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Analysis of Equilibria and Connecting Orbits in a Nonlinear Viral Infection Model*

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Abstract. Extensive modeling studies on viral infection have significantly improved immunological insights into the dynamics of host responses to infectious agents and helped to design new avenues for experimentation. Various dynamical behaviors have been found in existing models, in particular, the global stability of the boundary equilibrium or the positive equilibrium, as well as different types of bifurcations. However, limited studies have been performed on the connection of invariant sets when global stability results no longer hold. This motivates the current study through considering the dynamics of a viral infection model, with new features that nonmonotonic functional responses are contained in the cytotoxic T lymphocytes (CTL) growth rate and incidence rate. The well-posedness of the four-dimensional differential equation model is established, and the model is further reduced into a three-dimensional nonmonotone system. The reduced system is demonstrated to admit three types of equilibria that represent different states of viral infection. The local stability and global stability of these equilibria are established under some suitable conditions. The coexistence of two positive equilibria poses challenges to model analysis, which is addressed through an algebraic-topological invariant, the Conley index. The index provides a topological description of the local dynamics around each equilibrium. With the aid of connection matrices, nontrivial invariant sets are detected, and the existence of connecting orbits between these invariant sets are determined. Further numerical simulations are conducted to supplement and verify the analytical results. It is shown that the model exhibits the rich dynamical phenomenon including bistability and periodic solutions due to diverse nonmonotonicities. Global dynamics from local stability analysis in the current study extensively extend and improve some existing studies on virus dynamics models.

Key words. viral infection, CTL immune response, nonmonotone system, global dynamics, Conley index, connection matrix

MSC codes. 34C60, 34D23, 92C50, 92D30

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1. Introduction.

Mathematical models of viral infections, which are based on a firm understanding of biological interactions, have significantly improved immunological insights into

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the dynamics of host responses to infectious agents and helped to design new avenues for experimentation [5, 9, 10, 18, 20]. To explore the basic dynamics of virus-host cell interaction and immune responses on reducing the virus load, the interplay between infection process and immune responses should be incorporated simultaneously into a model. Starting with the smallest number of essential assumptions, a model was formulated in [17] to illustrate the relation among antiviral immune responses, virus load, and virus diversity:

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = \beta xv - ay - pyz, \\ \dot{v} = ky - uv, \\ \dot{z} = cyz - bz \end{cases} \tag{1.1}$$

with four variables: uninfected cells $x(t)$, infected cells $y(t)$, free virus particles $v(t)$, and the magnitude of the cytotoxic T lymphocytes (CTL) response $z(t)$. In (1.1), uninfected cells are produced at a constant rate λ and die at a rate dx. Infected cells are produced from uninfected cells and free virus at rate βxv and decline at rate ay. Free virus particles are released from infected cells at rate ky and die at rate uv. cyz represents the rate of CTL cells (CTLs) proliferation in response to antigen, and bz is the CTLs decay rate. The response of immune system on killing infected cells is described by the term pyz, with p specifying the rate at which CTLs kill infected cells.

In (1.1), the intrinsic growth rate of uninfected cells is given by the growth function $\lambda - dx$, which is linear. The contacts between uninfected cells and viruses are described by the incidence function βxv, following a simple mass action process. The CTL immune response is characterized by bilinear terms cyz and pyz for virus-specific CTLs proliferation and CTL induced death rate, respectively.

The human immune system, as one of organismic physiological systems, is highly complex. Therefore, extensive modeling studies have been performed to extend the above model to accommodate various immunological aspects [13, 30, 33, 36, 37], including the delayed effect of responses, and age structure of infected cells. One specific aspect to extend the model is incorporating other types of functional responses in the growth function and incidence function [25]. By considering various immunity forms (specific and nonspecific immunity, cell-mediated immunity, and immune impairment), some chronic viral infection models with nonlinear immune functions like $\frac{cyz}{1+\eta y} - myz$ were proposed to describe the immune stimulation and impairment of infected cells [22, 34]. Other expressions, such as $\frac{cyz}{1+\eta y}K(y)$ for immune response of HIV infection, were proposed in [32] to consider the effects of the oxidative stress on the process of viral infection, and the Monod–Haldane function of the form $\frac{qyz}{\alpha+\gamma y+y^2}$ was used in [31] to characterize the nonmonotonic immune response in a simplified viral infection system.

The main focus of the current study is to investigate the effects of nonlinear rate functions (i.e., growth function, incidence function, and immune function) on the dynamics of interactions among virus, host cells, and immune systems. For that purpose, we modify the model with different assumptions on the growth rate, the incidence function, and the rate of CTLs proliferation. In particular, we make the following assumptions: (i) uninfected cells are produced at a nonlinear rate $\lambda - dx + rx(1 - \frac{x}{K})$ [3]; (ii) the incidence rate for the virus-to-cell

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infection is not monotonic: instead, it takes the form $\beta x((v-b)e^{-cv}+b)$ [25]; and (iii) the rate of CTLs proliferation in response to antigen is in the Monod–Haldane form $\frac{qyz}{\alpha+\gamma y+y^2}$ [31], and correspondingly the rate at which CTLs kill infected cells is assumed to be $\frac{pyz}{\alpha+\gamma y+y^2}$. Then the classical model in [17] (system (1.1)) can be replaced with the following one:

$$\begin{cases} \dot{x} = \lambda - dx + rx\left(1 - \dfrac{x}{K}\right) - \beta x((v-b)e^{-cv}+b), \\ \dot{y} = \beta x((v-b)e^{-cv}+b) - ay - \dfrac{pyz}{\alpha+\gamma y+y^2}, \\ \dot{v} = ky - \mu_1 v, \\ \dot{z} = \dfrac{qyz}{\alpha+\gamma y+y^2} - \mu_2 z. \end{cases} \tag{1.2}$$

The initial condition of (1.2) is specified as

$$x(0) \geq 0, \quad y(0) \geq 0, \quad v(0) \geq 0, \quad z(0) \geq 0, \tag{1.3}$$

and all parameters are assumed to be positive.

Based on the assumptions on the nonlinear growth rate for uninfected cells, nonmonotonic incidence function in the virus-to-cell infection, and immune function, the Jacobian matrix of system (1.2) at an arbitrary point of $\mathbb{R}^4_+$ may have one of the following structures:

$$\begin{pmatrix} * & 0 & - & 0 \\ + & * & + & - \\ 0 & + & * & 0 \\ 0 & \pm & 0 & * \end{pmatrix}, \quad \begin{pmatrix} * & 0 & 0 & 0 \\ + & * & 0 & - \\ 0 & + & * & 0 \\ 0 & \pm & 0 & * \end{pmatrix}, \quad \begin{pmatrix} * & 0 & + & 0 \\ + & * & - & - \\ 0 & + & * & 0 \\ 0 & \pm & 0 & * \end{pmatrix}, \tag{1.4}$$

where some of the $+$ and $-$ signs can be zero for points on the boundary of $\mathbb{R}^4_+$. The coexistence of these diverse positive and negative feedbacks among variables makes the system nonmonotone [26] in the usual cone

$$\mathbb{R}^4_+ := \left\{(x_1, x_2, x_3, x_4) \in \mathbb{R}^4 : x_i \geq 0 \text{ for all } i = 1,2,3,4\right\}.$$

This observation makes the powerful techniques for monotone dynamical systems [26] invalid. The Lyapunov functional method [8] is a powerful tool for global analysis. However, its construction here becomes a challenging task due to the involvement of multiple nonlinear and nonmonotonic functions in the system. On the other hand, it is expected from three cases of rich structure of the Jacobian matrix in (1.4) that solutions to system (1.2) may display a variety of behaviors.

Although rich dynamics is expected intuitively for model (1.2), it becomes challenging and interesting to develop rigorous techniques to illustrate the behavior of solutions. This poses the main objective of the current study, which will be addressed by studying the global dynamics of system (1.2) on its critical manifold. Specifically, the well-posedness of model (1.2) will be justified and the model with four equations will be reduced into a three-dimensional system through fast-slow systems in section 2. The solution dynamics of boundary behavior will be investigated through studying its subsystems in $\mathbb{R}^2_+$ in section 3. The existence of various equilibria and their linear stability will be explored in section 4. The global stability

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of the model will be argued through considering appropriate Lyapunov functionals, and the possible connections between invariant sets without global attractivity will be presented via the Conley index in section 5. Numerical simulations are performed to supplement and verify the theoretical results. A brief summary and discussion of our findings will be given in section 6.

2. Well-posedness and model reduction.

This section is devoted to establishing some basic properties of model (1.2) and reducing the model into a system of three variables under some mild and immunologically reasonable assumptions.

2.1. Basic properties of solutions.

Since model (1.2) describes the time evolution of the population sizes/densities of agents, the first critical step is to validate that all related variables are nonnegative and bounded ultimately, which is given by the lemma below.

Lemma 2.1. *Let $(x(t), y(t), v(t), z(t))$ be a solution of system (1.2) under the initial condition (1.3). Then it is nonnegative and ultimately uniformly bounded for all $t \ge 0$. Furthermore, all solutions of (1.2) with (1.3) eventually enter the following region:*

$$\Omega = \left\{ (x, y, v, z) \in \mathbb{R}^4_+ : x + y + \frac{a}{2k} v + \frac{p}{q} z \le \frac{rK + 4\lambda}{4\nu} \right\},$$

where $\nu = \min\left\{d, \frac{a}{2}, \mu_1, \mu_2\right\}$.

Proof. For any initial value $\psi = (x(0), y(0), v(0), z(0)) \in \mathbb{R}^4$, it easily follows from the fundamental theory of ordinary differential equations that system (1.2) admits a unique solution $(x(t), y(t), v(t), z(t))$ on $[0, t_\psi)$, with t_ψ being the maximal time of existence, dependent on the initial value ψ. We can further observe that for any $(x, y, v, z) \in \mathbb{R}^4_+$, the right-hand sides of system (1.2) admit

$$\dot{x}|_{x=0} = \lambda > 0, \quad \dot{y}|_{y=0} = \beta x((v - b)e^{-cv} + b) \ge 0, \quad \dot{v}|_{v=0} = ky \ge 0, \quad \dot{z}|_{z=0} = 0.$$

Therefore, by Remark 2.1 in Chapter 5 of [26], we conclude that $(x(t), y(t), v(t), z(t)) \in \mathbb{R}^4_+$ for all $t \in [0, t_\psi)$. Furthermore, by considering a new variable $W(t) = x(t) + y(t) + \frac{a}{2k} v(t) + \frac{p}{q} z(t)$, we have

$$\begin{aligned}
\dot{W} &= \lambda - dx + rx\left(1 - \frac{x}{K}\right) - \frac{a}{2} y - \frac{a\mu_1}{2k} v - \frac{p\mu_2}{q} z \\
&\le \frac{rK + 4\lambda}{4} - dx - \frac{a}{2} y - \frac{a\mu_1}{2k} v - \frac{p\mu_2}{q} z \\
&\le \frac{rK + 4\lambda}{4} - \min\left\{d, \frac{a}{2}, \mu_1, \mu_2\right\} W.
\end{aligned}$$

Suppose that $\widetilde{W}(t)$ is the solution of

$$\begin{cases} \dot{\widetilde{W}} = \dfrac{rK + 4\lambda}{4} - \nu W, \\ \widetilde{W}(0) = x(0) + y(0) + \dfrac{a}{2k} v(0) + \dfrac{p}{q} z(0), \end{cases}$$

where $\nu = \min\{d, \frac{a}{2}, \mu_1, \mu_2\}$. Then

$$\widetilde{W}(t) = \frac{rK + 4\lambda}{4\nu} + \left(\widetilde{W}(0) - \frac{rK + 4\lambda}{4\nu}\right) \exp(-\nu t)$$

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exists for all $t \in [0,\infty)$ and the comparison principle [26] implies that $W(t) \le \widetilde{W}(t)$. Therefore, the maximal interval of existence for the solution $(x(t), y(t), v(t), z(t))$ is $[0,\infty)$. Moreover, it is easy to observe that $\limsup_{t\to\infty} \widetilde{W}(t) = \frac{rK+4\lambda}{4\nu}$. Therefore, $x(t), y(t), v(t)$, and $z(t)$ are ultimately uniformly bounded. This completes the proof. ■

2.2. Four-dimensional model reduction. In this subsection, we are going to reduce the four-dimensional viral infection model (1.2) to a three-dimensional system on the normally hyperbolic critical manifold. Experimental observations have shown that μ_1 is significantly greater than the rate a in system (1.2) [21], that is, $a \ll \mu_1$. Setting $\epsilon = \frac{a}{\mu_1} \ll 1$, we can convert system (1.2) into a fast-slow system.

First, we introduce rescaled variables

$$\lambda = \epsilon\widetilde{\lambda},\ d = \epsilon\widetilde{d},\ r = \epsilon\widetilde{r},\ \beta = \epsilon\widetilde{\beta},\ a = \epsilon\widetilde{a},\ p = \epsilon\widetilde{p},\ q = \epsilon\widetilde{q},\ \mu_2 = \epsilon\widetilde{\mu_2},\ s = \epsilon t.$$

By implementing these changes and omitting the tildes from the resulting equations for the sake of notational simplicity, we obtain the following system:

$$\begin{cases} \dfrac{dx}{ds} = \lambda - dx + rx\left(1 - \dfrac{x}{K}\right) - \beta x((v-b)e^{-cv} + b), \\ \dfrac{dy}{ds} = \beta x((v-b)e^{-cv} + b) - ay - \dfrac{pyz}{\alpha + \gamma y + y^2}, \\ \epsilon\dfrac{dv}{ds} = ky - \mu_1 v, \\ \dfrac{dz}{ds} = \dfrac{qyz}{\alpha + \gamma y + y^2} - \mu_2 z. \end{cases} \tag{2.1}$$

Letting $\epsilon = 0$ on the fast time scale formulation, we obtain the fast subsystem

$$\frac{dv}{dt} = ky - \mu_1 v. \tag{2.2}$$

The zero set of $ky - \mu_1 v$ thus defines the critical manifold [11]:

$$\mathcal{M}_0 = \left\{ (y,v) \in \mathbb{R}_+^2 : v = \frac{ky}{\mu_1},\ y \in [0, M] \right\},$$

with $M = \frac{rK+4\lambda}{4\min\left\{d, \frac{a}{2}, \mu_1, \mu_2\right\}}$.

It can be easily shown that $\mathcal{M}_0$ is normally hyperbolic and each point $(y, v(y))$ on $\mathcal{M}_0$ is an asymptotically stable fixed point of (2.2). That is, $\mathcal{M}_0$ is hyperbolically asymptotically stable. Therefore, on the critical manifold $\mathcal{M}_0$, by setting $\epsilon = 0$ in the formulation of the slow time scale (2.1), we obtain the following slow subsystem:

$$\begin{cases} \dot{x} = \lambda - dx + rx\left(1 - \dfrac{x}{K}\right) - \beta x\left(\left(\dfrac{k}{\mu_1}y - b\right)e^{-\frac{ck}{\mu_1}y} + b\right), \\ \dot{y} = \beta x\left(\left(\dfrac{k}{\mu_1}y - b\right)e^{-\frac{ck}{\mu_1}y} + b\right) - ay - \dfrac{pyz}{\alpha + \gamma y + y^2}, \\ \dot{z} = \dfrac{qyz}{\alpha + \gamma y + y^2} - \mu_2 z. \end{cases} \tag{2.3}$$

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The slow subsystem (2.3) is also referred to as the reduced problem [11]. In what follows, we shall study the reduced system (2.3) of model (1.2).

Remark 2.2. The reduced system (1.2) can also be derived using the quasi-steady-state approximation [24], a method frequently employed in existing immunological modeling studies [23, 31]. It's important to note that this approximation is only valid when the decay rate of the infected cell population, a, is significantly lower than that of the free virus, μ_1. Figure 1 illustrates that the reduced system (2.3) can approximate the original system (1.2) for given initial and parameter values.

For notational simplicity, we introduce the following new variables:

$$\bar{x} = \frac{x}{K}, \quad \bar{y} = \frac{ck}{\mu_1} y, \quad \bar{z} = \frac{z}{\mu_2}, \quad \tau = \mu_2 t;$$

then system (2.3) can be rewritten into

$$\begin{cases} \dot{\bar{x}} = \bar{\lambda} - \bar{d}x + \bar{r}\bar{x}(1-\bar{x}) - \bar{\beta}\bar{x}((\bar{y}-\bar{b})e^{-\bar{y}} + \bar{b}), \\ \dot{\bar{y}} = \bar{k}\bar{\beta}\bar{x}((\bar{y}-\bar{b})e^{-\bar{y}} + \bar{b}) - \bar{a}\bar{y} - \dfrac{\bar{p}\bar{y}\bar{z}}{\bar{\alpha} + \bar{\gamma}\bar{y} + \bar{y}^2}, \\ \dot{\bar{z}} = \dfrac{\bar{q}\bar{y}\bar{z}}{\bar{\alpha} + \bar{\gamma}\bar{y} + \bar{y}^2} - \bar{z}, \end{cases} \tag{2.4}$$

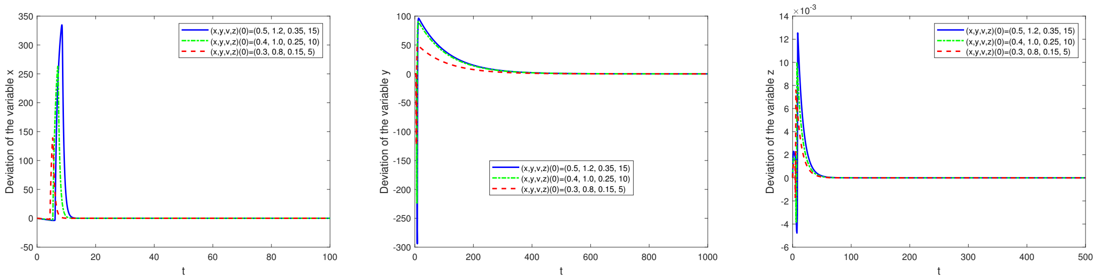
where

$$\bar{\lambda} = \frac{\lambda}{\mu_2 K}, \quad \bar{d} = \frac{d}{\mu_2}, \quad \bar{r} = \frac{r}{\mu_2}, \quad \bar{\beta} = \frac{\beta}{c\mu_2}, \quad \bar{b} = bc,$$

$$\bar{k} = \frac{ckK}{\mu_1}, \quad \bar{a} = \frac{a}{\mu_2}, \quad \bar{p} = p(ck/\mu_1)^2, \quad \bar{\alpha} = \alpha(ck/\mu_1)^2, \quad \bar{\gamma} = \gamma\frac{ck}{\mu_1}, \quad \bar{q} = \frac{ckq}{\mu_1\mu_2}.$$

Dropping the bars and denoting τ by t, system (2.4) becomes

$$\begin{cases} \dot{x} = \lambda - dx + rx(1-x) - \beta x((y-b)e^{-y} + b), \\ \dot{y} = k\beta x((y-b)e^{-y} + b) - ay - \dfrac{pyz}{\alpha + \gamma y + y^2}, \\ \dot{z} = \dfrac{qyz}{\alpha + \gamma y + y^2} - z \end{cases} \tag{2.5}$$



(a) (b) (c)

Figure 1. *Deviation between solutions of original model system (1.2) with initial value $(x(0), y(0), v(0), z(0))$ and the reduced model (2.3) with initial value $(x(0), y(0), z(0))$. The parameter values for the simulations are listed in Table 1.*

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Table 1

Parameters (PAR for abbreviation) and their values of systems (1.2) and (2.3) used in Figure 1.

PAR	Value	PAR	Value	PAR	Value	PAR	Value
λ	10 [25]	β	0.1 [25]	c	1 (Assumed)	p	9 [25]
d	0.1 [25]	k	0.8 [25]	b	20 (Assumed)	α	1 [31]
r	0.6 [25]	μ_1	3.5 [25]	a	0.01 (Assumed)	γ	1 [31]
K	500 [25]	μ_2	0.1 [31]	q	0.03 [25]		

with initial condition

$$x(0) \geq 0, \quad y(0) \geq 0, \quad z(0) \geq 0. \tag{2.6}$$

Using arguments similar to Lemma 2.1, we can show that system (2.5) is still well-posed. That is, the solution of system (2.5) through initial value (2.6) exists and is nonnegative and ultimately uniformly bounded in $\mathbb{R}^3_+$. In addition, we can estimate the upper limits of three components in (2.5). The first equation of (2.5) indicates that $\dot{x} \leq \lambda - dx + rx(1-x)$, and thus we obtain

$$\limsup_{t\to\infty} x(t) \leq x_m := \frac{r - d + \sqrt{(r-d)^2 + 4\lambda r}}{2r}.$$

From the first two equations of (2.5), it follows that

$$\begin{aligned}(kx+y)' &= k[\lambda - dx + rx(1-x)] - ay - \frac{pyz}{\alpha + \gamma y + y^2} \\ &\leq \frac{k(4\lambda + r)}{4} - \min\{a, d\}(kx+y),\end{aligned}$$

and thus $\limsup_{t\to\infty}(kx(t)+y(t)) \leq \frac{k(4\lambda+r)}{4\min\{a,d\}}$ and therefore $\limsup_{t\to\infty} y(t) \leq y_m := \frac{k(4\lambda+r)}{4\min\{a,d\}}$. Furthermore, the differential inequality

$$\begin{aligned}(kx + y + \frac{p}{q}z)' &= k[\lambda - dx + rx(1-x)] - ay - \frac{p}{q}z \\ &\leq \frac{k(4\lambda + r)}{4} - \min\{1, a, d\}(kx + y + \frac{p}{q}z)\end{aligned}$$

implies that

$$\limsup_{t\to\infty} z(t) \leq \limsup_{t\to\infty} \frac{q}{p}\Big(kx(t) + y(t) + \frac{p}{q}z(t)\Big) \leq z_m := \frac{kq(4\lambda + r)}{4p\min\{1, a, d\}}.$$

We will mainly investigate the dynamics on the bounded feasible region below:

$$\Gamma = \left\{(x, y, z) \in \mathbb{R}^3_+ : x \leq x_m, y \leq y_m, z \leq z_m\right\},$$

which contains all ω-limit sets of system (2.5). Furthermore, Γ is positively invariant.

3. Solution dynamics on the boundary.

This section investigates the dynamics on the boundary of the feasible region Γ of system (2.5). Obviously, the flow of (2.5) in the yz-plane always points to the inside of Γ, so there is no invariant subsystem in the yz-plane. To this end, the boundary dynamics of (2.5) will be illustrated through analyzing its two subsystems in the xy-plane and the xz-plane.

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3.1. Subsystem in the xy-plane. Let $z=0$ in (2.5), then the subsystem in the xy-plane can be described by

$$\begin{cases} \dot{x} = \lambda - dx + rx(1-x) - \beta x((y-b)e^{-y}+b) := h_1(x,y), \\ \dot{y} = k\beta x((y-b)e^{-y}+b) - ay := h_2(x,y), \end{cases} \tag{3.1}$$

and it is defined in the set

$$\Gamma_{xy} = \left\{(x,y) \in \mathbb{R}^2_+ : x \le x_m, y \le y_m\right\}.$$

This subsystem reflects the infection dynamics when immunity responses are not activated. Denote

$$f(x) := \lambda - dx + rx(1-x), \quad g(x,y) := \beta x((y-b)e^{-y}+b).$$

To investigate the dynamics of subsystem (3.1), we will define two threshold parameters as follows:

$$R_0 = \frac{k\beta x_m(1+b)}{a}, \quad R(x,y) = \frac{kg(x,y)}{ay},$$

where R_0 is commonly known as the basic reproduction number of viral infection without CTL immune response and can be derived by using the next generation matrix method as shown in [4, 29]. $R(x,y)$ can be regarded as the time-dependent infection reproduction number, and R_0 can be evaluated through $R(x,y)$ at the absence of infected cells ($y=0$), that is,

$$R_0 = R(x_m, 0) := \lim_{y\to 0^+} R(x_m, y).$$

Taking advantage of the properties of the function $g(x,y)$, we can show that

$$R_0 = R(x_m,0) > R(x_m,y) > R(x,y) \quad \text{for} \quad x \in [0,x_m),\ y \in (0,y_m], \tag{3.2}$$

due to

$$\frac{\partial R(x,y)}{\partial x} = \frac{k\beta((y-b)e^{-y}+b)}{ay} > 0, \quad \frac{\partial R(x,y)}{\partial y} = \frac{k\beta x\left[e^{-y}(b+by-y^2)-b\right]}{ay^2} < 0$$

for $x \in (0,x_m),\ y \in (0,y_m]$.

Let us define the following set:

$$X_g = \left\{\xi \in [0,x_m] : (x-\xi)\left(g_2\left(\tfrac{k}{a}f(x)\right) - g_2\left(\tfrac{k}{a}f(\xi)\right)\right) \ge 0 \text{ for } x \ne \xi,\ x \in [0,x_m]\right\},$$

where $g_2(y) = (y-b)e^{-y}+b$. This indicates that the compound function $m(x) = g_2\left(\frac{k}{a}f(x)\right)$ is monotonically increasing in X_g, which will be used to guarantee the uniqueness of the positive equilibrium in subsystem (3.1).

Then we establish a lemma concerning the existence of equilibria in subsystem (3.1).

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Lemma 3.1. *Consider system* (3.1).

(1) *If* $R_0 \le 1$, *then* $E_0(x_m, 0)$ *is the unique equilibrium in* Γ_{xy}.

(2) *If* $R_0 > 1$, *in addition to* E_0, *there is at least one positive equilibrium* $E_1(\hat{x}, \hat{y})$ *in* $\operatorname{int}(\Gamma_{xy})$. *Furthermore, the followings hold:*

 (2a) *if* $\hat{x}$ *of* $E_1(\hat{x}, \hat{y})$ *satisfies* $\hat{x} \in X_g$, *then* E_1 *is the unique positive equilibrium in* $\operatorname{int}(\Gamma_{xy})$;

 (2b) *if the largest root of* $g(x, \frac{k}{a}f(x)) - f(x) = 0$ *on the interval* $(0, x_m)$, *still denoted by* $\hat{x}$, *satisfies* $\hat{x} > 1 - \frac{d}{r}$, *then* E_1 *is the unique positive equilibrium in* $\operatorname{int}(\Gamma_{xy})$.

Proof. The equilibrium (x, y) of (3.1) should satisfy

$$\begin{cases} \lambda - dx + rx(1-x) - \beta x((y-b)e^{-y} + b) = 0, \\ k\beta x((y-b)e^{-y} + b) - ay = 0. \end{cases}$$

Clearly, $E_0(x_m, 0)$ is an equilibrium that always exists. Here, x_m is the cell concentration when the host is infection free.

Note that the positive equilibrium $E_1(\hat{x}, \hat{y})$ exists if $(\hat{x}, \hat{y})$ satisfies

$$\frac{a}{k}y = g(x, y) = f(x). \tag{3.3}$$

Solving $\frac{a}{k}y = f(x)$ for y gives

$$y = \phi(x) := \frac{k}{a}f(x).$$

Clearly, $\phi(x_m) = 0$ and $\phi(0) = \frac{k\lambda}{a}$. Define

$$F(x) = g(x, \phi(x)) - \frac{a}{k}\phi(x) = g(x, \phi(x)) - f(x).$$

Then $F(0) = -\lambda < 0$ and $F(x_m) = g(x_m, \phi(x_m)) - f(x_m) = 0$. Note that

$$\begin{aligned} &F'(x) \\ &= \tfrac{\partial g(x,\phi(x))}{\partial x} + \tfrac{\partial g(x,\phi(x))}{\partial y}\phi'(x) - f'(x) \\ &= \beta((\phi(x) - b)e^{-\phi(x)} + b) + \beta x\left[\phi'(x)e^{-\phi(x)} - \phi'(x)e^{-\phi(x)}(\phi(x) - b)\right] - \tfrac{a}{k}\phi'(x) \\ &= \beta((\phi(x) - b)e^{-\phi(x)} + b) + \beta x\phi'(x)e^{-\phi(x)}(1 + b - \phi(x)) - \tfrac{a}{k}\phi'(x) \end{aligned}$$

for $x \in [0, x_m]$. Noticing that $\phi(x_m) = 0$, we have

$$\begin{aligned} F'_-(x_m) &= \beta x_m\phi'(x_m)(1+b) - \frac{a}{k}\phi'(x_m) \\ &= \frac{a}{k}\phi'(x_m)\left(\frac{k\beta x_m(1+b)}{a} - 1\right) = \frac{a}{k}\phi'(x_m)(R_0 - 1). \end{aligned}$$

Since $\phi'(x_m) = \frac{k}{a}f'(x_m) < 0$, we have $F'_-(x_m) < 0$ if $R_0 > 1$. This indicates that $F(\hat{x}) = 0$ possesses at least one positive root $\hat{x} \in (0, x_m)$. Then we obtain $\hat{y} = \phi(\hat{x}) > 0$. Thus, we can ensure that E_1 exists if $R_0 > 1$. To proceed, we claim that $R_0 > 1$ is also necessary for the existence of a positive equilibrium E_1. For $0 < x < x_m$ and $y > 0$, we get $ayR_0 > kg(x, y)$ from

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the inequality (3.2). We further obtain $ay \geq ayR_0 > kg(x,y)$ if $R_0 \leq 1$. This is obviously in contradiction with the equality (3.3). Hence, there is no positive equilibrium for system (3.1) if $R_0 \leq 1$. This implies that a positive equilibrium $E_1(\hat{x},\hat{y})$ exists if and only if $R_0 > 1$.

Let $g_1(x) = \beta x$ and $g_2(y) = (y-b)e^{-y} + b$. Now we deal with the case in item (2a) about the uniqueness of $E_1(\hat{x},\hat{y})$ with $\hat{x}$ satisfying $\hat{x} \in X_g$ through proof by contradiction. Suppose not, then there is another positive equilibrium $E_{\check{1}}(\check{x},\check{y})$. Without losing generality, we suppose that $\hat{x} < \check{x}$; then $g_2(\hat{y}) \leq g_2(\check{y})$ since $\hat{x}$ and $\check{x}$ are in the set X_g. Moreover, we have

$$\frac{d}{dx}\left(\frac{f(x)}{g_1(x)}\right) = -\frac{\lambda + rx^2}{\beta x^2} < 0 \quad \text{for } x \in (0, x_m).$$

This implies $\frac{f(\hat{x})}{g_1(\hat{x})} > \frac{f(\check{x})}{g_1(\check{x})}$. Since $g_2(y) = \frac{f(x)}{g_1(x)}$ as specified in (3.3), we obtain $g_2(\hat{y}) > g_2(\check{y})$. This is a contradiction, and therefore E_1 is the unique positive equilibrium in system (3.1).

Item (2b) can also be established through proof by contradiction. If the largest root $\hat{x}$ of $g(x, \frac{k}{a}f(x)) - f(x) = 0$, $x \in (0, x_m)$ satisfies $\hat{x} > 1 - \frac{d}{r}$, then for $x \neq \hat{x}$, $x \in [0, x_m]$, we can obtain $(x-\hat{x})(f(x) - f(\hat{x})) < 0$. Assume that there exists $\check{x} \in (0, x_m)$ with $\hat{x} > \check{x}$ such that $E_2(\check{x},\check{y})$ is also an interior equilibrium of (3.1). This implies $f(\check{x}) > f(\hat{x})$ (i.e., $\check{y} > \hat{y}$). By (3.2), we easily get $\frac{g(\check{x},\check{y})}{\check{y}} < \frac{g(\hat{x},\check{y})}{\check{y}} < \frac{g(\hat{x},\hat{y})}{\hat{y}}$. On the flip side, as the pairs $(\hat{x},\hat{y})$ and $(\check{x},\check{y})$ satisfy (3.3), we get $\frac{g(\hat{x},\hat{y})}{\hat{y}} = \frac{g(\check{x},\check{y})}{\check{y}} = \frac{a}{k}$, which gives a contradiction. Thus, E_1 is the unique positive equilibrium in system (3.1). This completes the proof. ■

Remark 3.2. The semitrivial equilibrium $E_0(x_m, 0)$ of system (3.1) always exists. However, when $R_0 > 1$, system (3.1) may admit multiple positive equilibria; see Figure 2. The parameter values used are primarily taken from [25, 31].

We first discuss the local stability of $E_0(x_m, 0)$ through the Jacobian matrix of system (3.1) at E_0:

$$J_{xy}(x_m, 0) = \begin{bmatrix} r - d - 2rx_m & -\beta x_m(1+b) \\ 0 & k\beta x_m(1+b) - a \end{bmatrix}.$$

It is clear that the eigenvalues of matrix $J_{xy}(x_m, 0)$ are $\rho_1 = r - d - 2rx_m < 0$ and $\rho_2 = k\beta x_m(1+b) - a = a(R_0 - 1)$. So E_0 is a locally asymptotically stable node if $R_0 < 1$, and it is a saddle if $R_0 > 1$. If $R_0 = 1$, then there is a locally invariant center manifold tangent to the y-axis.

The Jacobian matrix of system (3.1) at the positive equilibrium $E_1(\hat{x},\hat{y})$ is

$$J_{xy}(\hat{x},\hat{y}) = \begin{bmatrix} \widehat{J}_{11} & \widehat{J}_{12} \\ \widehat{J}_{21} & \widehat{J}_{22} \end{bmatrix},$$

Table 2

The parameter values (PAR for abbreviation) for the rescaled system (3.1) *in Figure* 2.

PAR	Value	PAR	Value	PAR	Value	PAR	Value
λ	0.001	d	0.01	r	0.5	β	1000
b	0	k	1	a	0.001		

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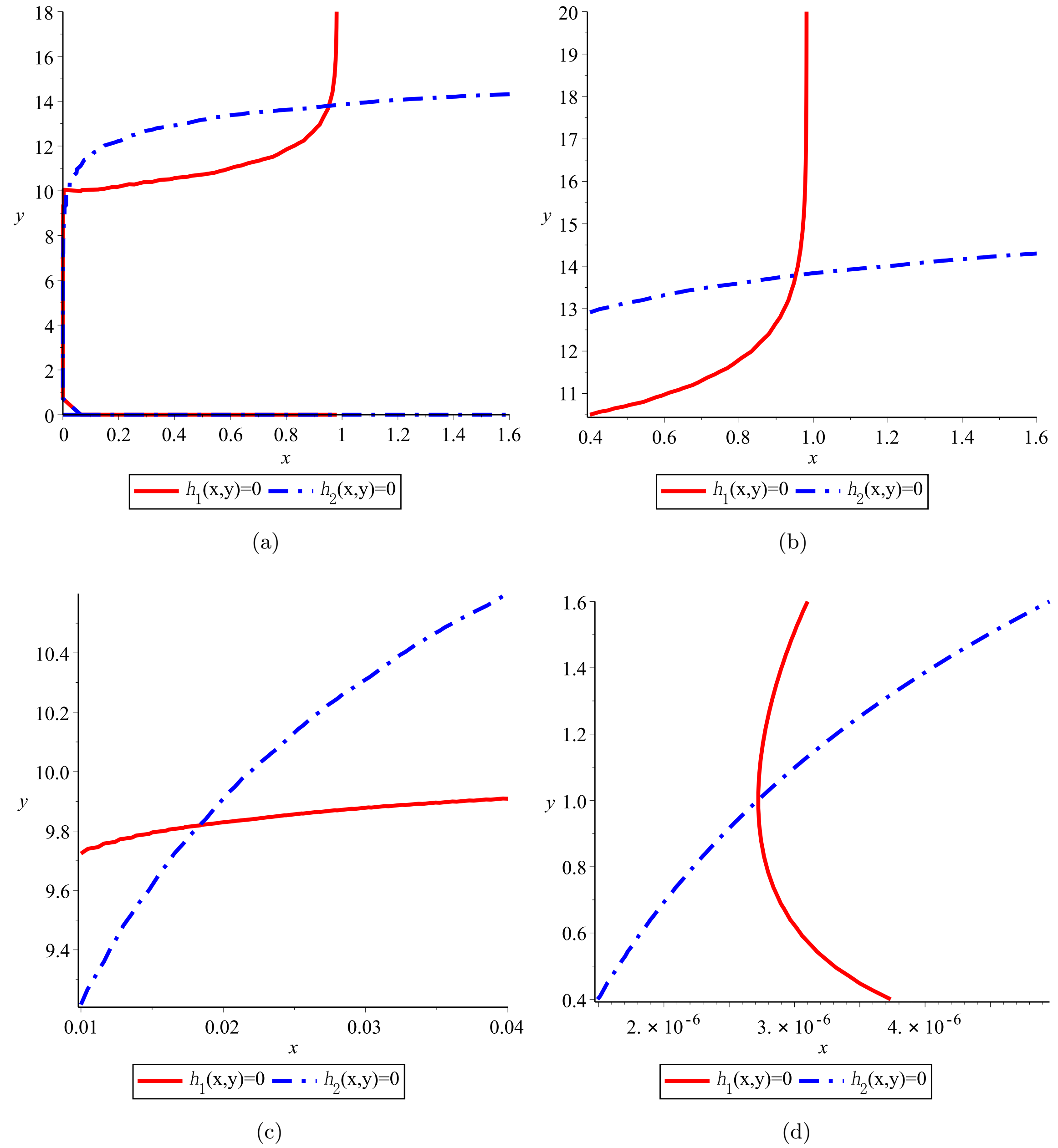

Figure 2. *The graphs of equilibrium equations and positive equilibria of system* (3.1)*. The parameter values for the simulations are listed in Table* 2*.* (a) *The graphs of* $h_1(x,y) = 0$ *and* $h_2(x,y) = 0$ *with functions* h_1 *and* h_2 *being defined in* (3.1)*;* (b) *positive equilibrium* $(0.9532114161, 13.767592)$*;* (c) *positive equilibrium* $(0.01833620633, 9.816632872)$*; and* (d) *positive equilibrium* $(2.721909707 \times 10^{-6}, 1.001333732)$.

where

$$\widehat{J}_{11} = r - d - 2r\hat{x} - \beta((\hat{y} - b)e^{-\hat{y}} + b) < 0, \quad \widehat{J}_{12} = -\beta\hat{x}e^{-\hat{y}}(1 + b - \hat{y}),$$
$$\widehat{J}_{21} = k\beta((\hat{y} - b)e^{-\hat{y}} + b) > 0, \quad \widehat{J}_{22} = k\beta\hat{x}e^{-\hat{y}}(1 + b - \hat{y}) - a.$$

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The determinant of $J_{xy}(\hat{x},\hat{y})$ is

$$\begin{aligned}\mathrm{Det}(J_{xy}(\hat{x},\hat{y})) = &\left[r-d-2r\hat{x}-\beta((\hat{y}-b)e^{-\hat{y}}+b)\right]\left(k\beta\hat{x}e^{-\hat{y}}(1+b-\hat{y})-a\right)\\ &+k\beta^2\hat{x}e^{-\hat{y}}(1+b-\hat{y})((\hat{y}-b)e^{-\hat{y}}+b),\end{aligned}$$

and its sign is determined by

$$a_1^c = k\beta\hat{x}e^{-\hat{y}}(1+b-\hat{y})\left(1+\frac{\beta((\hat{y}-b)e^{-\hat{y}}+b)}{r-d-2r\hat{x}-\beta((\hat{y}-b)e^{-\hat{y}}+b)}\right).$$

The trace of $J_{xy}(\hat{x},\hat{y})$ is

$$\mathrm{Tr}(J_{xy}(\hat{x},\hat{y})) = r-d-2r\hat{x}-\beta((\hat{y}-b)e^{-\hat{y}}+b)+k\beta\hat{x}e^{-\hat{y}}(1+b-\hat{y})-a,$$

and its sign is determined by

$$a_2^c = r-d-2r\hat{x}-\beta((\hat{y}-b)e^{-\hat{y}}+b)+k\beta\hat{x}e^{-\hat{y}}(1+b-\hat{y}).$$

Let

$$k^c = \frac{[r-d-2r\hat{x}-\beta((\hat{y}-b)e^{-\hat{y}}+b)]^2}{k\beta\hat{x}e^{-\hat{y}}(1+b-\hat{y})}, \quad \hat{y}\neq 1+b. \tag{3.4}$$

The above arguments establish the following statement.

Lemma 3.3. *If $R_0<1$, then system (3.1) has a unique stable equilibrium $E_0(x_m, 0)$ in Γ_{xy}. If $R_0>1$, then $E_0(x_m,0)$ is unstable and system (3.1) has at least one positive equilibrium $E_1(\hat{x},\hat{y})$ in $\mathrm{int}(\Gamma_{xy})$. In this case, the followings hold:*

(I) *when $\hat{y}=1+b$ (i.e., $a_2^c<a_1^c=0$), E_1 is a stable hyperbolic node (or focus) due to $a>a_1^c$;*

(II) *when $\hat{y}>1+b$ (i.e., $k>0>k^c$ and $a_1^c<a_2^c<0$), E_1 is a stable hyperbolic node (or focus) due to $a>a_2^c$;*

(III) *when $\hat{y}<1+b$ (i.e., $k^c>0$), we have*
- (i) *if $k<k^c$ (i.e., $a_1^c>a_2^c$), then*
  - (i1) *E_1 is a hyperbolic saddle when $0<a<a_1^c$;*
  - (i2) *E_1 is an attracting saddle-node when $a=a_1^c>0$;*
  - (i3) *E_1 is a stable hyperbolic node (or focus) when $a>a_1^c\geq 0$;*
- (ii) *if $k=k^c$ (i.e., $a_1^c=a_2^c$), then*
  - (ii1) *E_1 is a hyperbolic saddle when $0<a<a_1^c$;*
  - (ii2) *E_1 is a cusp when $a=a_1^c>0$;*
  - (ii3) *E_1 is a stable hyperbolic node (or focus) when $a>a_1^c\geq 0$;*
- (iii) *if $k>k^c$ (i.e., $a_1^c<a_2^c$), then*
  - (iii1) *E_1 is a hyperbolic saddle when $0<a<a_1^c$;*
  - (iii2) *E_1 is a repelling saddle-node when $a=a_1^c>0$;*
  - (iii3) *E_1 is an unstable hyperbolic node (or focus) when $0\leq a_1^c<a<a_2^c$;*
  - (iii4) *E_1 is a weak focus (or a center) when $a=a_2^c>0$;*
  - (iii5) *E_1 is a stable hyperbolic node (or focus) when $a>a_2^c\geq 0$.*

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3.2. Subsystem in the xz-plane. When there is no infection, we let $y = 0$ in (2.5) and the subsystem in the xz-plane can be described by

$$\begin{cases} \dot{x} = \lambda - dx + rx(1-x), \\ \dot{z} = -z. \end{cases} \tag{3.5}$$

It is evident that system (3.5) has only one feasible equilibrium $E_0(x_m, 0)$. The Jacobian matrix of system (3.5) at E_0 is

$$J_{xz}(x_m, 0) = \begin{bmatrix} r - d - 2rx_m & 0 \\ 0 & -1 \end{bmatrix}.$$

The eigenvalues of $J_{xz}(x_m, 0)$ are $\rho_1 = r - d - 2rx_m < 0$ and $\rho_2 = -1$, and thus the equilibrium E_0 of (3.5) is always stable.

Until now, we have completed the analysis of the dynamics on the boundary. Before proceeding with further analysis, we present a flowchart (Figure 3) to outline the analytical techniques that will be used to investigate the local and global dynamics in sections 4 and 5, respectively.

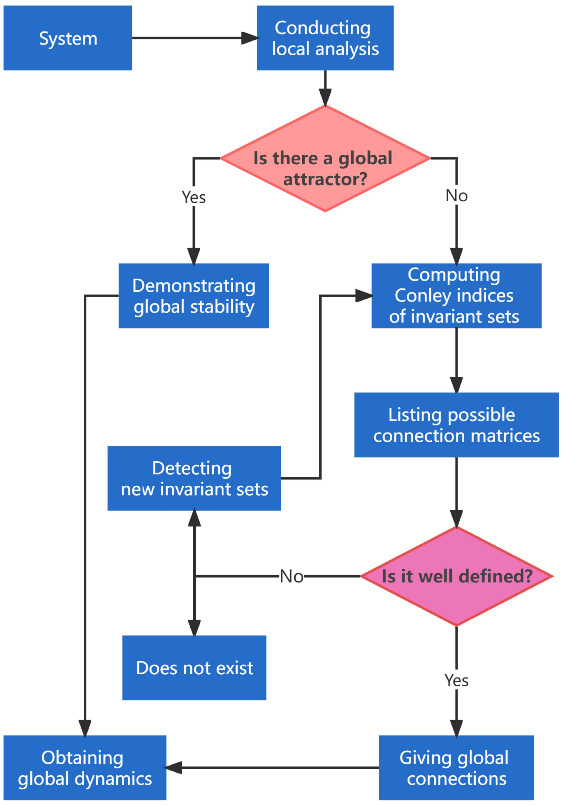

Figure 3. *A schematic diagram of the techniques utilized in sections 4 and 5.*

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4. Local dynamics of the three-dimensional system. This section focuses on the existence of various equilibria for system (2.5) and their stability properties.

4.1. Existence of equilibria. Based on the analysis for the boundary dynamics of system (2.5) in the previous section, we see that system (2.5) has two types of boundary equilibria, known as the infection-free equilibrium $E_0(x_m,0,0)$ and CTL-inactivated equilibrium (CTL-IE) $E_1(\hat{x},\hat{y},0)$. There may be interior equilibria with positive coordinates, called CTL-activated equilibrium (CTL-AE). Now we establish the necessary and sufficient conditions ensuring the existence of interior equilibria in system (2.5). For this purpose, we first define several indices as follows:

$$R_+ := R(x_+,y_+) = \frac{kg(x_+,y_+)}{ay_+}, \quad R_* := R(x_*,y_*) = \frac{kg(x_*,y_*)}{ay_*},$$
$$\text{and} \quad R_- := R(x_-,y_-) = \frac{kg(x_-,y_-)}{ay_-},$$

where $x_\pm = \frac{r-d-\beta g_2(y_\pm)+\sqrt{\Delta_x^\pm}}{2r}$, $x_* = \frac{r-d-\beta g_2(y_*)+\sqrt{\Delta_x^*}}{2r}$, $y_\pm = \frac{q-\gamma\pm\sqrt{(\gamma-q)^2-4\alpha}}{2}$, $y_* = \frac{q-\gamma}{2}$, with

$$\Delta_x^\pm = (\beta g_2(y_\pm)+d-r)^2+4r\lambda, \quad \Delta_x^* = (\beta g_2(y_*)+d-r)^2+4r\lambda.$$

Then we present the following proposition.

Proposition 4.1. *Let* $\alpha_c := \frac{(\gamma-q)^2}{4}$. *For system* (2.5), *the existence of positive equilibria is stated as follows.*

(I) *When* $\gamma = q$, *system* (2.5) *has no positive equilibrium in* $\mathrm{int}(\Gamma)$.

(II) *When* $\gamma \neq q$, *i.e.,* $\alpha_c > 0$, *we have*

(i) *there is no positive equilibrium in* $\mathrm{int}(\Gamma)$ *if and only if one of the following conditions holds:*

(i1) $q < \gamma$;

(i2) $q > \gamma, \alpha > \alpha_c$;

(i3) $q > \gamma$, $\alpha = \alpha_c$, *and* $R_* \le 1$;

(i4) $q > \gamma$, $0 < \alpha < \alpha_c$, *and* $\max\{R_-, R_+\} \le 1$;

(ii) *there is a unique positive equilibrium* $E^*(x^*,y^*,z^*)$ *(*E_*, E_+, *or* E_-*) in* $\mathrm{int}(\Gamma)$ *if and only if one of the following conditions holds:*

(ii1) $q > \gamma$, $\alpha = \alpha_c$, *and* $R_* > 1$;

(ii2) $q > \gamma$, $0 < \alpha < \alpha_c$, $R_- \le 1$, *and* $R_+ > 1$;

(ii3) $q > \gamma$, $0 < \alpha < \alpha_c$, $R_- > 1$, *and* $R_+ \le 1$;

(iii) *there are exactly two different positive equilibria* $E_-(x_-,y_-,z_-)$ *and* $E_+(x_+,y_+,z_+)$ *in* $\mathrm{int}(\Gamma)$ *if and only if* $q > \gamma$, $0 < \alpha < \alpha_c$, *and* $\min\{R_-,\ R_+\} > 1$.

Proof. Note that any positive equilibrium $E(x,y,z) \in \mathrm{int}(\Gamma)$ for system (2.5) satisfies the following equations:

$$\begin{cases} \lambda - dx + rx(1-x) - \beta x((y-b)e^{-y}+b) = 0, \\ k\beta x((y-b)e^{-y}+b) - ay - \dfrac{pyz}{\alpha+\gamma y+y^2} = 0, \\ \dfrac{qy}{\alpha+\gamma y+y^2} - 1 = 0. \end{cases} \tag{4.1}$$

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It follows from the third equation of (4.1) that

$$y^2 + (\gamma - q)y + \alpha = 0, \tag{4.2}$$

which determines the number of positive equilibria in system (2.5).

Especially, when $\gamma = q$, (4.2) is turned into $y^2 + \alpha = 0$. Obviously, it has no real root. Below, we only consider the case where $\gamma \neq q$. Equation (4.2) has at most two roots y_- and y_+, which may coalesce into a unique root y_*, where

$$y_+ = \frac{q-\gamma+\sqrt{\Delta_y}}{2}, \quad y_* = \frac{q-\gamma}{2}, \quad y_- = \frac{q-\gamma-\sqrt{\Delta_y}}{2},$$

with the discriminant

$$\Delta_y = (\gamma - q)^2 - 4\alpha.$$

Notice that $\Delta_y \geq 0$ is equivalent to $\alpha \leq \frac{(\gamma-q)^2}{4} = \alpha_c$. Therefore, it possesses a unique positive root if and only if $q > \gamma$ and $\alpha = \alpha_c$; it has two different positive roots if and only if $q > \gamma$ and $\alpha < \alpha_c$; and it has no positive root if and only if $q < \gamma$ or $q > \gamma$ and $\alpha > \alpha_c$.

Now we are discussing each case one by one.

(i) $q > \gamma$ and $\alpha = \alpha_c$. Substituting y_* into the first equation of (4.1) yields

$$rx^2 + (\beta g_2(y_*) + d - r)x - \lambda = 0, \tag{4.3}$$

where $g_2(y_*) = (y_* - b)e^{-y_*} + b$. Let $\Delta_x^* = (\beta g_2(y_*) + d - r)^2 + 4r\lambda$. Obviously, (4.3) always has a positive root:

$$x_* = \frac{r - d - \beta g_2(y_*) + \sqrt{\Delta_x^*}}{2r}.$$

We have

$$z_* = \frac{q\left(k\beta x_*((y_* - b)e^{-y_*} + b) - ay_*\right)}{p} = \frac{aqy_*\left(R_* - 1\right)}{p}$$

by solving the second equation in (4.1). If $R_* > 1$, then $z_* > 0$; otherwise, $z_* \leq 0$. So there is a unique positive equilibrium in system (2.5) if $R_* > 1$.

(ii) $q > \gamma$ and $\alpha < \alpha_c$. Substituting $y_\pm$ into the first equation of (4.1) yields

$$rx^2 + (\beta g_2(y_\pm) + d - r)x - \lambda = 0, \tag{4.4}$$

where $g_2(y_\pm) = (y_\pm - b)e^{-y_\pm} + b$. In a similar way, we can prove that (4.4) always has a positive root:

$$x_\pm = \frac{r - d - \beta g_2(y_\pm) + \sqrt{\Delta_x^\pm}}{2r},$$

where $\Delta_x^\pm = (\beta g_2(y_\pm) + d - r)^2 + 4r\lambda$. Then we solve the second equation of (4.1) for z to obtain

$$z_\pm = \frac{aqy_\pm\left(R_\pm - 1\right)}{p}.$$

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Thus, if $R_+ > 1$, then E_+ exists; if $R_- > 1$, then E_- exists; if $\min\{R_-, R_+\} > 1$, then E_- and E_+ exist simultaneously; and if $\max\{R_-, R_+\} \le 1$, then neither E_- nor E_+ exists. The proof is completed. ∎

Remark 4.2. Proposition 4.1 indicates that system (2.5) has at most two positive equilibria. If $q > \gamma$ and $\alpha \in (0, \alpha_c]$, then $R_\pm$ and R_* are well-defined. The maximum of $g_2(y) = (y-b)e^{-y}+b$ is achieved at $y = b+1$ as $g_2(y)$ is decreasing for $y \in [b+1, \infty)$, and it is increasing for $y \in [0, b+1)$. We cannot judge the size relationship among $g_2(y_-)$, $g_2(y_*)$, and $g_2(y_+)$ according to $y_- < y_* < y_+$, so we cannot further determine the order of x_-, x_*, and x_+. This also leads to various possibilities among R_-, R_*, and R_+, but they are all less than R_0 by (3.2).

4.2. Local stability of equilibria. To analyze the local stability of various equilibria, we linearize system (2.5) in a small neighborhood of these equilibria. The Jacobian matrix associated with system (2.5) at an arbitrary equilibrium $E = (x, y, z) \in \Gamma$ is given as follows:

$$J(x,y,z) = \begin{bmatrix} J_{11} & J_{12} & 0 \\ J_{21} & J_{22} & J_{23} \\ 0 & J_{32} & J_{33} \end{bmatrix},$$

where

$$\begin{aligned} &J_{11} = r - d - 2rx - \beta((y-b)e^{-y} + b), \quad J_{12} = -\beta x e^{-y}(1+b-y), \\ &J_{21} = k\beta((y-b)e^{-y} + b) \ge 0, \quad J_{22} = k\beta x e^{-y}(1+b-y) - a - \frac{pz(\alpha - y^2)}{(\alpha + \gamma y + y^2)^2}, \\ &J_{23} = -\frac{py}{\alpha + \gamma y + y^2} \le 0, \quad J_{32} = \frac{qz(\alpha - y^2)}{(\alpha + \gamma y + y^2)^2}, \quad J_{33} = \frac{qy}{\alpha + \gamma y + y^2} - 1. \end{aligned}$$

First, we compute the Jacobian matrix $J(x_m, 0, 0)$ at $E_0(x_m, 0, 0)$ as follows:

$$J(x_m, 0, 0) = \begin{bmatrix} r - d - 2rx_m & -\beta x_m(1+b) & 0 \\ 0 & k\beta x_m(1+b) - a & 0 \\ 0 & 0 & -1 \end{bmatrix}.$$

It is obvious that the matrix $J(x_m, 0, 0)$ has three eigenvalues $\rho_1 = r - d - 2rx_m < 0$, $\rho_2 = k\beta x_m(1+b) - a = a(R_0 - 1)$, and $\rho_3 = -1$. Thus, E_0 is locally asymptotically stable (node) if $R_0 < 1$, while it is unstable in the y-direction (saddle) if $R_0 > 1$. When $R_0 = 1$, there exists a locally invariant center manifold tangent to the y-axis.

Next, we consider the Jacobian matrix $J(\hat{x}, \hat{y}, 0)$ evaluated at the boundary equilibrium $E_1(\hat{x}, \hat{y}, 0)$ as below:

$$J(\hat{x}, \hat{y}, 0) = \begin{bmatrix} \widehat{J}_{11} & \widehat{J}_{12} & 0 \\ \widehat{J}_{21} & \widehat{J}_{22} & \widehat{J}_{23} \\ 0 & 0 & \widehat{J}_{33} \end{bmatrix},$$

where

$$\begin{aligned} &\widehat{J}_{11} = r - d - 2r\hat{x} - \beta((\hat{y} - b)e^{-\hat{y}} + b) < 0, \quad \widehat{J}_{12} = -\beta\hat{x}e^{-\hat{y}}(1 + b - \hat{y}), \\ &\widehat{J}_{21} = k\beta((\hat{y} - b)e^{-\hat{y}} + b) > 0, \quad \widehat{J}_{22} = k\beta\hat{x}e^{-\hat{y}}(1 + b - \hat{y}) - a, \\ &\widehat{J}_{23} = -\frac{p\hat{y}}{\alpha + \gamma\hat{y} + \hat{y}^2} < 0, \quad \widehat{J}_{33} = \frac{q\hat{y}}{\alpha + \gamma\hat{y} + \hat{y}^2} - 1. \end{aligned}$$

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Clearly, $\rho_1 = \frac{q\hat{y}}{\alpha+\gamma\hat{y}+\hat{y}^2} - 1$ is one eigenvalue of $J(\hat{x}, \hat{y}, 0)$, so the planar equilibrium E_1 is unstable or stable in the z-direction (i.e., the positive direction orthogonal to the xy-plane), depending on whether ρ_1 is positive or negative, respectively. Specifically, its sign admits the following situations:

(a) if $q \le \gamma$ or $q > \gamma, \alpha > \alpha_c$, then $\rho_1 < 0$ for all $\hat{y} > 0$;
(b) if $q > \gamma$ and $\alpha = \alpha_c$, then $\rho_1 = 0$ for $\hat{y} = y_*$ or $\rho_1 < 0$ for $\hat{y} \ne y_*$;
(c) if $q > \gamma$ and $\alpha < \alpha_c$, then $\rho_1 < 0$ for $\hat{y} \in (0, y_-) \cup (y_+, y_m)$, or $\rho_1 > 0$ for $\hat{y} \in (y_-, y_+)$, or $\rho_1 = 0$ for $\hat{y} = y_\pm$.

The other two eigenvalues of $J(\hat{x}, \hat{y}, 0)$ are determined by

$$J_{xy}(\hat{x}, \hat{y}) = \begin{bmatrix} \widehat{J}_{11} & \widehat{J}_{12} \\ \widehat{J}_{21} & \widehat{J}_{22} \end{bmatrix}.$$

Then we present the conditions for the local stability of $E_1(\hat{x}, \hat{y}, 0)$ in combination with Lemma 3.3.

Proposition 4.3. *Suppose that $R_0 > 1$, then system (2.5) possesses at least one planar equilibrium $E_1(\hat{x}, \hat{y}, 0)$ in $\operatorname{int}(\Gamma_{xy})$. Moreover, the followings hold:*

(I) *when $q \le \gamma$ or $q > \gamma, \alpha > \alpha_c$, then E_1 is locally asymptotically stable if one of the following conditions holds:*
  (i) *$\hat{y} \ge 1 + b$;*
  (ii) *$\hat{y} < 1 + b$, $k \le k^c$, and $a > a_1^c \ge 0$;*
  (iii) *$\hat{y} < 1 + b$, $k > k^c$, and $a > a_2^c \ge 0$;*

(II) *when $q > \gamma$ and $\alpha = \alpha_c$, then E_1 is locally asymptotically stable if $\hat{y} \ne y_*$ and one of the conditions* (I)(i)–(iii) *holds;*

(III) *when $q > \gamma$ and $\alpha < \alpha_c$, then E_1 is locally asymptotically stable if one of the following conditions holds:*
  (i) *$\hat{y} = 1 + b \in (0, y_-) \cup (y_+, y_m)$;*
  (ii) *$\hat{y} \in (1 + b, y_-) \cup (\max\{y_+, 1 + b\}, y_m)$;*
  (iii) *$\hat{y} \in (0, \min\{y_-, 1 + b\})$ or $\hat{y} \in (y_+, \min\{y_m, 1 + b\})$, $k \le k^c$, and $a > a_1^c \ge 0$;*
  (iv) *$\hat{y} \in (0, \min\{y_-, 1 + b\})$ or $\hat{y} \in (y_+, \min\{y_m, 1 + b\})$, $k > k^c$, and $a > a_2^c \ge 0$;*

here, k^c is defined in (3.4) and $y_m = \frac{k(4\lambda+r)}{4\min\{a,d\}}$.

Then we continue to investigate the local properties of interior equilibria in system (2.5). By Proposition 4.1, we see that system (2.5) may have one or two positive equilibria. We first consider that there exists a unique positive equilibrium $E^*(x^*, y^*, z^*)$ (E_*, E_+ or E_-) in $\operatorname{int}(\Gamma)$ and then study its stability. The Jacobian matrix at $E^*(x^*, y^*, z^*)$ is

$$J(x^*, y^*, z^*) = \begin{bmatrix} J_{11}^* & J_{12}^* & 0 \\ J_{21}^* & J_{22}^* & J_{23}^* \\ 0 & J_{32}^* & 0 \end{bmatrix},$$

where

$$J_{11}^* = r - d - 2rx^* - \beta((y^* - b)e^{-y^*} + b), \quad J_{12}^* = -\beta x^* e^{-y^*}(1 + b - y^*),$$
$$J_{21}^* = k\beta((y^* - b)e^{-y^*} + b) > 0, \quad J_{22}^* = k\beta x^* e^{-y^*}(1 + b - y^*) - a - \frac{pz^*(\alpha - (y^*)^2)}{(\alpha + \gamma y^* + (y^*)^2)^2},$$
$$J_{23}^* = -\frac{py^*}{\alpha + \gamma y^* + (y^*)^2} < 0, \quad J_{32}^* = \frac{qz^*(\alpha - (y^*)^2)}{(\alpha + \gamma y^* + (y^*)^2)^2}.$$

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When $E^* = E_*$, i.e., $q > \gamma$, $\alpha = \alpha_c$, and $R_* > 1$, using the equilibrium relations, we have

$$\begin{aligned}
&J^*_{11} = \tilde{J}^*_{11} = r - d - 2rx_* - \beta((y_* - b)e^{-y_*} + b), \quad J^*_{12} = \tilde{J}^*_{12} = -\beta x_* e^{-y_*}(1 + b - y_*),\\
&J^*_{21} = \tilde{J}^*_{21} = k\beta((y_* - b)e^{-y_*} + b) > 0, \quad J^*_{22} = \tilde{J}^*_{22} = k\beta x^* e^{-y^*}(1 + b - y^*) - a,\\
&J^*_{23} = \tilde{J}^*_{23} = -\frac{py_*}{\alpha + \gamma y_* + (y_*)^2} < 0, \quad J^*_{32} = \tilde{J}^*_{32} = 0.
\end{aligned}$$

So the Jacobian matrix $J(x^*, y^*, z^*)$ at $E_*(x_*, y_*, z_*)$ becomes

$$J(x_*, y_*, z_*) = \begin{bmatrix} \tilde{J}^*_{11} & \tilde{J}^*_{12} & 0 \\ \tilde{J}^*_{21} & \tilde{J}^*_{22} & \tilde{J}^*_{23} \\ 0 & 0 & 0 \end{bmatrix}.$$

It is clear that $\rho_1 = 0$ is one eigenvalue of $J(x_*, y_*, z_*)$, and hence E_* is always a degenerate equilibrium, and there is a center manifold tangent to the z-axis. E_* is nonhyperbolic, so we cannot say anything about its stability. To consider the stability of $E_*(x_*, y_*, z_*)$ in the z-direction, let $\tilde{x} = x - x_*$, $\tilde{y} = y - y_*$, $\tilde{z} = z - z_*$, and $dt = (\alpha + \gamma y + y^2)d\tau$. Under this transformation, dropping the tildes and denoting τ by t, then system (2.5) converts into

$$(4.5) \qquad \begin{cases} \dot{x} = [\lambda - d(x + x_*) + r(x + x_*)(1 - x - x_*) - \beta(x + x_*)((y + y_* - b)e^{-y-y_*} + b)] \\ \qquad [\alpha + \gamma(y + y_*) + (y + y_*)^2], \\ \dot{y} = [k\beta(x + x_*)((y + y_* - b)e^{-y-y_*} + b) - a(y + y_*)][\alpha + \gamma(y + y_*) + (y + y_*)^2] \\ \qquad -p(y + y_*)(z + z_*), \\ \dot{z} = q(y + y_*)(z + z_*) - (z + z_*)[\alpha + \gamma(y + y_*) + (y + y_*)^2]. \end{cases}$$

Correspondingly, $E_*(x_*, y_*, z_*)$ is shifted to $\widetilde{E}_0(0, 0, 0)$. Linearizing (4.5) around this point and omitting the third- and higher-order terms, we get

$$(4.6) \qquad \begin{bmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} + \begin{bmatrix} b_1x^2 + b_2xy + b_3y^2 \\ b_4xy + b_5y^2 + b_6yz \\ -z_*y^2 \end{bmatrix},$$

where $a_{ij} = \tilde{J}^*_{ij}[\alpha + \gamma(y + y_*) + (y + y_*)^2]$, $i, j = 1, 2$, $a_{23} = \tilde{J}^*_{23}[\alpha + \gamma(y + y_*) + (y + y_*)^2]$. The eigenvalues of the linear part of (4.6) are

$$\begin{aligned}
\widetilde{\rho}_1 &= \frac{a_{11} + a_{22} + \sqrt{a_{11}^2 - 2a_{11}a_{22} + 4a_{12}a_{21} + a_{22}^2}}{2},\\
\widetilde{\rho}_2 &= \frac{a_{11} + a_{22} - \sqrt{a_{11}^2 - 2a_{11}a_{22} + 4a_{12}a_{21} + a_{22}^2}}{2},
\end{aligned}$$

and 0, and the associated eigenvectors are $v_1 = (v_{11}, 1, 0)^T$, $v_2 = (v_{21}, 1, 0)^T$, and $v_3 = (v_{31}, v_{32}, 1)^T$, with

$$\begin{aligned}
v_{11} &= \frac{2a_{12}}{a_{22} - a_{11} + \sqrt{a_{11}^2 - 2a_{11}a_{22} + 4a_{12}a_{21} + a_{22}^2}}, \quad v_{31} = \frac{a_{12}a_{23}}{a_{11}a_{22} - a_{12}a_{21}},\\
v_{21} &= \frac{2a_{12}}{a_{22} - a_{11} - \sqrt{a_{11}^2 - 2a_{11}a_{22} + 4a_{12}a_{21} + a_{22}^2}}, \quad v_{32} = -\frac{a_{11}a_{23}}{a_{11}a_{22} - a_{12}a_{21}}.
\end{aligned}$$

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Now we use the center manifold theorem [35] to draw a conclusion about the stability of E_*. Let

$$\mathcal{T} = (v_1 \quad v_2 \quad v_3) = \begin{bmatrix} v_{11} & v_{21} & v_{31} \\ 1 & 1 & v_{32} \\ 0 & 0 & 1 \end{bmatrix}.$$

Using the transformation $(x, y, z)^T = \mathcal{T}(u, v, w)^T$, the linear part of system (4.6) is diagonalized and (4.6) is reduced into the following form:

$$\begin{bmatrix} \dot{u} \\ \dot{v} \\ \dot{w} \end{bmatrix} = \begin{bmatrix} \rho_1 & 0 & 0 \\ 0 & \rho_2 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u \\ v \\ w \end{bmatrix} + \begin{bmatrix} G_1 \\ G_2 \\ G_3 \end{bmatrix} \tag{4.7}$$

for some constants G_i. The center manifold theorem concludes that there is a center manifold, denoted by

$$W^c(0) = \left\{(u, v, w) \in \mathbb{R}^3 : u = h_1(w),\ v = h_2(w),\ |w| < \delta,\ h_1(0) = h_2(0) = \mathrm{D}h_1(0) = \mathrm{D}h_2(0) = 0\right\},$$

where $\mathrm{D}h_i$ is the derivative of h_i with regard to w for $i = 1, 2$ and δ is small enough. To determine the approximate expression of the center manifold $W^c(0)$, we put

$$u = h_1(w) = m_{11}w^2 + m_{12}w^3 + O\left(\|w\|^4\right), \quad v = h_2(w) = m_{21}w^2 + m_{22}w^3 + O\left(\|w\|^4\right). \tag{4.8}$$

Substituting (4.8) into the first two equations of (4.7), simple mathematical calculation yields $m_{11} = m_{12} = m_{21} = m_{22} = 0$. Thus, from the third equation of (4.7), we obtain

$$\dot{w} = m_3 w^2 + O\left(\|w\|^3\right), \tag{4.9}$$

where

$$m_3 = -z_* \frac{[py_*(e^{-y_*}b\beta - e^{-y_*}\beta y_* - b\beta - 2rx_* - d + r)]^2}{N^2},$$

with N

$$\begin{aligned} &= (e^{-y_*}b\beta - e^{-y_*}\beta y_* - b\beta - 2rx_* - d + r)(k\beta x_* e^{-y_*}\gamma b y_* - k\beta x_* e^{-y_*}\gamma y_*^2 \\ &\quad + k\beta x_* e^{-y_*} b y_*^2 - k\beta x_* e^{-y_*} y_*^3 - e^{-y_*}\gamma b\beta k x_* + 2k\beta x_* e^{-y_*}\gamma y_* + k\beta x_* e^{-y_*}\alpha b \\ &\quad - k\beta x_* e^{-y_*}\alpha y_* - 2e^{-y_*} b\beta k x_* y_* + 3k\beta x_* e^{-y_*} y_*^2 + k\beta x_* e^{-y_*}\alpha + \gamma b\beta k x_* + 2b\beta k x_* y_* \\ &\quad - 2\gamma a y_* - 3a y_*^2 - a\alpha - p z_*) k\beta(e^{-y_*} b - e^{-y_*} y_* - b)(-\beta x_* e^{-y_*}\gamma b y_* + \beta x_* e^{-y_*}\gamma y_*^2 \\ &\quad - \beta x_* e^{-y_*} b y_*^2 + \beta x_* e^{-y_*} y_*^3 + e^{-y_*}\gamma b\beta x_* - 2\beta x_* e^{-y_*}\gamma y_* - \beta x_* e^{-y_*}\alpha b + \beta x_* e^{-y_*}\alpha y_* \\ &\quad + 2e^{-y_*} b\beta x_* y_* - 3\beta x_* e^{-y_*} y_*^2 - \beta x_* e^{-y_*}\alpha - \gamma b\beta x_* - \gamma r x_*^2 - 2b\beta x_* y_* - 2r x_*^2 y_* - \gamma d x_* \\ &\quad + \gamma r x_* - 2d x_* y_* + 2r x_* y_* + \gamma\lambda + 2\lambda y_*). \end{aligned}$$

Obviously, the zero point $w = 0$ in (4.9) is locally asymptotically stable; that is, the zero point $z = 0$ in (4.6) is also locally asymptotically stable.

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Besides, the other eigenvalues of $J(x_*, y_*, z_*)$ are determined by

$$J_{xy}(x_*, y_*) = \begin{bmatrix} \tilde{J}_{11}^* & \tilde{J}_{12}^* \\ \tilde{J}_{21}^* & \tilde{J}_{22}^* \end{bmatrix}.$$

Its determinant is

$$\begin{aligned}\operatorname{Det}(J_{xy}(x_*, y_*)) = &\left[r - d - 2rx_* - \beta((y_* - b)e^{-y_*} + b)\right] \left(k\beta x_* e^{-y_*}(1 + b - y_*) - a\right) \\ &+ k\beta^2 x_* e^{-y_*}(1 + b - y_*)((y^* - b)e^{-y^*} + b),\end{aligned}$$

whose sign is determined by

$$a_{*1}^c = k\beta x_* e^{-y_*}(1 + b - y_*) \left(1 + \frac{\beta((y_* - b)e^{-y_*} + b)}{r - d - 2rx_* - \beta((y_* - b)e^{-y_*} + b)}\right),$$

while the trace of $J_{xy}(x_*, y_*)$ is

$$\operatorname{Tr}(J_{xy}(x_*, y_*)) = r - d - 2rx_* - \beta((y_* - b)e^{-y_*} + b) + k\beta x_* e^{-y_*}(1 + b - y_*) - a,$$

whose sign is determined by

$$a_{*2}^c = r - d - 2rx_* - \beta((y_* - b)e^{-y_*} + b) + k\beta x_* e^{-y_*}(1 + b - y_*).$$

To study the topological type of the interior equilibrium E_* of system (2.5) in the xy-plane, we define

$$k_*^c = \frac{[r - d - 2rx_* - \beta((y_* - b)e^{-y_*} + b)]^2}{k\beta x_* e^{-y_*}(1 + b - y_*)}, \quad y_* \neq 1 + b,$$

which will be used in the following proposition.

Based on the above analysis, the local property of the positive equilibrium $E_*(x_*, y_*, z_*)$ is clarified by the following proposition.

Proposition 4.4. *Suppose that $q > \gamma$, $\alpha = \alpha_c$, and $R_* > 1$, then system (2.5) possesses a unique interior equilibrium E_* in $\operatorname{int}(\Gamma)$. Moreover, the followings hold:*

(I) *when $y_* = 1 + b$ (i.e., $a_{*2}^c < a_{*1}^c = 0$), E_* is locally asymptotically stable due to $a > 0 > a_{*1}^c$;*

(II) *when $y_* > 1 + b$ (i.e., $k > 0 > k_*^c$ and $a_{*1}^c < a_{*2}^c < 0$), E_* is locally asymptotically stable due to $a > 0 > a_{*2}^c$;*

(III) *when $y_* < 1 + b$ (i.e., $k_*^c > 0$), E_* is locally asymptotically stable if one of the following conditions holds:*

(i) *$0 < k < k_*^c$ (i.e., $a_{*1}^c > a_{*2}^c$) and $a > a_{*1}^c \geq 0$;*

(ii) *$k = k_*^c$ (i.e., $a_{*1}^c = a_{*2}^c$) and $a > a_{*1}^c \geq 0$;*

(iii) *$k > k_*^c$ (i.e., $a_{*1}^c < a_{*2}^c$) and $a > a_{*2}^c \geq 0$.*

When $E^* = E_-$, i.e., $q > \gamma$, $\alpha < \alpha_c$, $R_- > 1$, and $R_+ \leq 1$, the Jacobian matrix $J(x^*, y^*, z^*)$ at $E_-(x_-, y_-, z_-)$ simplifies to

$$J(x_-, y_-, z_-) = \begin{bmatrix} J_{11}^- & J_{12}^- & 0 \\ J_{21}^- & J_{22}^- & J_{23}^- \\ 0 & J_{32}^- & 0 \end{bmatrix},$$

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where

$$J_{11}^- = r - d - 2rx_- - \beta((y_- - b)e^{-y_-} + b) < 0,\ J_{21}^- = k\beta((y_- - b)e^{-y_-} + b) > 0,$$
$$J_{12}^- = -\beta x_- e^{-y_-}(1 + b - y_-),\ J_{23}^- = -\frac{py_-}{\alpha + \gamma y_- + (y_-)^2} < 0,$$
$$J_{22}^- = k\beta x_- e^{-y_-}(1 + b - y_-) - a - \frac{pz_-(\alpha - (y_-)^2)}{(\alpha + \gamma y_- + (y_-)^2)^2},\ J_{32}^- = \frac{qz_-(\alpha - (y_-)^2)}{(\alpha + \gamma y_- + (y_-)^2)^2} > 0.$$

The characteristic equation of $J(x_-, y_-, z_-)$ is

$$\rho(\rho - J_{11}^-)(\rho - J_{22}^-) - J_{23}^- J_{32}^-(\rho - J_{11}^-) - J_{12}^- J_{21}^- \rho = 0.$$

For convenience, the above equation can further be rewritten as

$$\rho^3 + A_2\rho^2 + A_1\rho + A_0 = 0, \tag{4.10}$$

where $A_2 = -(J_{11}^- + J_{22}^-),\ A_1 = J_{11}^- J_{22}^- - J_{12}^- J_{21}^- - J_{23}^- J_{32}^-,\ A_0 = J_{11}^- J_{23}^- J_{32}^- > 0.$

The Routh theorem [7] indicates that the number of roots with positive real part for the cubic equation (4.10) equals the number of variations of signs in the first column of the Routh array (FCRA). A straightforward calculation concludes that the Routh array for (4.10) is

$$1, \quad A_2, \quad A_1 - \frac{A_0}{A_2}, \quad A_0.$$

To this end, we need to judge the signs of A_2 and $A_1 - \frac{A_0}{A_2}$. Solving $A_2A_1 - A_0$ gives

$$\begin{aligned} A_2A_1 - A_0 &= -(J_{11}^- + J_{22}^-)(J_{11}^- J_{22}^- - J_{12}^- J_{21}^- - J_{23}^- J_{32}^-) - J_{11}^- J_{23}^- J_{32}^- \\ &= -(J_{11}^-)^2 J_{22}^- + J_{11}^- J_{12}^- J_{21}^- - J_{11}^-(J_{22}^-)^2 + J_{12}^- J_{21}^- J_{22}^- + J_{22}^- J_{23}^- J_{32}^-. \end{aligned}$$

We regard the above polynomial as a quadratic polynomial about the unknown variable J_{22}^-, denoted by

$$H(J_{22}^-) = l_2(J_{22}^-)^2 + l_1 J_{22}^- + l_0,$$

where $l_2 = -J_{11}^-$, $l_1 = J_{12}^- J_{21}^- + J_{23}^- J_{32}^- - (J_{11}^-)^2$, and $l_0 = J_{11}^- J_{12}^- J_{21}^-$.

When $y_- = 1 + b$, we have $J_{12}^- = 0$ and $J_{22}^- < 0$. Since $J_{11}^- < 0$, $J_{23}^- < 0$, and $J_{32}^- > 0$, we obtain

$$A_2 > 0, \quad A_1 - \frac{A_0}{A_2} > 0, \quad A_0 > 0.$$

Then the sign in FCRA is $+, +, +, +$. Thus, the number of changes of signs is zero, and there is no eigenvalue with positive real part in (4.10). Utilizing the Routh–Hurwitz criterion for stability [1] yields that E_- is locally asymptotically stable (node or focus-node).

When $y_- > 1 + b$, we have $J_{12}^- > 0$ and $J_{22}^- < 0$. Since $J_{11}^- < 0$, $J_{23}^- < 0$, and $J_{32}^- > 0$, we obtain

$$A_2 > 0, \quad A_0 > 0.$$

Observing that the coefficients $l_2 > 0$ and $l_0 < 0$ (due to $J_{21}^- > 0$) of the quadratic polynomial $H(J_{22}^-)$, we have the following results:

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(a) If $J_{22}^- \leq J_{22}^{>l} := \frac{-l_1-\sqrt{l_1^2-4l_2l_0}}{2l_2}$, then $H(J_{22}^-) \geq 0$, indicating that $A_1 - \frac{A_0}{A_2} \geq 0$; namely, all eigenvalues of $J(x_-, y_-, z_-)$ possess negative real parts and E_- is locally asymptotically stable (node or focus-node).

(b) If $J_{22}^{>l} < J_{22}^- < 0$, then $H(J_{22}^-) < 0$, indicating that $A_1 - \frac{A_0}{A_2} < 0$; namely, $J(x_-, y_-, z_-)$ has two eigenvalues with positive real part and E_- is unstable, i.e., a saddle (or focus-saddle) possessing a two-dimensional unstable manifold.

When $y_- < 1 + b$, we have $J_{12}^- < 0$; however, J_{22}^- remains unknown. Let

$$\begin{aligned}\Delta_J &= (J_{12}^- J_{21}^- + J_{23}^- J_{32}^- - (J_{11}^-)^2)^2 + 4(J_{11}^-)^2 J_{12}^- J_{21}^- \\ &= (J_{12}^- J_{21}^- + (J_{11}^-)^2)^2 + 2J_{23}^- J_{32}^- (J_{12}^- J_{21}^- - (J_{11}^-)^2) + (J_{23}^- J_{32}^-)^2.\end{aligned}$$

Since $J_{11}^- < 0$, $J_{21}^- > 0$, $J_{23}^- < 0$, and $J_{32}^- > 0$, it would be easy to conclude that $\Delta_J > 0$. Together with $-\frac{l_1}{2l_2} > 0$, we have $0 < J_{22}^{<l} < J_{22}^{<r}$, where $J_{22}^{<l} = \frac{-l_1-\sqrt{l_1^2-4l_2l_0}}{2l_2}$ and $J_{22}^{<r} = \frac{-l_1+\sqrt{l_1^2-4l_2l_0}}{2l_2}$. Meanwhile, we can show that $0 < J_{22}^{<l} < J_{22}^{<c} < J_{22}^{<r}$, with $J_{22}^{<c} := -J_{11}^- > 0$ based on the following calculations:

$$\begin{aligned}J_{22}^{<r} - J_{22}^{<c} &= \frac{-J_{12}^- J_{21}^- - J_{23}^- J_{32}^- - (J_{11}^-)^2 + \sqrt{\Delta_J}}{-2J_{11}^-} \\ &> \frac{-J_{12}^- J_{21}^- - J_{23}^- J_{32}^- - (J_{11}^-)^2 + |J_{12}^- J_{21}^- + (J_{11}^-)^2|}{-2J_{11}^-} \\ &> \frac{-J_{23}^- J_{32}^-}{-2J_{11}^-} > 0\end{aligned}$$

and

$$\begin{aligned}J_{22}^{<c} - J_{22}^{<l} &= \frac{(J_{11}^-)^2 + J_{12}^- J_{21}^- + J_{23}^- J_{32}^- + \sqrt{\Delta_J}}{-2J_{11}^-} \\ &> \frac{(J_{11}^-)^2 + J_{12}^- J_{21}^- + J_{23}^- J_{32}^- + |(J_{11}^-)^2 + J_{12}^- J_{21}^- + J_{23}^- J_{32}^-|}{-2J_{11}^-} \geq 0.\end{aligned}$$

Therefore,

$$A_2 > 0, \quad A_0 > 0.$$

Observing that the coefficients $l_2 > 0$ and $l_0 < 0$ of the quadratic polynomial $H(J_{22}^-)$, we have the following:

(a) if $J_{22}^- \leq J_{22}^{<l}$, then the sign in FCRA is $+, +, +, +$;

(b) if $J_{22}^{<l} < J_{22}^- < J_{22}^{<c}$, then the sign in FCRA is $+, +, -, +$;

(c) if $J_{22}^{<c} < J_{22}^- < J_{22}^{<r}$, then the sign in FCRA is $+, -, +, +$;

(d) if $J_{22}^- > J_{22}^{<r}$, then the sign in FCRA is $+, -, -, +$.

In case (a), the real parts of all eigenvalues of $J(x_-, y_-, z_-)$ are negative and thus E_- is a locally asymptotically stable node (or focus-node). In cases (b)–(d), there are two eigenvalues with positive real parts for $J(x_-, y_-, z_-)$, meaning that E_- is unstable, i.e., it is a saddle (or focus-saddle) possessing a two-dimensional unstable manifold.

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When $E^* = E_+$, i.e., $q > \gamma$, $\alpha < \alpha_c$, $R_- \leq 1$, and $R_+ > 1$, a direct computation using the equilibrium relations can simplify the Jacobian matrix $J(x^*, y^*, z^*)$ at $E_+(x_+, y_+, z_+)$ as below:

$$J(x_+, y_+, z_+) = \begin{bmatrix} J_{11}^+ & J_{12}^+ & 0 \\ J_{21}^+ & J_{22}^+ & J_{23}^+ \\ 0 & J_{32}^+ & 0 \end{bmatrix},$$

where

$$J_{11}^+ = r - d - 2rx_+ - \beta((y_+ - b)e^{-y_+} + b) < 0, \quad J_{12}^+ = -\beta x_+ e^{-y_+}(1 + b - y_+),$$
$$J_{21}^+ = k\beta((y_+ - b)e^{-y_+} + b) > 0, \quad J_{22}^+ = k\beta x_+ e^{-y_+}(1 + b - y_+) - a - \frac{pz_+(\alpha - (y_+)^2)}{(\alpha + \gamma y_+ + (y_+)^2)^2},$$
$$J_{23}^+ = -\frac{py}{\alpha + \gamma y_+ + (y_+)^2} < 0, \quad J_{32}^+ = \frac{qz_+(\alpha - (y_+)^2)}{(\alpha + \gamma y_+ + (y_+)^2)^2} < 0.$$

The characteristic equation of $J(x_+, y_+, z_+)$ is a cubic equation below:

$$\rho^3 - (J_{11}^+ + J_{22}^+)\rho^2 + (J_{11}^+ J_{22}^+ - J_{12}^+ J_{21}^+ - J_{23}^+ J_{32}^+)\rho + J_{11}^+ J_{23}^+ J_{32}^+ = 0. \tag{4.11}$$

Simplifying (4.11) in a similar fashion, we then have

$$\rho^3 + B_2\rho^2 + B_1\rho + B_0 = 0, \tag{4.12}$$

where $B_2 = -(J_{11}^+ + J_{22}^+)$, $B_1 = J_{11}^+ J_{22}^+ - J_{12}^+ J_{21}^+ - J_{23}^+ J_{32}^+$, $B_0 = J_{11}^+ J_{23}^+ J_{32}^+ < 0$.

Notice that the Routh array for (4.12) is

$$1, \quad B_2, \quad B_1 - \frac{B_0}{B_2}, \quad B_0,$$

and thus the sign in FCRA must be $+, *, *, -$. This indicates that the Jacobian matrix $J(x_+, y_+, z_+)$ possesses at least one eigenvalue with positive real part, and its other two eigenvalues remain to be determined.

To investigate the specific type of $E_+(x_+, y_+, z_+)$, we make the following calculations:

$$\begin{aligned} B_2 B_1 - B_0 = &- (J_{11}^+ + J_{22}^+)(J_{11}^+ J_{22}^+ - J_{12}^+ J_{21}^+ - J_{23}^+ J_{32}^+) - J_{11}^+ J_{23}^+ J_{32}^+ \\ = &- (J_{11}^+)^2 J_{22}^+ + J_{11}^+ J_{12}^+ J_{21}^+ - J_{11}^+ (J_{22}^+)^2 + J_{12}^+ J_{21}^+ J_{22}^+ + J_{22}^+ J_{23}^+ J_{32}^+, \end{aligned}$$

and we define

$$\widetilde{H}(J_{22}^+) = \tilde{l}_2 (J_{22}^+)^2 + \tilde{l}_1 J_{22}^+ + \tilde{l}_0, \quad \widetilde{\Delta}_J = \tilde{l}_1^2 - 4\tilde{l}_2\tilde{l}_0,$$

where $\tilde{l}_2 = -J_{11}^+$, $\tilde{l}_1 = J_{12}^+ J_{21}^+ + J_{23}^+ J_{32}^+ - (J_{11}^+)^2$, and $\tilde{l}_0 = J_{11}^+ J_{12}^+ J_{21}^+$.

When $y_+ > 1 + b$, we have $J_{12}^+ > 0$, which means $l_0 < 0$. Thus, $\widetilde{H}(J_{22}^+) = 0$ must have a positive root and a negative root, denoted by $J_{22}^{>r}$ and $J_{22}^{>l}$. Furthermore,

$$\begin{aligned} J_{22}^{>c} - J_{22}^{>r} = &\frac{(J_{11}^+)^2 + J_{12}^+ J_{21}^+ + J_{23}^+ J_{32}^+ - \sqrt{\Delta_J}}{-2J_{11}^-} \\ > &\frac{(J_{11}^+)^2 + J_{12}^+ J_{21}^+ + J_{23}^+ J_{32}^+ - |(J_{11}^+)^2 + J_{12}^+ J_{21}^+ + J_{23}^+ J_{32}^+|}{-2J_{11}^-} = 0. \end{aligned}$$

Then we have the following results:

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(a) if $J_{22}^{+} < J_{22}^{>l}$, then the sign in FCRA is $+,+,+,-$;
(b) if $J_{22}^{>l} < J_{22}^{+} < J_{22}^{>r}$, then the sign in FCRA is $+,+,-,-$;
(c) if $J_{22}^{>r} < J_{22}^{+} < J_{22}^{>c}$, then the sign in FCRA is $+,+,+,-$;
(d) if $J_{22}^{+} > J_{22}^{>c}$, then the sign in FCRA is $+,-,-,-$.

Hence, in cases (a)–(d), $J(x_+,y_+,z_+)$ has one and only one eigenvalue with positive real part; i.e., E_+ is a saddle (or focus-saddle) with a two-dimensional stable manifold.

When $y_+ \leq 1+b$, $J_{12}^{+} \leq 0$, and therefore $B_2 > 0$ always holds. This implies that the sign in FCRA is $+,+,*,-$, so $J(x_+,y_+,z_+)$ has one and only one eigenvalue with positive real part and E_+ is a saddle (or focus-saddle) with a one-dimensional unstable manifold.

Finally, we discuss the situation where $E_-(x_-,y_-,z_-)$ and $E_+(x_+,y_+,z_+)$ are both located in $\operatorname{int}(\Gamma)$. Through similar arguments, we get the following results.

Proposition 4.5. *Suppose that $q > \gamma$, $0 < \alpha < \alpha_c$, and $\min\{R_-,R_+\} > 1$; then system (2.5) has two different positive equilibria $E_-(x_-,y_-,z_-)$ and $E_+(x_+,y_+,z_+)$ in $\operatorname{int}(\Gamma)$. Moreover, the followings hold:*

(i) *when $y_- < y_+ \leq 1+b$, E_- is a saddle (or focus-saddle) possessing a two-dimensional unstable manifold or a locally asymptotically stable node (or focus-node), and E_+ is a saddle (or focus-saddle) possessing a one-dimensional unstable manifold;*
(ii) *when $y_- < 1+b < y_+$, E_- is a saddle (or focus-saddle) possessing a two-dimensional unstable manifold or a locally asymptotically stable node (or focus-node), and E_+ is a saddle (or focus-saddle) possessing a one-dimensional unstable manifold;*
(iii) *when $y_- = 1+b < y_+$, E_- is a locally asymptotically stable node (or focus-node) and E_+ is a saddle (or focus-saddle) possessing a one-dimensional unstable manifold;*
(iv) *when $1+b < y_- < y_+$, E_- is a saddle (or focus-saddle) possessing a two-dimensional unstable manifold or a locally asymptotically stable node (or focus-node), and E_+ is a saddle (or focus-saddle) possessing a one-dimensional unstable manifold.*

5. Global dynamics of the three-dimensional system.

To illustrate the possibility of other complicated invariant sets including periodic solutions, this section is devoted to the global dynamical behavior of system (2.5).

5.1. Global stability.

Based on the linear stability analysis in subsection 4.2, we observe that there are three kinds of equilibria: the axial equilibrium $E_0(x_m,0,0)$, the planar equilibrium $E_1(\hat{x},\hat{y},0)$, and the isolated positive equilibrium $E_*(x_*,y_*,z_*)$ (or $E_-(x_-,y_-,z_-)$. We aim to identify suitable conditions that ensure the global asymptotic stability of these equilibria by applying the direct Lyapunov method. It should be noted that the construction of Lyapunov functionals here is strongly motivated by earlier works in [12, 25].

The stability property of the axial equilibrium $E_0(x_m,0,0)$ is stated as follows.

Theorem 5.1. *For system (2.5), if $R_0 \leq 1$, then E_0 is globally asymptotically stable in Γ, whereas it is unstable if $R_0 > 1$.*

Proof. We consider the following Lyapunov functional:

$$V_0(x,y,z) = x - x_m - \int_{x_m}^{x} \lim_{y\to 0^+} \frac{g(x_m,y)}{g(\xi,y)} d\xi + \frac{1}{k}y + \frac{p}{kq}z.$$

We easily confirm that for any $x,y,z > 0$, $V_0(x,y,z) > 0$.

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We calculate the derivative of V_0 along the solutions of (2.5) as follows:

$$\begin{aligned}
\frac{dV_0}{dt}&\\
&=\left(1-\lim_{y\to 0^+}\frac{g(x_m,y)}{g(x,y)}\right)(f(x)-g(x,y))+\frac{1}{k}(kg(x,y)-ay-ph(y)z)+\frac{p}{kq}(qh(y)z-z)\\
&=g(x,y)\lim_{y\to 0^+}\frac{g(x_m,y)}{g(x,y)}+f(x)\left(1-\lim_{y\to 0^+}\frac{g(x_m,y)}{g(x,y)}\right)-\frac{a}{k}y-\frac{p}{kq}z\\
&=\frac{a}{k}\left(\frac{kg(x,y)}{ay}\frac{\partial g(x_m,0)/\partial y}{\partial g(x,0)/\partial y}-1\right)y+(f(x)-f(x_m))\left(1-\frac{\partial g(x_m,0)/\partial y}{\partial g(x,0)/\partial y}\right)-\frac{p}{kq}z,
\end{aligned}$$

where $f(x_m)=0$ was used. Since

$$\frac{kg(x,y)}{ay}\le\lim_{y\to 0^+}\frac{kg(x,y)}{ay}=\frac{k}{a}\frac{\partial g(x,0)}{\partial y},$$

we get

$$\frac{kg(x,y)}{ay}\frac{\partial g(x_m,0)/\partial y}{\partial g(x,0)/\partial y}\le\frac{k}{a}\frac{\partial g(x_m,0)}{\partial y}=R_0.$$

In addition, we have

$$\begin{aligned}
(f(x)-f(x_m))\left(1-\frac{\partial g(x_m,0)/\partial y}{\partial g(x,0)/\partial y}\right)&=(f(x)-f(x_m))\left(1-\frac{g_1(x_m)g_2'(0)}{g_1(x)g_2'(0)}\right)\\
&=\frac{1}{x}(x-x_m)(f(x)-f(x_m))\le 0.
\end{aligned}$$

Thus, we obtain

$$\frac{dV_0}{dt}\le\frac{a}{k}(R_0-1)y\le 0\quad\text{if}\quad R_0\le 1$$

for any $x,y,z>0$. We notice that $\frac{dV_0}{dt}=0$ indicates that $x(t)=x_m$ and $y(t)=z(t)=0$ for $t\ge 0$, so the singleton $\{E_0\}$ is the maximal compact invariant set in $\frac{dV_0}{dt}=0$. LaSalle's invariance principle yields that E_0 is globally asymptotically stable in Γ if $R_0\le 1$.

Finally, we suppose that

$$R_0=\frac{k}{a}\lim_{y\to 0^+}\frac{\partial g(x_m,0)}{\partial y}>1;$$

then there is a constant $y_c>0$ such that

$$\frac{k}{a}\frac{\partial g(x_m,y)}{\partial y}>1\quad\text{for}\quad y\in(0,y_c).$$

According to the continuity of $g(x,y)$, we derive that $\frac{dV_0}{dt}>0$ in a neighborhood of $E_0(x_m,0,0)$ with $y\ne 0$. Therefore, the solutions of system (2.5) starting from an arbitrarily small punctured neighborhood of E_0 in Γ move away from E_0. This means that E_0 is unstable if $R_0>1$. The proof is completed. ∎

To obtain the conditions for the global stability of $E_1(\hat{x},\hat{y},0)$, we require one additional assumption.

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(H1) System (2.5) has a planar equilibrium $E_1(\hat{x},\hat{y},0)$ satisfying

$$\left(\frac{\hat{y}}{y}-\frac{g(x,\hat{y})}{g\left(x,y\right)}\right)\left(\frac{g(x,y)}{g\left(x,\hat{y}\right)}-1\right)\leq 0.$$

Then we present the following theorem to characterize the global stability of E_1.

Theorem 5.2. *Suppose that $R_0>1$, $0<r<\frac{d}{1-\hat{x}}$, and hypothesis (H1) hold; then $E_1(\hat{x},\hat{y},0)$ is globally asymptotically stable in Γ if $\hat{y}\leq\frac{\alpha}{q}$, whereas it is unstable if $\hat{y}$ fulfills $\hat{y}^2+(\gamma-q)\hat{y}+\alpha>0$.*

Proof. If $0<r<\frac{d}{1-\hat{x}}$ and $R_0>1$ are satisfied, then from Lemma 3.1, it follows that there exists a unique planar equilibrium $E_1(\hat{x},\hat{y},0)$ for system (2.5). A Lyapunov functional $V_1:\Gamma\to\mathbb{R}$ is constructed as below:

$$V_1(x,y,z)=x-\hat{x}-\int_{\hat{x}}^{x}\frac{g\left(\hat{x},\hat{y}\right)}{g\left(\xi,\hat{y}\right)}d\xi+\frac{1}{k}\left(y-\hat{y}-\int_{\hat{y}}^{y}\frac{\hat{y}}{\xi}d\xi\right)+\frac{p}{kq}z,$$

which is positive definite for $x,\ y,\ z>0$.

Calculating the derivative of V_1 along the solutions of (2.5) yields

$$\begin{aligned}
\frac{dV_1}{dt}&=\left(1-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)\left(f(x)-g(x,y)\right)+\frac{1}{k}\left(1-\frac{\hat{y}}{y}\right)\left(kg(x,y)-ay-ph(y)z\right)+\frac{p}{kq}\left(qh(y)z-z\right)\\
&=g(x,y)\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}-g(x,y)+f(x)\left(1-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)-\frac{\hat{y}}{y}g(x,y)+\frac{a}{k}\hat{y}+\frac{p}{k}\frac{\hat{y}}{y}h(y)z+g(x,y)\\
&\quad-\frac{a}{k}y-\frac{p}{k}h(y)z+\frac{p}{k}h(y)z-\frac{p}{kq}z\\
&=g(x,y)\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}+f(x)\left(1-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)-\frac{a}{k}y-\frac{\hat{y}}{y}g(x,y)+\frac{a}{k}\hat{y}+\frac{p}{k}\frac{\hat{y}}{y}h(y)z-\frac{p}{kq}z.
\end{aligned}\tag{5.1}$$

Using the following equilibrium equations for E_1,

$$\frac{a}{k}\hat{y}=g\left(\hat{x},\hat{y}\right)=f\left(\hat{x}\right),$$

(5.1) can be further converted into

$$\begin{aligned}
\frac{dV_1}{dt}&=g\left(\hat{x},\hat{y}\right)-g\left(\hat{x},\hat{y}\right)\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}+g(x,y)\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}-\frac{y}{\hat{y}}g\left(\hat{x},\hat{y}\right)-\frac{\hat{y}}{y}g(x,y)+g\left(\hat{x},\hat{y}\right)\\
&\quad+\left(f(x)-f(\hat{x})\right)\left(1-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)+\frac{p}{kq}\left(q\frac{\hat{y}}{y}h(y)-1\right)z\\
&=g\left(\hat{x},\hat{y}\right)\left(2-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}+\frac{g(x,y)}{g\left(x,\hat{y}\right)}-\frac{y}{\hat{y}}-\frac{\hat{y}}{y}\frac{g(x,y)}{g\left(\hat{x},\hat{y}\right)}\right)\\
&\quad+\left(f(x)-f(\hat{x})\right)\left(1-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)+\frac{p}{kq}\left(q\frac{\hat{y}}{y}h(y)-1\right)z\\
&=g\left(\hat{x},\hat{y}\right)\left(3-\frac{\hat{y}}{y}\frac{g(x,y)}{g\left(\hat{x},\hat{y}\right)}-\frac{y}{\hat{y}}\frac{g\left(x,\hat{y}\right)}{g\left(x,y\right)}-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)+g\left(\hat{x},\hat{y}\right)\frac{y}{\hat{y}}\left(\frac{\hat{y}}{y}-\frac{g(x,\hat{y})}{g\left(x,y\right)}\right)\left(\frac{g(x,y)}{g\left(x,\hat{y}\right)}-1\right)\\
&\quad+\left(f(x)-f(\hat{x})\right)\left(1-\frac{g\left(\hat{x},\hat{y}\right)}{g\left(x,\hat{y}\right)}\right)+\frac{p}{kq}\left(q\frac{\hat{y}}{y}h(y)-1\right)z.
\end{aligned}$$

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Since the geometrical mean is not greater than the arithmetical mean, we have

$$3-\frac{\hat{y}}{y}\frac{g(x,y)}{g(\hat{x},\hat{y})}-\frac{y}{\hat{y}}\frac{g(x,\hat{y})}{g(x,y)}-\frac{g(\hat{x},\hat{y})}{g(x,\hat{y})}\leq 0.$$

From hypothesis (H1), we get

$$\left(\frac{\hat{y}}{y}-\frac{g(x,\hat{y})}{g(x,y)}\right)\left(\frac{g(x,y)}{g(x,\hat{y})}-1\right)\leq 0.$$

Furthermore, since $0<r<\frac{d}{1-\hat{x}}$, we have

$$(f(x)-f(\hat{x}))\left(1-\frac{g(\hat{x},\hat{y})}{g(x,\hat{y})}\right)\leq 0.$$

Based on the condition that $\hat{y}\leq\frac{\alpha}{q}$, we get $q\frac{\hat{y}}{y}h(y)-1\leq 0$ for any $y>0$. So $\frac{dV_1}{dt}\leq 0$ for any x, y, $z>0$. Moreover, $\frac{dV_1}{dt}=0$ if and only if $x(t)=\hat{x}$, $y(t)=\hat{y}$, and $z(t)=0$, which implies that the singleton $E_1(\hat{x},\hat{y},0)$ is the largest invariant subset of $\left\{(x,y,z)\in\Gamma:\frac{dV_1}{dt}=0\right\}$. Hence, the global asymptotic stability of E_1 is proved by the aid of LaSalle's invariance principle.

When $\hat{y}$ satisfies $\hat{y}^2+(\gamma-q)\hat{y}+\alpha>0$, by the continuity of the functions, we have $q\frac{\hat{y}}{y}h(y)-1>0$ in a small enough neighborhood of $E_1(\hat{x},\hat{y},0)$, except for the points with $z=0$. So the solutions of system (2.5) starting from an arbitrarily small neighborhood of E_1 with $z\neq 0$ leave away from E_1. Therefore, E_1 is unstable if $\hat{y}$ fulfills $\hat{y}^2+(\gamma-q)\hat{y}+\alpha>0$. The proof is completed. ∎

Next, we consider the global stability of the isolated interior equilibrium $E^*(x^*, y^*, z^*)$. For this reason, the following hypothesis is given.

(H2) There exists a unique positive equilibrium $E^*(x^*,y^*,z^*)$ (E_* or E_-) in $\mathrm{int}(\Gamma)$ for system (2.5), whose components satisfy

$$\left(\frac{y^*}{y}-\frac{g(x,y^*)}{g(x,y)}\right)\left(\frac{g(x,y)}{g(x,y^*)}-1\right)\leq 0$$

and

$$\frac{y}{y^*}\frac{h(y^*)}{h(y)}+qh(y)\leq\frac{y}{y^*}+1.$$

Under this condition, the global stability of $E^*(x^*,y^*,z^*)$ can be established.

Theorem 5.3. *Suppose that $R_0>1$ and hypothesis* (H2) *hold for system* (2.5)*; then we have the following:*

(i) *if $q>\gamma$, $\alpha=\alpha_c$, $R_*>1$, and $0<r<\frac{d}{1-x_*}$, then E_* is globally asymptotically stable in Γ;*

(ii) *if $q>\gamma$, $\alpha<\alpha_c$, $R_->1$, $R_+\leq 1$, and $0<r<\frac{d}{1-x_-}$, then E_- is globally asymptotically stable in Γ.*

Proof. We only present a proof of (i) here, and (ii) can be argued in a similar manner.

If $q>\gamma$, $\alpha=\alpha_c$, and $R_*>1$, then from Proposition 4.1, it follows that there is a unique positive equilibrium $E_*(x_*,y_*,z_*)$ in system (2.5). We define a Lyapunov functional $V_*:\Gamma\to\mathbb{R}$ as

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$$V_*(x,y,z) \\ = x - x_* - \int_{x_*}^{x} \frac{g(x_*,y_*)}{g(\xi,y_*)} d\xi + \frac{1}{k}\left(y - y_* - \int_{y_*}^{y} \frac{h(y_*)}{h(\xi)} d\xi\right) + \frac{p}{kq}\left(z - z_* - \int_{z_*}^{z} \frac{z_*}{\xi} d\xi\right),$$

which is positive definite for $x,\ y,\ z > 0$.

The derivative of V_* along the solutions of system (2.5) can be computed as below:

$$\begin{aligned}\frac{dV_*}{dt} &= \left(1 - \frac{g(x_*,y_*)}{g(x,y_*)}\right)(f(x) - g(x,y)) + \frac{1}{k}\left(1 - \frac{h(y_*)}{h(y)}\right)(kg(x,y) - ay - ph(y)z) \\ &\quad + \frac{p}{kq}\left(1 - \frac{z_*}{z}\right)(qh(y)z - z) \\ &= g(x,y)\frac{g(x_*,y_*)}{g(x,y_*)} - g(x,y) + f(x)\left(1 - \frac{g(x_*,y_*)}{g(x,y_*)}\right) - g(x,y)\frac{h(y_*)}{h(y)} + \frac{a}{k}y\frac{h(y_*)}{h(y)} \\ &\quad + \frac{p}{k}h(y_*)z + g(x,y) - \frac{a}{k}y - \frac{p}{k}h(y)z + \frac{p}{k}h(y)z - \frac{p}{kq}z - \frac{p}{k}h(y)z_* + \frac{p}{kq}z_* \\ &= g(x,y)\frac{g(x_*,y_*)}{g(x,y_*)} + f(x)\left(1 - \frac{g(x_*,y_*)}{g(x,y_*)}\right) - g(x,y)\frac{h(y_*)}{h(y)} + \frac{a}{k}y\frac{h(y_*)}{h(y)} \\ &\quad + \frac{p}{k}h(y_*)z - \frac{a}{k}y - \frac{p}{kq}z - \frac{p}{k}h(y)z_* + \frac{p}{kq}z_*. \end{aligned} \tag{5.2}$$

Note that the following relations hold for the equilibrium $E_*(x_*,y_*,z_*)$:

$$g(x_*,y_*) = f(x_*) = \frac{1}{k}(ay_* + ph(y_*)z_*) \quad \text{and} \quad qh(y_*) = 1.$$

Then we can simplify (5.2) into

$$\begin{aligned}\frac{dV_*}{dt} &= \left(1 - \frac{g(x_*,y_*)}{g(x,y_*)}\right)(f(x) - f(x_*)) - g(x_*,y_*)\frac{g(x_*,y_*)}{g(x,y_*)} + g(x,y)\frac{g(x_*,y_*)}{g(x,y_*)} \\ &\quad + g(x_*,y_*) - g(x,y)\frac{h(y_*)}{h(y)} + \frac{a}{k}y\frac{h(y_*)}{h(y)} - \frac{a}{k}y + \frac{1}{k}(1 - qh(y))(kg(x_*,y_*) - ay_*).\end{aligned}$$

Since $0 < r < \frac{d}{1-x_*}$, we have

$$\left(1 - \frac{g(x_*,y_*)}{g(x,y_*)}\right)(f(x) - f(x_*)) \le 0.$$

Therefore,

$$\begin{aligned}\frac{dV_*}{dt} &\le g(x_*,y_*) + g(x,y)\frac{g(x_*,y_*)}{g(x,y_*)} - g(x,y)\frac{h(y_*)}{h(y)} - g(x_*,y_*)\frac{g(x_*,y_*)}{g(x,y_*)} \\ &\quad + \frac{a}{k}y\frac{h(y_*)}{h(y)} - \frac{a}{k}y + g(x_*,y_*) - \frac{a}{k}y_* - qh(y)g(x_*,y_*) + \frac{aq}{k}h(y)y_* \\ &= 3g(x_*,y_*) + g(x,y)\frac{g(x_*,y_*)}{g(x,y_*)} - g(x,y)\frac{h(y_*)}{h(y)} - g(x_*,y_*)\frac{g(x_*,y_*)}{g(x,y_*)} \\ &\quad + \frac{a}{k}y\frac{h(y_*)}{h(y)} - \frac{a}{k}y - \frac{a}{k}y_* - qh(y)g(x_*,y_*) + \frac{aq}{k}h(y)y_* \\ &\quad + g(x_*,y_*)\frac{h(y)}{h(y_*)}\left(\frac{g(x,y)}{g(x,y_*)} - 1\right)\left(\frac{h(y_*)}{h(y)} - \frac{g(x,y_*)}{g(x,y)}\right) \\ &\quad - g(x_*,y_*)\frac{g(x,y)}{g(x,y_*)} + g(x_*,y_*)\frac{h(y)}{h(y_*)} - g(x_*,y_*)\frac{h(y)}{h(y_*)}\frac{g(x,y_*)}{g(x,y)}.\end{aligned}$$

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According to hypothesis (H2), we have

$$\begin{aligned}\frac{dV_*}{dt} \leq & 3g(x_*,y_*)+g(x,y)\frac{g(x_*,y_*)}{g(x,y_*)}-g(x,y)\frac{h(y_*)}{h(y)}-g(x_*,y_*)\frac{g(x_*,y_*)}{g(x,y_*)}+\frac{a}{k}y\frac{h(y_*)}{h(y)}\\ &-\frac{a}{k}y-\frac{a}{k}y_*+\frac{aq}{k}h(y)y_*-g(x_*,y_*)\frac{g(x,y)}{g(x,y_*)}-g(x_*,y_*)\frac{h(y)}{h(y_*)}\frac{g(x,y_*)}{g(x,y)}\\ =&g(x_*,y_*)\left(3-\frac{h(y)}{h(y_*)}\frac{g(x,y_*)}{g(x,y)}-\frac{h(y_*)}{h(y)}\frac{g(x,y)}{g(x_*,y_*)}-\frac{g(x_*,y_*)}{g(x,y_*)}\right)\\ &+\frac{a}{k}y\frac{h(y_*)}{h(y)}+\frac{aq}{k}h(y)y_*-\frac{a}{k}y-\frac{a}{k}y_*.\end{aligned}$$

The relation between the arithmetical mean and geometrical mean and hypothesis (H2) conclude that

$$\frac{dV_*}{dt} \leq \frac{a}{k}y\frac{h(y_*)}{h(y)}+\frac{aq}{k}h(y)y_*-\frac{a}{k}y-\frac{a}{k}y_*=\frac{a}{k}y_*\left(\frac{y}{y_*}\frac{h(y_*)}{h(y)}+qh(y)-\frac{y}{y_*}-1\right)\leq 0$$

for any $x,y,z>0$. In addition, we can verify that the singleton $E_*(x_*,y_*,z_*)$ is the largest invariant subset of

$$\left\{(x,y,z)\in\Gamma:\frac{dV_*}{dt}=0\right\}.$$

Thus, E_* is globally asymptotically stable with the help of LaSalle's invariance principle. This completes the proof. ∎

5.2. Global phase portraits with double interior equilibria. When system (2.5) has two different positive equilibria $E_+(x_+,y_+,z_+)$ and $E_-(x_-,y_-,z_-)$ (see Proposition 4.1(II.iii)), E_+ is always a saddle through Proposition 4.5. That is, the global attractivity of solutions becomes invalid. This makes the traditional methods fail to obtain the global dynamics of (2.5). To this end, this subsection intends to apply the Conley index to detect other nonequilibrium invariant sets in (2.5) and then to further analyze the global dynamics of (2.5) in the presence of E_- and E_+. Appendixes 7.1 and 7.2 provide concise introduction to the Conley index for the reader's reference.

From Proposition 4.1 (II)(iii), it follows that $\min\{R_-,R_+\}>1$ if E_- and E_+ coexist. By (3.2), we see that R_- and R_+ are all less than R_0. This implies that $R_0>1$. Thus, it can be concluded that $E_0(x_m,0,0)$ and $E_1(\hat{x},\hat{y},0)$ also exist simultaneously in this situation (see Lemma 3.1(2)). In the following, we assume that there are four critical points of (2.5) lying in Γ, denoted as $M(0)$, $M(1)$, $M(2)$, and $M(3)$, which correspond to E_0, E_1, E_-, and E_+, respectively. $M(0)$ is located in the coordinate axis, and $M(1)$ lies on the xy-plane. The other two, $M(2)$ and $M(3)$, are located in the interior of Γ.

Throughout this subsection, S will always represent the set of all bounded solutions in feasible set Γ, and $CH_*(S)=(CH_0(S),CH_1(S),CH_2(S),CH_3(S))$ denotes the homological Conley index of S, where $CH_i(S)\cong H_i(N,L)$ is an i-dimensional relative homology group and (N,L) is an index pair of S with $L\subset N\subset\mathbb{R}^3$. Let $CH_*(k)=(CH_i(k))_{i=0,1,2,3}$ represent the homological Conley index of the Morse set $M(k)$ for $k\in\{0,1,2,3\}$. Referring to subsection 4.2, we always have $CH_1(0)\cong\mathbb{Z}_2$ and $CH_i(0)\cong 0$ if $i=0,2,3$, and $CH_1(3)\cong\mathbb{Z}_2$ and $CH_i(3)\cong 0$

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Table 3

Possible combinations between homological Conley indices of $M(1)$ and $M(2)$ in system (2.5). HCI is the abbreviation of homological Conley index.

	HCI of $M(1)$	HCI of $M(2)$	Type
a	$(\mathbb{Z}_2,0,0,0)$	$(\mathbb{Z}_2,0,0,0)$	Bistability
b	$(\mathbb{Z}_2,0,0,0)$	$(0,0,\mathbb{Z}_2,0)$	Monostability
c	$(0,\mathbb{Z}_2,0,0)$	$(\mathbb{Z}_2,0,0,0)$	Monostability
d	$(0,\mathbb{Z}_2,0,0)$	$(0,0,\mathbb{Z}_2,0)$	Saddle-Saddle
e	$(0,0,\mathbb{Z}_2,0)$	$(\mathbb{Z}_2,0,0,0)$	Monostability
f	$(0,0,\mathbb{Z}_2,0)$	$(0,0,\mathbb{Z}_2,0)$	Saddle-Saddle
g	$(0,0,0,\mathbb{Z}_2)$	$(\mathbb{Z}_2,0,0,0)$	Monostability
h	$(0,0,0,\mathbb{Z}_2)$	$(0,0,\mathbb{Z}_2,0)$	Unstable-Saddle

if $i=0,2,3$ by taking coefficients in $\mathbb{Z}_2$. Combining Lemma 3.3 with the analysis of the Jacobian matrix of $M(1)$ before Proposition 4.3, we see that there are four situations for the homological Conley index of the Morse set $M(1)$, that is, $CH_i(1)\cong\mathbb{Z}_2$ and $CH_j(1)\cong 0$, where $i=0$, or 1, or 2, or 3; $j=\{0,1,2,3\}-\{i\}$. Through Proposition 4.5, we have $CH_*(2)=(\mathbb{Z}_2,0,0,0)$ or $CH_*(2)=(0,0,\mathbb{Z}_2,0)$. There exist eight scenarios, as listed in Table 3, for possible combinations between homological Conley indices of the Morse sets $M(1)$ and $M(2)$.

Remark 5.4. When $\hat{y}=1+b\in(y_-,y_+)$, combining Lemma 3.3 with the analysis of the Jacobian matrix of $M(1)$ before Proposition 4.3 yields $CH_*(1)=(0,\mathbb{Z}_2,0,0)$. Moreover, we have $CH_*(2)=(\mathbb{Z}_2,0,0,0)$ or $CH_*(2)=(0,0,\mathbb{Z}_2,0)$ through Proposition 4.5(ii). This implies cases (c) and (d) can be realized.

To present all possible connection matrices of system (2.5) with two positive equilibria, we first compute the Conley index of S in Γ, with the bounded solutions of (2.5) being confined. We choose an appropriate isolating neighborhood of S, $N=N_1\cap N_2$, with

$$\begin{aligned}N_1&=\left\{(x,y,z):x^2+y^2+z^2=R_M,\quad R_M>0\text{ is large enough}\right\},\\ N_2&=\{(x,y,z):x\ge-\varepsilon,y\ge-\varepsilon\text{ and }z\ge-\varepsilon,\quad\varepsilon>0\text{ is small enough}\},\end{aligned}$$

such that $\Gamma\cap\partial N=\emptyset$ and $\Gamma\subset N$. For given N, there is an index pair of S, (N_0,L_0), contained in N. Note that

$$\begin{aligned}L_x&:=\{(-\varepsilon,y,z)\in N:y>-\varepsilon,z>-\varepsilon\}\not\subset L_0,\\ L_y&:=\{(x,-\varepsilon,z)\in N:x>-\varepsilon,z>-\varepsilon\}\not\subset L_0,\\ L_{z1}&:=\{(x,y,-\varepsilon)\in N:x>-\varepsilon,-\varepsilon<y\le y_-\}\not\subset L_0,\\ L_{z2}&:=\{(x,y,-\varepsilon)\in N:x>-\varepsilon,y_-<y<y_+\}\subset L_0,\\ L_{z3}&:=\{(x,y,-\varepsilon)\in N:x>-\varepsilon,y\ge y_+\}\not\subset L_0\end{aligned}$$

for small ε.

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Obviously, the region L_{z2} is contractible. Moreover, the first octant does not intersect L_0 (otherwise, some orbits become unbounded in forward time). Thus, we obtain $CH_*(S;\mathbb{Z}_2) \cong (0,0,0,0)$ by calculating the homology of N_0/L_0. This implies that $\ker(\Delta) - \operatorname{im}(\Delta) = 0$.

Let $\mathcal{M}(S) = \{M(p) : p \in (\mathcal{P}, >_i)\}$ denote a Morse decomposition, with $\mathcal{P} = (0,1,2,3)$ being an indexing set for $\mathcal{M}(S)$ and Δ^i representing the related connection matrix under partial order $>_i$. Using the admissible flow defined partial order, $>_i$ $(i = a, b, \ldots, h)$, on $\mathcal{P}$ in cases a–h of Table 3, we determine the possible connection matrices for system (2.5) as follows.

Case a. Define the flow determined partial order $>_a$ on $\mathcal{P}$ by

$$0 >_a 1, \quad 3 >_a 1, \quad 3 >_a 2;$$

then the connection matrix Δ^a can be represented as

$$\Delta^a = \begin{array}{c} \\ H_0(1) \\ H_0(2) \\ H_1(0) \\ H_1(3) \end{array} \!\!\begin{array}{c} \begin{array}{cccc} H_0(1) & H_0(2) & H_1(0) & H_1(3) \end{array} \\ \begin{pmatrix} 0 & 0 & 1 & \alpha \\ 0 & 0 & 0 & \beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

By Definition 7.7, we see that Δ^a is strictly upper triangular. Since $\Delta^a(p,q)$ is a boundary map of degree -1, we get $\Delta^a(1,2) = \Delta^a(0,3) = 0$. Since $M(0)$ is unstable in the y-direction and $M(1)$ is stable in both directions of the xy-plane, there must be $0 \to 2$ connections in the xy-plane. Since there is only one orbit in the unstable manifold of $M(0)$ lying in Γ, there cannot be any double connections. Then we have $\Delta^a(1,0) = 1$. Moreover, we have $\Delta^a(2,0) = 0$ by (i) of Definition 7.7 because $M(0)$ and $M(2)$ are both stable in the z-direction (i.e., $0 \not>_a 2$). Two elements, α and β, in Δ^a remain undetermined. Recall that $CH_*(M(I)) \cong \frac{\ker \Delta(I)}{\operatorname{im} \Delta(I)}$ for every interval I. So $CH_i(S) \cong 0$ for $i = 0,1,2,3$, implying that $\operatorname{rank}(\Delta^a) = 2$. The rank condition forces $\beta = 1$. Finally, we consider the value of α. By (III) of Proposition 4.3, we see that there are only two situations for the position of $\hat{y}$: $\hat{y} < y_-$ or $\hat{y} > y_+$. If $\hat{y} < y_-$, let $N_3 = \left\{(x,y,z) : \varepsilon \le y \le \frac{1}{2}(\hat{y} + y_-)\right\} \cap N$ and L_3 represent the exit set of N_3. It is obvious that $L_3 \ne \emptyset$, so $h(I(N_3)) \ne h(M(1)) = \Sigma^0$, with $I(N_3)$ being the maximal invariant set contained in N_3. This indicates that there are invariant sets other than $M(1)$ inside N_3. That is, $\mathcal{M}(S)$ is not a valid Morse decomposition. If $\hat{y} > y_+$, let $N_4 = \left\{(x,y,z) : y \ge \frac{1}{2}(y_- + y_+)\right\} \cap N$. We can easily verify that the index $CH_*(I(N_4)) \cong 0$, so there is a single $3 \to 1$ connection inside N_4. Hence, we have $\alpha = 1$. This possibility is shown in Figure 4.

Table 4

The values of the original parameters (PAR for abbreviation) for system (2.5) in Figure 4.

PAR	Value	PAR	Value	PAR	Value	PAR	Value
λ	10	β	0.0015	c	1	α	1
d	0.01	k	0.27227	a	1.1	γ	1
r	0.6	μ_1	3.5	p	0.5	μ_2	0.1
K	500	b	20	q	0.419		

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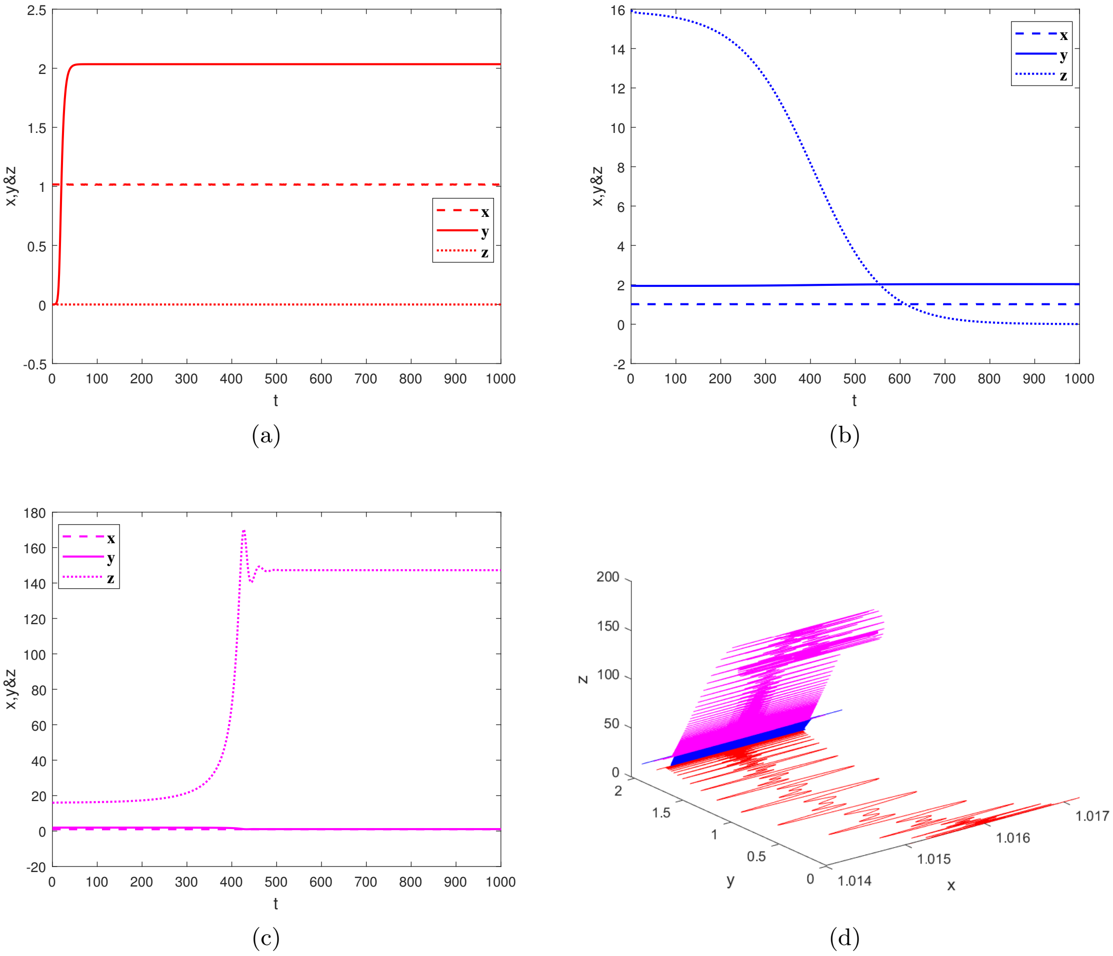

Figure 4. *Time series of three components and global phase portraits for system* (2.5) *with different initial conditions. The parameter values for the simulations are listed in Table* 4*, and the values of equilibria are listed in Table* 6. (a) *Initial condition is* $(x(0), y(0), z(0)) = (1.016, 0.0001, 0)$ *(near* $M(0)$*), then the corresponding solution converges to* $M(1)$; (b) *initial condition is* $(x(0), y(0), z(0)) = (1.0163, 1.9548, 15.9485)$ *(near* $M(3)$*), then the corresponding solution converges to* $M(1)$; (c) *initial condition is* $(x(0), y(0), z(0)) = (1.0143, 1.9348, 15.9465)$ *(near* $M(3)$*), then the corresponding solution converges to* $M(2)$; *and* (d) *the phase diagrams of system* (2.5) *in the above three cases.*

Case b. Introduce the flow defined partial order $>_b$ on $\mathcal{P}$ by

$$0 >_b 1, \quad 2 >_b 1, \quad 3 >_b 1.$$

Obviously, $0 \not>_b 3$, and the connection matrix Δ^b can be expressed as follows:

$$\Delta^b = \begin{array}{c} \\ H_0(1) \\ H_1(0) \\ H_1(3) \\ H_2(2) \end{array} \begin{array}{c} \begin{array}{cccc} H_0(1) & H_1(0) & H_1(3) & H_2(2) \end{array} \\ \begin{pmatrix} 0 & 1 & \alpha & 0 \\ 0 & 0 & 0 & \beta \\ 0 & 0 & 0 & \gamma \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

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Similar to the first half arguments for Δ^a, we can conclude that $\Delta^b(0,3) = \Delta^b(1,2) = 0$ and $\Delta^b(1,0) = 1$. Three elements, α, β, and γ, in Δ^b remain to be determined. As discussed in Case a, $\mathcal{M}(S)$ is not a valid Morse decomposition if $\hat{y} < y_-$. When $\hat{y} > y_+$, we set $N_5 = \left\{(x,y,z) : \varepsilon \le y \le \frac{1}{2}(y_- + y_+)\right\} \cap N$. Then we have $\mathbf{0} = h(I(N_5)) \neq h(M(2))$. Thus, there are other invariant sets inside N_5. This leads to a contradiction. Therefore, when $\hat{y} < y_-$ or $\hat{y} > y_+$, there is no valid Morse decomposition. There may exist complicated invariant sets, such as periodic orbits or invariant tori. This is illustrated through numerical simulations, as presented in Figure 5. It is shown that a periodic orbit appears inside the first octant (see Figure 5). It surrounds $M(2)$, and the inner trajectories approach it (see Figures 5(a) and 5(b)), while the outer trajectories leave away from it (see Figure 5(c)), and the trajectories are perpendicular to the plane on which it is run towards its interior (see Figure 5(a)). We denote this periodic orbit by $M(\pi)$; then its homology Conley index is

$$CH_i(S) \cong \begin{cases} \mathbb{Z}_2 & \text{if} \quad i = 0,1, \\ 0 & \text{otherwise.} \end{cases}$$

In this instance, we use $\mathcal{M}(S) = \{M(p) : p \in (\mathcal{P}, >_{b'})\}$ to denote the Morse decomposition of S, where $\mathcal{P} = (0,1,2,3,\pi)$, and the flow defined partial order $>_{b'}$ is defined by

$$0 >_{b'} 1, \quad 2 >_{b'} \pi, \quad 3 >_{b'} 1.$$

Obviously, $0 \not>_{b'} 3$; then the associated connection matrix $\Delta^{b'}$ is as follows:

$$\Delta^{b'} = \begin{array}{c} \\ H_0(1) \\ H_0(\pi) \\ H_1(\pi) \\ H_1(0) \\ H_1(3) \\ H_2(2) \end{array} \begin{array}{c} \begin{array}{cccccc} H_0(1) & H_0(\pi) & H_1(\pi) & H_1(0) & H_1(3) & H_2(2) \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & \alpha & \beta & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

$\Delta^{b'}(1,\pi) = \Delta^{b'}(1,2) = \Delta^{b'}(\pi,\pi) = \Delta^{b'}(\pi,2) = \Delta^{b'}(\pi,0) = \Delta^{b'}(\pi,3) = \Delta^{b'}(0,3) = 0$ can follow from the algebraic properties of the connection matrix. An argument similar to Δ^b results in $\Delta^{b'}(1,0) = \Delta^{b'}(1,3) = 1$. The fact that $\Delta^{b'} \circ \Delta^{b'} = 0$ implies $\Delta^{b'}(0,2) = \Delta^{b'}(3,2) = 0$. The rank condition forces $\Delta^{b'}(\pi,2) = 1$. Utilizing $\Delta^{b'} \circ \Delta^{b'} = 0$ again yields $\Delta^{b'}(1,\pi) = 0$. Finally, the rank condition requires $\alpha + \beta = 1$, i.e., $\alpha = 1, \beta = 0$ or $\alpha = 0, \beta = 1$. However, the unstable manifold of $M(0)$ has only one orbit lying in the first octant. So we obtain $\alpha = 0, \beta = 1$. This possibility is also verified in Figure 5.

Remark 5.5. In Figure 5, we computationally determine the existence and stability of a periodic orbit for system (2.5). Based on the local stability analysis of E_- $(M(2))$ in subsection 4.2, these results can also be confirmed analytically. Since the Routh–Hurwitz criteria are necessary and sufficient for stability, there is the possibility of nonconstant periodic solutions when $y_- > 1+b$ and $y_- < 1+b$. Notice that there are analytical proofs of the existence

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Table 5
The values of the original parameters (PAR for abbreviation) for system (2.5) in Figure 5.

PAR	Value	PAR	Value	PAR	Value	PAR	Value
λ	10	β	0.0015	c	1	α	350
d	0.01	k	0.27227	a	0.01	γ	1
r	0.6	μ_1	3.5	p	0.5	μ_2	0.1
K	500	b	0.0891	q	4		

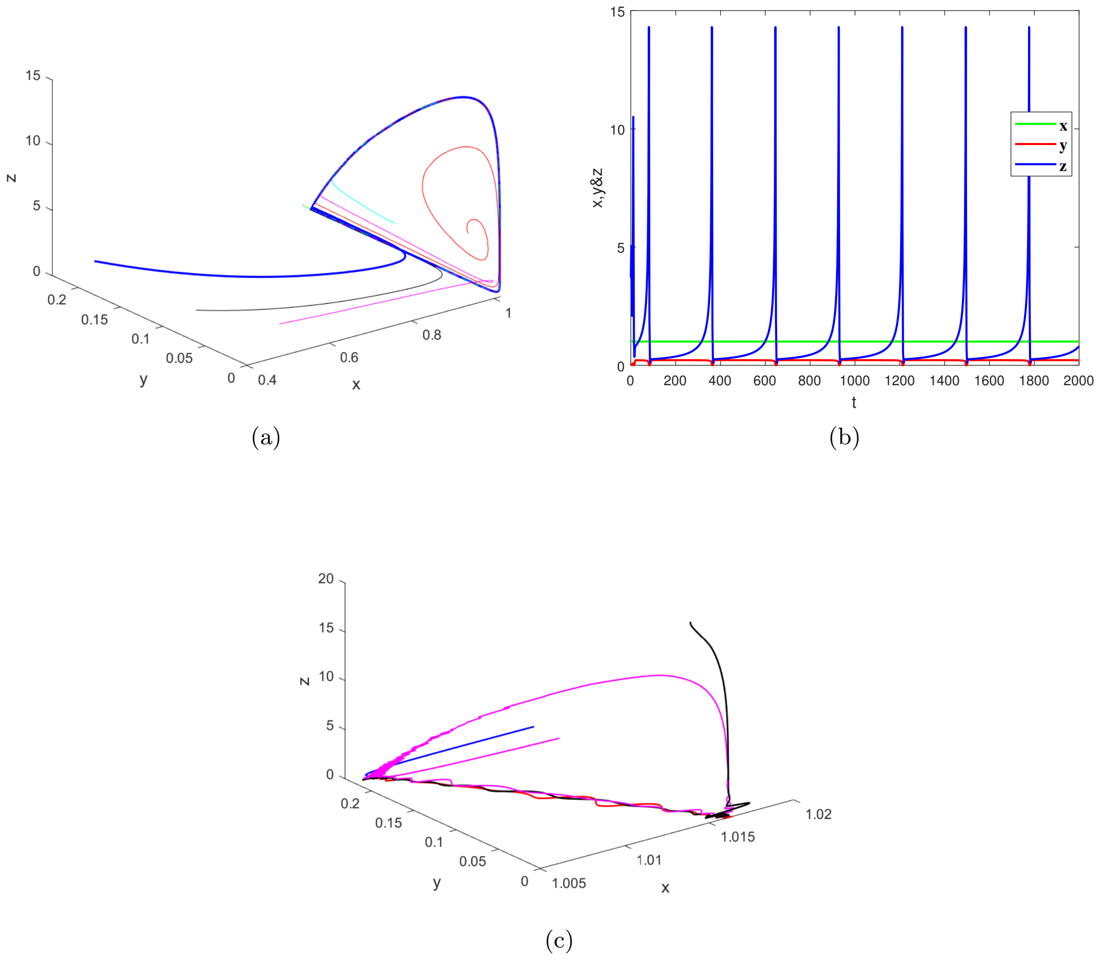

Figure 5. *Global phase portraits and time series of three components for system* (2.5) *with different initial conditions. The simulated parameter values are listed in Table* 5*, and the values of equilibria are listed in Table* 6*.* (a) *The solutions converge to a periodic orbit;* (b) *the time series of $x(t)$, $y(t)$, and $z(t)$ versus t of system* (2.5) *with initial condition* $(x(0), y(0), z(0)) = (1.0158, 0.0374, 3.7108)$ *(near $M(2)$); and* (c) *four solutions (red, manganese purple, blue, black) through different initial conditions* $(1.0160, 0.0001, 0)$ *(near $M(0)$),* $(1.0161, 0.2007, 0.138)$ *(near $M(3)$),* $(1.0161, 0.2307, 0.138)$ *(near $M(3)$),* $(1.0158, 0.0374, 18.7098)$ *(above $M(\pi)$), converge to $M(1)$, $M(\pi)$, $M(1)$, and $M(1)$, respectively.*

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Table 6
The equilibria of system (2.5) in Figures 4 and 5.

	$M(0)$	$M(1)$	$M(2)$	$M(3)$
Figure 4	$(1.016, 0, 0)$	$(1.015, 2.034, 0)$	$(1.015, 1.089, 147.229)$	$(1.015, 1.945, 15.948)$
Figure 5	$(1.016, 0, 0)$	$(1.006, 0.221, 0)$	$(1.014, 0.027, 3.709)$	$(1.006, 0.220, 0.128)$

of a Hopf bifurcation in [9, 16] and their techniques can be applied to systems which need not be monotone. Selecting a parameter (e.g., r) as the bifurcation parameter, we may possibly follow the proof ideas in [9, 16] to show the existence of a Hopf bifurcation point $r = r_*$. Arguments similar to Proposition 3.4 in [28] may further establish the stability properties of the Hopf bifurcation.

Cases c–d. In the flow defined partial orders $>_c$ and $>_d$, the connection matrices Δ^c and Δ^d take the following forms:

$$\Delta^c = \begin{array}{c} \\ H_0(2) \\ H_1(1) \\ H_1(0) \\ H_1(3) \end{array} \begin{array}{c} \begin{array}{cccc} H_0(2) & H_1(1) & H_1(0) & H_1(3) \end{array} \\ \begin{pmatrix} 0 & * & * & * \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array},$$

and

$$\Delta^d = \begin{array}{c} \\ H_1(1) \\ H_1(0) \\ H_1(3) \\ H_2(2) \end{array} \begin{array}{c} \begin{array}{cccc} H_1(1) & H_1(0) & H_1(3) & H_2(2) \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & * \\ 0 & 0 & 0 & * \\ 0 & 0 & 0 & * \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array},$$

where $*$ represents an undetermined entry. In both cases, the rank condition does not hold.

Case e. In the flow defined partial order $>_e$, $0 \not>_e 3$, the associated connection matrix becomes

$$\Delta^e = \begin{array}{c} \\ H_0(2) \\ H_1(0) \\ H_1(3) \\ H_2(1) \end{array} \begin{array}{c} \begin{array}{cccc} H_0(2) & H_1(0) & H_1(3) & H_2(1) \end{array} \\ \begin{pmatrix} 0 & \alpha & \beta & 0 \\ 0 & 0 & 0 & \gamma \\ 0 & 0 & 0 & \delta \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

The property $\Delta^e \circ \Delta^e = 0$ gives $\alpha\gamma + \beta\delta = 0$. Combining the rank condition yields (i) $\alpha = 1, \beta = 0, \gamma = 0, \delta = 1$, (ii) $\alpha = 0, \beta = 1, \gamma = 1, \delta = 0$, or (iii) $\alpha = 1, \beta = 1, \gamma = 1, \delta = 1$. Since $0 \not>_e 2$, we have $\alpha = 0$ by (i) of Definition 7.7. By Theorem 7.8, there admits at least one connection matrix for every Morse decomposition. That is, only (ii) holds.

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Case f. In the flow defined partial order $>_f$, $0 \not>_f 3$ and $0 \not>_f 2$, the connection matrix Δ^f has the form indicated below:

$$\Delta^f = \begin{array}{c} \\ H_1(0) \\ H_1(3) \\ H_2(1) \\ H_2(2) \end{array} \begin{array}{c} \begin{array}{cccc} H_1(0) & H_1(3) & H_2(1) & H_2(2) \end{array} \\ \begin{pmatrix} 0 & 0 & \alpha & \beta \\ 0 & 0 & \gamma & \delta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

We have $\alpha\delta, \beta\gamma \not\equiv 0$ and $\alpha, \beta, \gamma, \delta \not\equiv 1$ due to $\operatorname{rank}(\Delta^f) = 2$.

Case g. In the flow defined partial order $>_g$, $0 \not>_g 3$, the associated connection matrix can be treated as a 4×4 matrix

$$\Delta^g = \begin{array}{c} \\ H_0(2) \\ H_1(0) \\ H_1(3) \\ H_3(1) \end{array} \begin{array}{c} \begin{array}{cccc} H_0(2) & H_1(0) & H_1(3) & H_3(1) \end{array} \\ \begin{pmatrix} 0 & * & * & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

Based on the definition of the connection matrix Δ^g, the rank of Δ^g must be 2. Obviously, the rank condition is not satisfied. Thus, the Morse decomposition $\mathcal{M}(S)$ is not valid.

Case h. In the flow defined partial order $>_h$, $0 \not>_h 3$, the connection matrix Δ^h has the following form:

$$\Delta^h = \begin{array}{c} \\ H_1(0) \\ H_1(3) \\ H_2(2) \\ H_3(1) \end{array} \begin{array}{c} \begin{array}{cccc} H_1(0) & H_1(3) & H_2(2) & H_3(1) \end{array} \\ \begin{pmatrix} 0 & 0 & \alpha & 0 \\ 0 & 0 & \beta & 0 \\ 0 & 0 & 0 & \gamma \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

Using $\Delta^h \circ \Delta^h = 0$ yields $\alpha\gamma = 0$ and $\beta\gamma = 0$. This indicates that $\alpha = \beta = 0$ or $\gamma = 0$. In either case, the rank condition is not established, and therefore $\mathcal{M}(S)$ misses some information in this case.

Remark 5.6. An algebraic-topological tool, called the connection matrix, is introduced in this subsection. By the aid of the connection matrix, we are able to find new invariant sets, except for equilibria. Furthermore, the connecting orbits between these invariant sets are detected via connection matrices and the global phase diagrams of the system are obtained. If there is no connection matrix satisfying Definition 7.7, it means that this combination does not exist or there are more complex invariant sets.

6. Discussion. This paper investigates a mechanistic model on the interplay between virus dynamics and immunological responses. The main features of the model (system (1.2)) include a general recruitment rate for uninfected cells, a nonmonotonic growth rate of immunity level, and a nonmonotonic incidence rate for virus infection. These features pose challenges to dynamics analysis while bring various dynamical outcomes. The model is first shown to be

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immunologically well-posed. With the help of fast-slow systems, the original model of four equations can be reduced into a system of three differential equations (system (2.5)).

The main techniques for illustrating the rich dynamics of the reduced system (2.5) involve (i) the Routh theorem and Routh–Hurwitz criteria for the local stability of feasible equilibria; (ii) the Lyapunov functional formulation and LaSalle's invariance principle for the global stability; (iii) the Conley index to describe the local behavior around each Morse set associated with a Morse decomposition for a given isolated invariant set; (iv) connection matrices to capture other invariant sets besides equilibria and to detect connecting orbits between Morse sets.

Most global results of existing viral infection models are established when the functional responses are assumed to be monotonic and equilibria are in a monostable case. The model in this manuscript includes two nonmonotonic functional functions for the growth rate of immunity level and the incidence rate of virus infection, and coexistence of two interior equilibria is possible. The current study extends and improves existing results. Different from those in some existing studies [3, 25, 31], the current manuscript illustrates the bistability and existence of periodic orbits. These interesting dynamical phenomena may be induced due to nonmonotonicity of the growth rate of immunity level and the incidence rate for virus infection.

7. Appendix.

Some results used in the main text concerning the Conley index and the connection matrix are provided in this appendix for easy reference. These materials are taken from existing references [2, 6, 14, 15, 27].

7.1. The Conley index.

Isolating neighborhoods and isolated invariant sets are main concepts in the Conley index.

Definition 7.1 (see [2, 27]). *Let $\varphi : X \times \mathbb{R} \to X$ be a flow on a locally compact topological space. A compact set $N \subset X$ is an isolating neighborhood if its maximal invariant set is contained strictly in its interior, i.e.,*

$$\mathrm{Inv}(N,\varphi) := \{x \in N : \varphi(x,\mathbb{R}) \subset N\} \subset \mathrm{Int}(N).$$

S is called an isolated invariant set if $S = \mathrm{Inv}(N,\varphi)$ for some isolating neighborhood N.

Index pair is a basic tool for studying isolated invariant set S, whose definition is as follows.

Definition 7.2 (see [2, 27]). *Let S be an isolated invariant set. A pair of compact sets (N,L) where $L \subset N$ is called an index pair for S if the following conditions are satisfied:*

(i) *$S = \mathrm{Inv}(\mathrm{cl}(N \setminus L))$ and $N \setminus L$ is a neighborhood of S, where $\mathrm{cl}(N \setminus L)$ is the closure of $N \setminus L$;*

(ii) *given $x \in L$ and $\varphi([0,t],x) \subset N$, then $\varphi([0,t],x) \subset L$ (L is positively invariant in N);*

(iii) *given $x \in N$ and $t_l > 0$ such that $\varphi(t_l,x) \notin N$, then there exists $t_0 \in [0,t_l]$ for which $\varphi([0,t_0],x) \subset N$ and $\varphi(t_0,x) \in L$ (L is an exit set for N).*

In the following, we give the definition for the (homotopy) Conley index of S.

Definition 7.3 (see [2, 27]). *The homotopy Conley index of S is*

$$h(S) = h(S,\varphi) \sim (N/L,[L]).$$

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To overcome the difficulty of homotopy calculation, one gives the definition of the (homology) Conley index of S as follows:

$$CH_*(S;\mathbb{F}) := H_*(h(S);\mathbb{F}) = H_*(N/L,[L]) \cong H_*(N,L),$$

where $H_*(h(S);\mathbb{F})$ denotes singular homology of $h(S)$ relative to special point with coefficients in a ring $\mathbb{F}$ and $H_*(N,L) = (H_k(N,L))_{k\in\mathbb{Z}_{\geq 0}} = (H_0(N,L), H_1(N,L), \dots)$ denotes the relative homology groups.

To simplify the computations even further, we usually take the coefficient in $\mathbb{Z}_2$. For some specific isolated invariant sets, we determine their homology Conley indices via the following standard results.

Proposition 7.4 (see [14, 15]). *If S is a hyperbolic critical point with an unstable manifold of dimension n, then*

$$CH_i(S) \cong \begin{cases} \mathbb{Z}_2 & \text{if} \quad i = n, \\ 0 & \text{otherwise.} \end{cases}$$

If $S = \emptyset$, then $CH_*(S) \cong (0, 0, \dots)$.

Proposition 7.5 (see [14, 15]). *Let S be a hyperbolic periodic orbit with an oriented unstable manifold of dimension $n+1$. Then*

$$CH_i(S) \cong \begin{cases} \mathbb{Z}_2 & \text{if} \quad i = n, n+1, \\ 0 & \text{otherwise.} \end{cases}$$

7.2. The connection matrix. The connection matrix is an important notion widely used in Conley index theory. Before we proceed, let us review some useful concepts. The decomposition of an attractor-repeller pair is the coarsest decomposition of an invariant set. We use the pair (A, A^*) to represent the decomposition of an attractor-repeller pair for S. Then the set of connecting orbits from A^* to A in S is given by

$$C(A^*, A; S) = \{x \in S : \omega(x) \subset A, \alpha(x) \subset A^*\},$$

where $\alpha(x)$ and $\omega(x)$ represent the alpha and omega limit sets of x, respectively.

A partial order on a set $\mathcal{P}$ is a relation $>$ satisfying the following:

(i) $p > p$ never holds for $p \in \mathcal{P}$;

(ii) if $p > q$ and $q > r$, then $p > r$.

We use $(\mathcal{P}, >)$ to represent a finite indexing set $\mathcal{P}$ with a partial order $>$.

Two elements $p, q \in \mathcal{P}$ are adjacent under $>$ if there is not $r \in \mathcal{P}$ such that $p > r > q$ or $q > r > p$. We refer to a subset $I \subset \mathcal{P}$ as an interval if $p > r > q$ and $p, q \in I$ imply that $r \in I$. We use $\mathcal{I}(\mathcal{P}, >)$ to represent the set of intervals on $(\mathcal{P}, >)$. The definition of a Morse decomposition is as follows.

Definition 7.6 (see [14, 15]). *A finite collection $\mathcal{M}(S) = \{M(p) : p \in \mathcal{P}\}$ of disjoint compact invariant subsets of S is a Morse decomposition if there exists a strict partial order $>$ on the indexing set $\mathcal{P}$ such that for every*

$$x \in S \setminus \bigcup_{p \in \mathcal{P}} M(p),$$

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there exist p, $q \in \mathcal{P}$ such that $p > q$ and

$$\omega(x) \subset M(q) \quad \text{and} \quad \alpha(x) \subset M(p),$$

that is, $x \in C(M(p), M(q))$.

The sets $M(p)$ are called Morse sets. An arbitrary order on $\mathcal{P}$ possessing the above property is called admissible. We usually record the Morse decomposition $\mathcal{M}(S)$ as

$$\mathcal{M}(S) = \{M(p) : p \in (\mathcal{P}, >)\}$$

after selecting an admissible order $>$. Furthermore, each $M(p)$ is also isolated if S is isolated.

Let $I \in \mathcal{I}(\mathcal{P}, >)$, then a new isolated invariant set can be defined by

$$M(I) = \left(\bigcup_{p\in I} M(p)\right) \cup \left(\bigcup_{qp\in I} C(M(q), M(p))\right).$$

$CH_*(M(I))$ is well-defined, as $M(I)$ is isolated. Let $CH_q(I) = CH_q(h(M(I)); \mathbb{Z}_2)$ be the singular homology of the pointed space $h(M(I))$. Particularly, given $p \in \mathcal{P}, CH_q(p) = CH_q(h(M(p)); \mathbb{Z}_2)$.

We consider the collection $\{CH_*(M(p)) : p \in (\mathcal{P}, >)\}$ of an Abelian group, indexed by $\mathcal{P}$, and a group homomorphism (i.e., a linear map)

$$\Delta : \bigoplus_{p\in\mathcal{P}} CH_*(M(p)) \to \bigoplus_{p\in\mathcal{P}} CH_*(M(p)).$$

Then a matrix of maps is written as

$$\Delta = (\Delta(p, q)),$$

where the corresponding (p, q)-component of Δ is denoted by $\Delta(p, q) : CH_*(M(q)) \to CH_*(M(p))$. Particularly, we use

$$\Delta(I) = (\Delta(p, q))_{p,q\in I} : \bigoplus_{p\in I} CH_*(M(p)) \to \bigoplus_{p\in I} CH_*(M(p))$$

to represent the homomorphism $\Delta(I)$ for $I \in \mathcal{I}(\mathcal{P}, >)$.

The definition of an associated connection matrix is stated as follows.

Definition 7.7 (see [14, 15]). *Δ is called a connection matrix for $\mathcal{M}(S)$ if the following four conditions are satisfied:*

(i) *if $q \not> p$, then $\Delta(p, q) = 0$; namely, $\Delta(p, q) \neq 0$ implies $q > p$ (Δ is strictly upper triangular);*
(ii) *$\Delta(p, q)\,(CH_n(M(q)) \subset CH_{n-1}(M(p)))$ (Δ is a boundary map of degree -1);*
(iii) *boundary operator: $\Delta \circ \Delta = 0$;*
(iv) *for each interval $I \in \mathcal{I}(\mathcal{P}, >)$, $H_*\Delta(I) := \frac{\text{kernel}\,\Delta(I)}{\text{image}\,\Delta(I)} \cong CH_*(M(I))$ (rank condition).*

The following theorem concerning connection matrices is used in the arguments of theoretical proofs.

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Theorem 7.8 (see [6]). *Given a Morse decomposition, there exists at least one connection matrix.*

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