldots)$. Particularly, model (3) has a positive order-1 periodic solution when $x_0 = x_1$ and a positive order-2 periodic solution when $x_0 \neq x_1$ and $x_0 = x_2$.

Now, we consider the general situation for $x_0 \neq x_1 \neq x_2 \neq \cdots \neq x_k$ $(k > 2)$. On the relation of x_0, x_1, and x_2, there are the following two different cases.

(C1) $x_0 < x_1$

In this case, we can get from (18) that $x_1 > x_2$. This results in the relation of x_0, x_1, and x_2 to be one of the following two cases.

(i) $x_2 < x_0 < x_1$

In this case, $x_3 > x_1 > x_2$ by (18). Repeating the above process, we have

$$x^* < \cdots < x_{2k} < \cdots < x_0 < x_1 < \cdots < x_{2k+1} < \cdots < \frac{\lambda}{\delta}.$$

(ii) $x_0 < x_2 < x_1$

Similar to (i), we have

$$x_0 < x_2 < \cdots < x_{2k} < \cdots < x_{2k+1} < \ldots < x_1 < \frac{\lambda}{\delta}.$$

(C2) $x_0 > x_1$.

In this case, it follows from (18) that $x_1 < x_2$. This results in the relation of x_0, x_1, and x_2 to be one of two cases.

(iii) $x_1 < x_0 < x_2$

In this case, $x_2 > x_1 > x_3$ by (18). Repeating the above process, we have

$$x^* < \cdots < x_{2k+1} < \cdots < x_0 < \cdots < x_{2k} < \cdots < \frac{\lambda}{\delta}.$$

(iv) $x_1 < x_2 < x_0$

Similar to (iii), we have

$$x^* < x_1 < \cdots < x_{2k+1} < \cdots < x_{2k} < \cdots < x_2 < x_0.$$

Further, in (i) of case (C1), we have $\lim_{k\to\infty} x_{2k} = \theta_*$ and $\lim_{k\to\infty} x_{2k+1} = \theta^*$, where $x^* < \theta_* < \theta^* < \frac{d}{\lambda}$. Hence $\theta_* = F_1(\theta^*)$ and $\theta^* = F_1(\theta_*)$. So model (3) has an orbitally asymptotically stable positive order-2 periodic solution. Similarly, in (ii) of case (C1) and (iv) of case (C2), model (3) has an orbitally asymptotically stable positive order-1 periodic solution. In (iii) of case (C2), model (3) has an orbitally asymptotically stable positive order-2 periodic solution. This proves (a).

Next, we prove conclusion (b). If for any $x_0 \in (0, x^*]$, trajectory $O^+(A_0, t_0)$ of model (3) starting from initial point $A_0(x_0, (1-q)Y_c)$ cuts the line $L : y = Y_c$ at point $A_1(x_1, Y_c)$, where $x^* < x_1 < \frac{\lambda}{\delta}$, then for any $E(x, Y_c) \in \Gamma_2$, trajectory $O^+(E, t_0)$ will intersect with section Γ_2 infinitely many times due to state feedback control strategies and the fact $(1-p)\frac{\lambda}{\delta} + \tau < x^*$. Similar to conclusion (a), we can also obtain that model (3) has a positive order-1 or order-2 periodic solution, which is orbitally asymptotically stable. Conclusion (b) thus follows.

Finally, we turn to (c). If for any $x \in (0, x^*]$, the trajectory $O^+(G, t_0)$ of model (3) starting from point $G(x, (1-q)Y_c)$ does not intersect with line $L : y = Y_c$, then trajectory starting from point $(x, (1-q)Y_c)$ of section Γ_1 with $x \in (0, x^*]$ will tend to virus equilibrium (x^*, y^*) and not intersect with section Γ_2. Furthermore, any other trajectory intersects section Γ_2 at most finitely many times, and then tends to virus equilibrium (x^*, y^*) due to $(1-p)\frac{\lambda}{\delta} + \tau < x^*$. In this case, model (3) has no positive order-k $(k \geq 1)$ periodic solution and virus equilibrium (x^*, y^*) is globally asymptotically stable. This is (c). This completes the proof.

Remark 3 From conclusion (a) of Theorem 3, we note that $(1-p)\frac{\lambda}{\delta} < \hat{x}$ is a sufficient condition for system (3) to have a positive order-1 or order-2 periodic solution.

Remark 4 Conclusion (c) of Theorem 3 shows that the state feedback control strategies are invalid when the controlled strengths p, q, and τ remain at a relatively low level and threshold value Y_c is greater than y^*.

4 Analysis of the virus dynamics model (4)

Similar to Sect. 3, we also divided two cases to give some sufficient conditions for the existence and stability of periodic solutions for model (4).

4.1 Case of $X_r \le x^*$

The following result is on the extinct of y.

Theorem 4 *For any solution $(x(t), y(t))$ of model (4) with initial condition $(x_0, y_0) \in R_+^2$, if $x_0 \le X_r$ then $\lim_{t\to\infty} y(t) = 0$.*

Proof Suppose that $(x(t), y(t))$ be any solution of model (4) with initial value $(x_0, y_0) \in \mathbb{R}_+^2$ and $x_0 \le X_r$. Since any trajectory of model (4) starting from domain I will enter into domain II , where I and II are given by (5), solution $(x(t), y(t))$ must intersect with section Γ_4 at a point $A(X_r, y_1)$, and then jump to section γ_3 at point $A^+((1-q)X_r+\tau, (1-q)y_1)$ due to state feedback control strategies. Obviously,

$$0 < y_1 < \frac{\lambda - \delta[(1-p)X_r + \tau]}{\beta[(1-p)X_r + \tau]} := \omega.$$

So we consider only trajectories which start from points $(x_0, y_0) \in \Gamma_3$ and $y_0 \le \omega$.

Suppose that trajectory $O^+(E_0, t_0)$ of model (4) starting from point $E_0((1-p)X_r+\tau, y_0)$ (where $0 < y_0 \le \omega$) first intersect section Γ_4 at point $E_1(X_r, y_1)$ and then jumps to point $E_1^+((1-p)X_r+\tau, y_1^+)$ on section Γ_3 due to control strategies, and reaches section Γ_4 at point $E_2(X_r, y_2)$ again, where $y_1, y_2 \in (0, \frac{\lambda-\delta X_r}{\beta X_r})$. Repeating the above process, we can get two point sequences $\{E_n^+((1-p)X_r+\tau, y_n^+)\}$ and $\{E_n(X_r, y_n)\}$, where $y_n^+ = (1-q)y_n$. The corresponding impulsive time sequences are marked by $\{t_n\}$.

Integrating both sides of the first equation of model (4) from the orbit $\widetilde{E_n^+ E_{n+1}}$ we have

$$t_{n+1} - t_n \ge \int_{(1-p)X_r+\tau}^{X_r} \frac{\mathrm{d}x}{\lambda - \delta x} = \frac{1}{\delta}\ln\left(\frac{\lambda - \delta(1-p)X_r - \delta\tau}{\lambda - \delta X_r}\right) > 0. \tag{19}$$

Further, integrating both sides of the second equation of model (4) from the orbit $\widetilde{E_n^+ E_{n+1}}$, we can get

$$\int_{y_n^+}^{y_{n+1}} \frac{\mathrm{d}y}{y} = \int_{t_n}^{t_{n+1}} (\beta x - \mu)\,\mathrm{d}t \le \int_{t_n}^{t_{n+1}} (\beta X_r - \mu)\,\mathrm{d}t.$$

This together with (19) shows that

$$\begin{aligned} y_{n+1} &\le y_n^+ \left(\frac{\lambda - \delta(1-p)X_r - \delta\tau}{\lambda - \delta X_r}\right)^{\frac{\beta X_r - \mu}{\delta}} \\ &= (1-q)y_n \left(\frac{\lambda - \delta(1-p)X_r - \delta\tau}{\lambda - \delta X_r}\right)^{\frac{\beta X_r - \mu}{\delta}}. \end{aligned}$$

From the above recursive formula, it can be easily shown that

$$y_{n+1} \le (1-q)^n y_1 \left(\frac{\lambda - \delta(1-p)X_r - \delta\tau}{\lambda - \delta X_r}\right)^{\frac{n(\beta X_r - \mu)}{\delta}}.$$

This results in $\lim_{n\to\infty} y_n = 0$, where we used the facts $(1-p)X_r + \tau < X_r$ and $\beta X_r - \mu < 0$. Moreover, $\lim_{t\to\infty} y(t) = 0$. This completes the proof.

Let $y \equiv 0$ for $t \in [0, \infty)$ in model (4), we can get the following reduce model

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - \delta x(t), & x \ne X_r, \\ \triangle x(t) = -px(t) + \tau, & x = X_r. \end{cases} \tag{20}$$

It can be easy to calculate that model (20) has a T periodic solution which is given by

$$x(t) = \frac{\lambda e^{\delta(t-nT)} - \lambda + \delta[(1-p)X_r + \tau]}{\delta e^{\delta(t-nT)}}$$

for all $nT < t \le (n+1)T$, where

$$T = \frac{1}{\delta}\ln\left\{\frac{\lambda - \delta[(1-p)X_r + \tau]}{\lambda - \delta X_r}\right\},$$

$x(0) = (1-p)X_r + \tau$ and $x(T) = X_r$. This means that model (4) has the following semi-trivial periodic solution for $nT < t \le (n+1)T$ $(n = 0, 1, 2, \ldots)$

$$\begin{cases} \phi(t) = \dfrac{\lambda e^{\delta(t-nT)} - \lambda + \delta[(1-p)X_r + \tau]}{\delta e^{\delta(t-nT)}}, \\ \psi(t) = 0. \end{cases} \tag{21}$$

On the stability of this semi-trivial periodic solution, we have the following Theorem 5.

Theorem 5 *For any $p, q \in (0,1)$, $\tau > 0$, and $X_r \le x^*$, the semi-trivial periodic solution (21) is orbitally asymptotically stable.*

Proof Suppose that $(\widetilde{x}(t), \widetilde{y}(t))$ is a solution of of small-amplitude perturbation of periodic solution $(\phi(t), \psi(t))$ with initial value $(\widetilde{x}(0), \widetilde{y}(0)) = ((1-p)X_r + \tau, \widetilde{y}_0)$, which first intersects section Γ_4 at point $(X_r, \widetilde{y}_1)$ and then jumps to point $((1-p)X_r + \tau, \widetilde{y}_1^+)$. Further, solution $(\widetilde{x}(t), \widetilde{y}(t))$ intersects section Γ_4 at point $(X_r, \widetilde{y}_2)$ again. Repeating the above process, we have two point sequences $\{((1-p)X_r + \tau, \widetilde{y}_n^+)\}$ and $\{(X_r, \widetilde{y}_n)\}$, where $\widetilde{y}_n^+ = (1-q)\widetilde{y}_n$. Further, by Theorem 4, it is clear that $\lim_{t\to\infty} \widetilde{y}(t) = 0$. This shows that semi-trivial periodic solution (21) is orbitally asymptotically stable. This completes the proof.

4.2 Case of $x^* < X_r < \frac{\lambda}{\delta}$

From the properties (5) of the phase space of model (4), we know that there a point $E_0((1-p)X_r + \tau, \gamma)$ such that trajectory $O^+(E_0, t_0)$ is tangent to the section Γ_4 at the intersection $E_1(X_r, \frac{\lambda - \delta X_r}{\beta X_r})$ of section Γ and isocline $\frac{dx}{dt} = 0$, where $\gamma = \gamma(X_r, p, \tau)$.

If $(1-q)\frac{\lambda - \delta X_r}{\beta X_r} < \gamma$, then trajectory $O^+(E, t_0)$ starting from point $E(X_r, y)$ (where $y \le \frac{\lambda - \delta X_r}{\beta X_r}$) will intersect with Γ_4 infinitely many times due to control strategies $\triangle x = -pX_r + \tau$ and $\triangle y(t) = -qy(t)$.

For any two points $E_i(X_r, y_i)$ and $E_j(X_r, y_j)$ on section Γ_4, where $y_i, y_j \in (0, \frac{\lambda - \delta X_r}{\beta X_r})$, and $y_i < y_j$, in view of control strategies, $E_i^+((1-p)X_r + \tau, (1-q)y_i)$ is on below $E_j^+((1-p)X_r + \tau, (1-q)y_j)$. Namely, $(1-q)y_i < (1-q)y_j$. It implies that

$$0 < y_{i+1} < y_{j+1} < \frac{\lambda - \delta X_r}{\beta X_r}. \tag{22}$$

Similar to the discussion of Theorem 3, we give the following result on the existence and orbital stability of periodic solution.

Theorem 6 *For any $p, q \in (0,1)$, $\tau > 0$, and $X_r > x^*$, if*

$$(1-q)\frac{\lambda - \delta X_r}{\beta X_r} < \gamma = \gamma(X_r, p, \tau),$$

then model (4) admits an order-1 periodic solution which is orbitally asymptotically stable.

Remark 5 We want to make clear that the order-1 periodic solution in Theorem 6 may be a positive periodic solution, or it may also be a semi-trivial periodic solution by condition (22).

5 Numerical simulation and discussion

To illustrate the theoretical results and the feasibility of state control strategies, we perform numerical simulations for different control parameters p, q, τ, Y_c, and X_r using the software MATLAB. We fixed parameters as those in papers [4,8,11] with $\lambda = 50$, $\delta = 0.1$, $\beta = 0.002$, and $\mu = 0.5$ in model (1). It is easy to calculate that model (1) has a unique globally asymptotically stable virus equilibrium $(x^*, y^*) = (250, 50)$, which is illustrated here by the blue line in Fig. 1a.

Firstly, we choose the control parameters to be $p = 0.3$, $q = 0.5$, $\tau = 50$, and $Y_c = 45 < y^*$, respectively. Using Theorem 1, we know that model (3) has a positive order-1 periodic solution $(\phi(t), \psi(t))$ which is shown by red line in Fig. 1a. At the same time, Fig. 1a also shows that the periodic solution starting from the initial point $(\phi(0), \psi(0)) = (251.8965, 22.5000)$. Further, by the condition of Corollary 1, it can be easily shown that

$$\begin{aligned} |\mu| &= \left|(1-p)\frac{\beta[(1-p)\phi(T) + \tau] - \mu}{\beta\phi(T) - \mu}\right| e^{-\delta T} \\ &= 0.7 \times \frac{0.002 \times 251.8965 - 0.5}{0.002 \times 288.4236 - 0.5} \times e^{-0.1T} < 1. \end{aligned}$$

Therefore, it follows that $(\phi(t), \psi(t))$ is orbitally asymptotically stable by Corollary 1, which is shown in Fig. 1b.

Further, we fixed the values of q, τ, and Y_c as mentioned before and choose p to be 0.2, 0.4, 0.6, and 0.8, respectively. Numerical simulations show that the density of y can be controlled within a certain limit and the period T of order-1 periodic solution for model (3) increases with the increase of immune strength p, which is shown in Fig. 2a. The similar numerical results are presented in Fig. 2b.

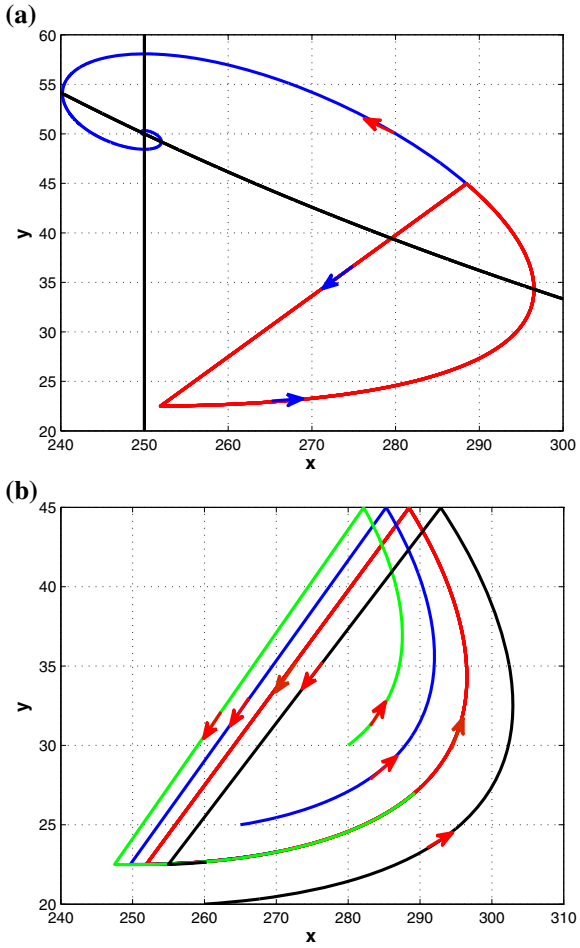

Fig. 1 The existence and orbital asymptotical stability of order-1 periodic solution of model (3) with $p = 0.3$, $q = 0.5$, $\tau = 50$, and $Y_c = 45 < y^*$: **a** the blue line shows that equilibrium (x^*, y^*) of model (3) without control is globally asymptotically stable, the red line shows the existence of periodic solution of model (3); **b** the orbitally asymptotical stability

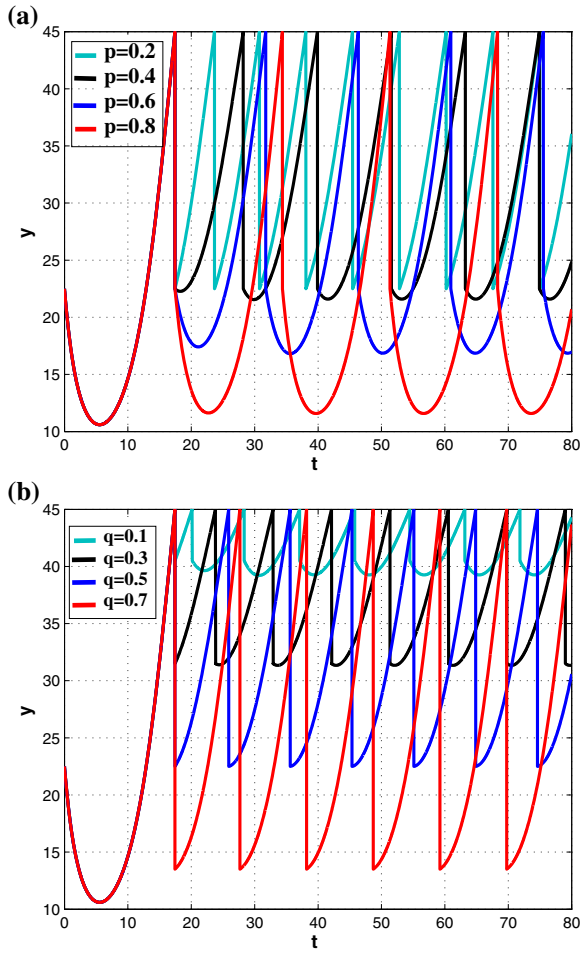

Fig. 2 The trajectories of model (3) with $\tau = 50$, $Y_c = 45$, and **a**: $q = 0.5$, $p = 0.2$, 0.4, 0.6, and 0.8, respectively; **b** $p = 0.3$, $q = 0.1$, 0.3, 0.5, and 0.7, respectively

Secondly, let $p = 0.3$, $q = 0.5$, $\tau = 50$, and $Y_c = 55 > y^*$; it is easy to see that model (3) has a positive locally orbitally asymptotically stable order-1 periodic solution by parts (a) or (b) of Theorem 3, which is shown in Fig. 3. However, we only change model parameter $Y_c = 56$, and fixed $x(0) = 250$ and $y(0) \in [5, 35]$, it can be found that the attraction domains of positive order-1 periodic solution and virus equilibrium appear alternately from Fig. 4. It is different from the case of $Y_c = 55$. Therefore, the value of control threshold value Y_c plays an important role in the treatment of various diseases.

Further, we fixed $Y_c = 55$, $q = 0.5$, and $\tau = 50$ and change the control strength p to be 0.35, 0.45, 0.55, 0.65, and 0.75, respectively. Numerical simulations in Fig. 5 show that trajectories intersect with section Γ_2 finitely many times and then tend to virus equilibrium (x^*, y^*) when p is small, but trajectories intersect with section Γ_2 infinitely many times and model has a orbitally asymptotically stable periodic solution with increase of parameter p. The plots in Fig. 5 show also that control strength p has only a small effect on the periodic of treatment cycle. Similar results can be obtained if we choose q as a control parameter. However, if we fixed $Y_c = 55$, $p = 0.3$, $q = 0.5$, and change the control strength τ to be 120, 80, 40, and 0, respectively. As shown in Fig. 6, the periodic of treatment cycle decrease as control strength τ increases. This implies that when we reduce the concentration

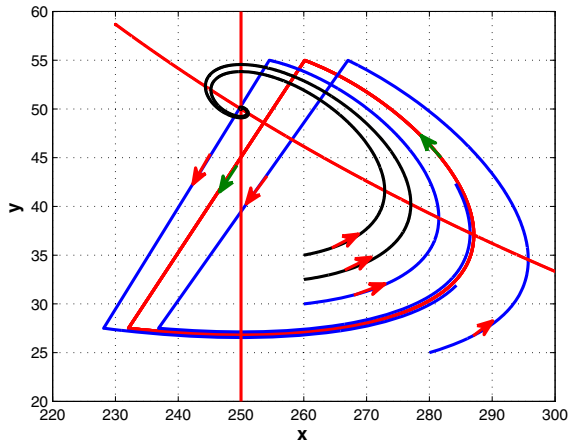

Fig. 3 The existence and orbital asymptotical stability of order-1 periodic solution of model (3) with $p = 0.3$, $q = 0.5$, $\tau = 50$, and $Y_c = 55 > y^*$

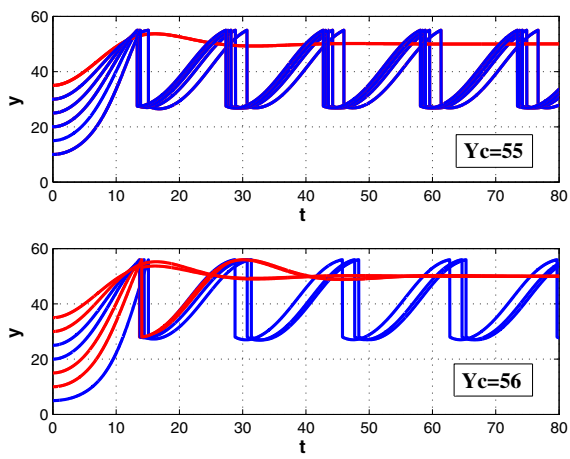

Fig. 4 Comparison of control threshold values $Y_c = 55$ with $Y_c = 56$, where $p = 0.3$, $q = 0.5$, and $\tau = 50$

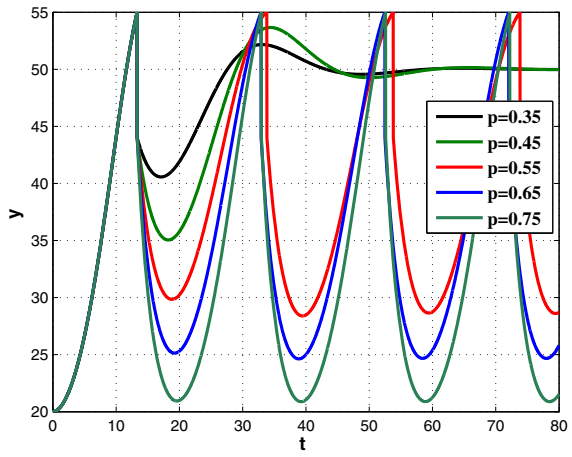

Fig. 5 The effect of control strength p for the dynamical behaviors of model (3) with $Y_c = 55$, $q = 0.5$, and $\tau = 50$

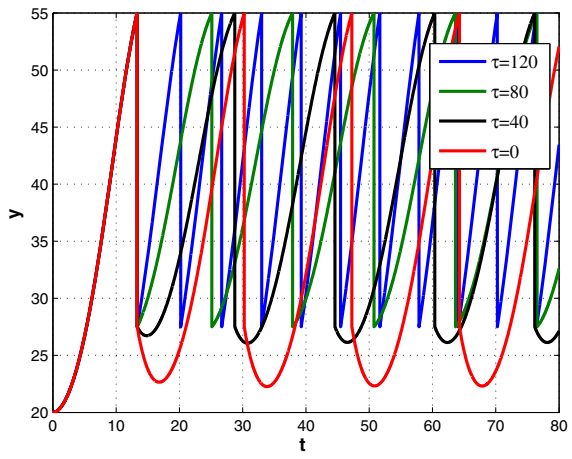

Fig. 6 The effect of control strength τ for the dynamical behaviors of model (3) with $Y_c = 55$, $p = 0.3$, and $q = 0.5$

of infected cells (or free virus) we also should reasonably control the concentration of uninfected cells in the course of treating disease because the high concentrations of uninfected cells will promote the growth of infected cells (or free virus).

Thirdly, we discuss the existence and stability of semi-trivial periodic solution of model (4). Here, we choose $p = 0.3$, $q = 0.5$, $\tau = 5$, and $X_r = 250 = x^*$. By Theorem 5, it follows that model (4) has a orbitally asymptotically stable semi-trivial periodic solution, which are shown in Fig. 7. Theoretical results and numerical simulations show clearly that infected cells (or free virus) y dies out if we control the density of uninfected cells x within a certain range. It also provides theoretical basis for finding a new measure to prevent the spread of virus disease. In fact, this is also consistent with the results in [42], where Ross proposed a mathematical model to study the spread between human beings and mosquitoes for malaria in earlier 1911. A concept of threshold density is introduced and it is concluded that "$\cdots$ *in order to counteract malaria anywhere we need not banish Anopheles there entirely–we need only to reduce their numbers below a certain figure.*"

Finally, fixing $p = 0.5$, $\tau = 10$, and $X_r = 350 > x^*$, model (4) has an orbitally asymptotical stability of positive order-1 periodic solution when $q = 0.4385$ as shown in Fig. 8. At the same time,

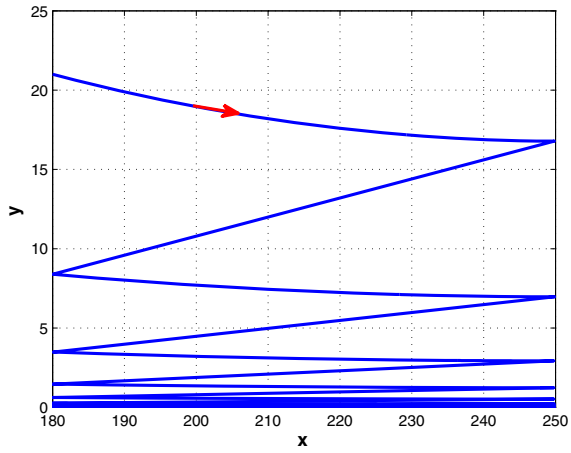

Fig. 7 The existence and orbitally asymptotical stability of semi-trivial periodic solution of model (4) with $p = 0.3$, $q = 0.5$, $\tau = 5$, and $X_r = 250 = x^*$

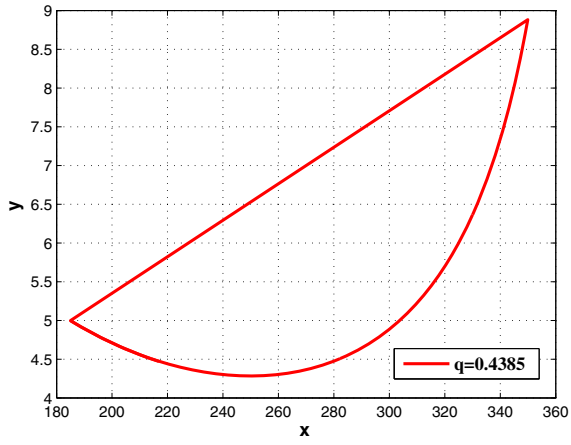

Fig. 8 The existence of positive periodic solution of model (4) with $p = 0.5$, $q = 0.4385$, $\tau = 10$, and $X_r = 350 > x^*$

many numerical simulations show that the attraction domain of this periodic solution is very small; that is, the stability of this periodic solution is very sensitive to the initial value of solution. The plots in Fig. 9 show that the solution tends to virus equilibrium for $q = 0.43$, tends to positive order-1 periodic solution for $q = 0.4385$, and tends to the semi-trivial periodic solution for $q = 0.44$, respectively. It implies that control strength q is sensitive for the persistence and extinction of infected cells (or free virus) y for $X_r > x^*$. This is the relevant contents of Theorem 6 and Remark 5.

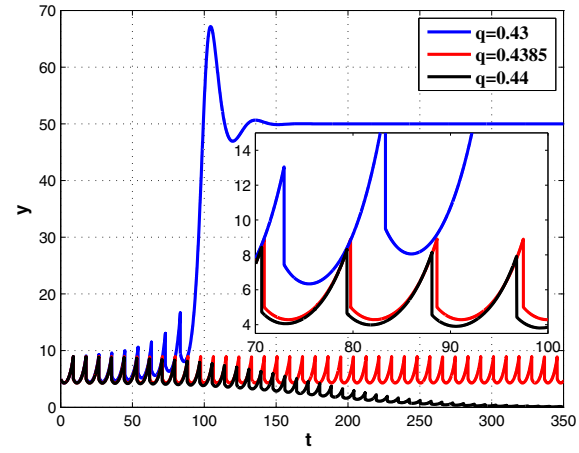

Fig. 9 The effect of control strength q for the dynamical behaviors of model (4) with $p = 0.5$, $\tau = 10$, and $X_r = 350 > x^*$

6 Concluding remarks

The dynamic complexity of two novel virus epidemic models with state feedback control strategies are analyzed systemically in this paper. Firstly, choosing the density of infected cells or free virus as a control threshold value, some sufficient conditions on the existence and orbitally asymptotical stability of positive order-1 or order-2 periodic solution of model (3) are presented by the Poincaré map, the analog of Poincaré criterion and qualitative analysis method. This amounts to that we can control the density of infected cells or free virus at a low level over a long period of time by adjusting control strength. It is concluded that the state feedback control strategies are feasible and effective. Further, choosing the density of uninfected cells x as control threshold value, we obtain that the existence and orbitally asymptotical stability of periodic solution. In particular, the existence and orbitally asymptotical stability of semi-trivial periodic are obtained. This implies that infected cells or free virus y dies out if we control the density of cells x within a certain range. It provides theoretical basis for finding a new measure to prevent and control the spread of viral disease.

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