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Research Article

A Viral Infection Model with a Nonlinear Infection Rate

Yumei Yu,[1] Juan J. Nieto,[2] Angela Torres,[3] and Kaifa Wang[4]

[1] *School of Science, Dalian Jiaotong University, Dalian 116028, China*
[2] *Departamento de Análisis Matemático, Facultad de Matemáticas, Universidad de Santiago de Compostela, 15782 Santioga de compostela, Spain*
[3] *Departamento de Psiquiatría, Radiología y Salud Pública, Facultad de Medicina, Universidad de Santiago de Compostela, 15782 Santioga de compostela, Spain*
[4] *Department of Computers Science, Third Military Medical University, Chongqing 400038, China*

Correspondence should be addressed to Kaifa Wang, kaifawang@yahoo.com.cn

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A viral infection model with a nonlinear infection rate is constructed based on empirical evidences. Qualitative analysis shows that there is a degenerate singular infection equilibrium. Furthermore, bifurcation of cusp-type with codimension two (i.e., Bogdanov-Takens bifurcation) is confirmed under appropriate conditions. As a result, the rich dynamical behaviors indicate that the model can display an Allee effect and fluctuation effect, which are important for making strategies for controlling the invasion of virus.

1. Introduction

Mathematical models can provide insights into the dynamics of viral load in vivo. A basic viral infection model [1] has been widely used for studying the dynamics of infectious agents such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), which has the following forms:

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xv, \\ \frac{dy}{dt} &= \beta xv - ay, \\ \frac{dv}{dt} &= ky - uv, \end{aligned} \tag{1.1}$$

where susceptible cells ($x(t)$) are produced at a constant rate λ, die at a density-dependent rate dx, and become infected with a rate βuv; infected cells ($y(t)$) are produced at rate βuv and die at a density-dependent rate ay; free virus particles ($v(t)$) are released from infected cells at the rate ky and die at a rate uv. Recently, there have been many papers on virus dynamics within-host in different aspects based on the (1.1). For example, the influences of spatial structures on virus dynamics have been considered, and the existence of traveling waves is established via the geometric singular perturbation method [2]. For more literature, we list [3, 4] and references cited therein.

Usually, there is a plausible assumption that the amount of free virus is simply proportional to the number of infected cells because the dynamics of the virus is substantially faster than that of the infected cells, $u \gg a$, $k \gg \lambda$. Thus, the number of infected cells $y(t)$ can also be considered as a measure of virus load $v(t)$ (e.g., see [5–7]). As a result, the model (1.1) is reduced to

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy, \\ \frac{dy}{dt} &= \beta xy - ay. \end{aligned} \tag{1.2}$$

As for this model, it is easy to see that the basic reproduction number of virus is given by $R_0 = \beta\lambda/ad$, which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process. Furthermore, we know that the infection-free equilibrium $E_0 = (\lambda/d, 0)$ is globally asymptotically stable if $R_0 < 1$, and so is the infection equilibrium $E_1 = (a/\beta, (\beta\lambda - ad)/a\beta)$ if $R_0 > 1$.

Note that both infection terms in (1.1) and (1.2) are based on the *mass-action principle* (Perelson and Nelson [8]); that is, the infection rate per susceptible cell and per virus is a constant β. However, infection experiments of Ebert et al. [9] and McLean and Bostock [10] suggest that the infection rate of microparasitic infections is an increasing function of the parasite dose and is usually sigmoidal in shape. Thus, as Regoes et al. [11], we take the nonlinear infection rate into account by relaxing the mass-action assumption that is made in (1.2) and obtain

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta(y)x, \\ \frac{dy}{dt} &= \beta(y)x - ay, \end{aligned} \tag{1.3}$$

where the infection rate per susceptible cell, $\beta(y)$, is a sigmoidal function of the virus (parasite) concentration because the number of infected cells $y(t)$ can also be considered as a measure of virus load (e.g., see [5–7]), which is represented in the following form:

$$\beta(y) = \frac{(y/\mathrm{ID}_{50})^{\kappa}}{1 + (y/\mathrm{ID}_{50})^{\kappa}}, \quad \kappa > 1. \tag{1.4}$$

Here, ID_{50} denotes the infectious dose at which 50% of the susceptible cells are infected, κ measures the slope of the sigmoidal curve at ID_{50} and approximates the average number

of virus that enters a single host cell at the begin stage of invasion, $(y/\mathrm{ID}_{50})^{\kappa}$ measures the infection force of the virus, and $1/(1+(y/\mathrm{ID}_{50})^{\kappa})$ measures the inhibition effect from the behavioral change of the susceptible cells when their number increases or from the production of immune response which depends on the infected cells.

In fact, many investigators have introduced different functional responses into related equations for epidemiological modeling, of which we list [12–17] and references cited therein. However, a few studies have considered the influences of nonlinear infection rate on virus dynamics. When the parameter $\kappa = 1$, [18, 19] considered a viral mathematical model with the nonlinear infection rate and time delay. Furthermore, some different types of nonlinear functional responses, in particular of the form $\beta x^{q} y$ or Holling-type functional response, were investigated in [20–23].

Note that $\kappa > 1$ in (1.4). To simplify the study, we fix the slope $\kappa = 2$ in the present paper, and system (1.3) becomes

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \lambda - dx - \frac{y^2}{\mathrm{ID}_{50}^2 + y^2}x, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{y^2}{\mathrm{ID}_{50}^2 + y^2}x - ay. \end{aligned} \tag{1.5}$$

To be concise in notations, rescale (1.5) by $X = x/\mathrm{ID}_{50}$, $Y = y/\mathrm{ID}_{50}$. For simplicity, we still use variables x, y instead of X, Y and obtain

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= m - dx - \frac{y^2}{1+y^2}x, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{y^2}{1+y^2}x - ay, \end{aligned} \tag{1.6}$$

where $m = \lambda/\mathrm{ID}_{50}$. Note that $1/d$ is the average life time of susceptible cells and $1/a$ is the average life-time of infected cells. Thus, $a \geq d$ is always valid by means of biological detection. If $a = d$, the virus does not kill infected cells. Therefore, the virus is non cytopathic in vivo. However, when $a > d$, which means that the virus kills infected cells before its average life time, the virus is cytopathic in vivo.

The main purpose of this paper is to study the effect of the nonlinear infection rate on the dynamics of (1.6). We will perform a qualitative analysis and derive the Allee-type dynamics which result from the appearance of bistable states or saddle-node state in (1.6). The bifurcation analysis indicates that (1.6) undergoes a Bogdanov-Takens bifurcation at the degenerate singular infection equilibrium which includes a saddle-node bifurcation, a Hopf bifurcation, and a homoclinic bifurcation. Thus, the nonlinear infection rate can induce the complex dynamic behaviors in the viral infection model.

The organization of the paper is as follows. In Section 2, the qualitative analysis of system (1.6) is performed, and the stability of the equilibria is obtained. The results indicate that (1.6) can display an Allee effect. Section 3 gives the bifurcation analysis, which indicates that the dynamics of (1.6) is more complex than that of (1.1) and (1.2). Finally, a brief discussion on the direct biological implications of the results is given in Section 4.

2. Qualitative Analysis

Since we are interested in virus pathogenesis and not initial processes of infection, we assume that the initial data for the system (1.6) are such that

$$x(0) > 0, \qquad y(0) > 0. \tag{2.1}$$

The objective of this section is to perform a qualitative analysis of system (1.6) and derive the Allee-type dynamics. Clearly, the solutions of system (1.6) with positive initial values are positive and bounded. Let $g(y) = y/(1+y^2)$, and note that (1.6) has one and only one infection-free equilibrium $E_0 = (m/d, 0)$. Then by using the formula of a basic reproduction number for the compartmental models in van den Driessche and Watmough [24], we know that the basic reproduction number of virus of (1.6) is

$$R_0 = \frac{1}{a} \cdot \frac{m}{d} \cdot g(0) = 0, \tag{2.2}$$

which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process as zero. Although it is zero, we will show that the virus can still persist in host.

We start by studying the equilibria of (1.6). Obviously, the infection-free equilibrium $E_0 = (m/d, 0)$ always exists and is a stable hyperbolic node because the corresponding characteristic equation is $(\omega + d)(\omega + a) = 0$.

In order to find the positive (infection) equilibria, set

$$\begin{aligned} m - dx - \frac{y^2}{1+y^2}x &= 0, \\ \frac{y}{1+y^2}x - a &= 0, \end{aligned} \tag{2.3}$$

then we have the equation

$$a(1+d)y^2 - my + ad = 0. \tag{2.4}$$

Based on (2.4), we can obtain that

(i) there is no infection equilibria if $m^2 < 4a^2d(1+d)$;

(ii) there is a unique infection equilibrium $E_1 = (x^*, y^*)$ if $m^2 = 4a^2d(1+d)$;

(iii) there are two infection equilibria $E_{11} = (\overline{x}_1, \overline{y}_1)$ and $E_{12} = (\overline{x}_2, \overline{y}_2)$ if $m^2 > 4a^2d(1+d)$.

Here,

$$y^* = \frac{m}{2a(1+d)}, \qquad x^* = \frac{a\left(1+y^{*2}\right)}{y^*},$$
$$\overline{y}_1 = \frac{m-\sqrt{m^2-4a^2d(1+d)}}{2a(1+d)}, \qquad \overline{x}_1 = \frac{a\left(1+\overline{y}_1^2\right)}{\overline{y}_1}, \tag{2.5}$$
$$\overline{y}_2 = \frac{m+\sqrt{m^2-4a^2d(1+d)}}{2a(1+d)}, \qquad \overline{x}_2 = \frac{a\left(1+\overline{y}_2^2\right)}{\overline{y}_2}.$$

Thus, the surface

$$\mathrm{SN} = \left\{(m,d,a) : m^2 = 4a^2d(1+d)\right\} \tag{2.6}$$

is a *Saddle-Node bifurcation* surface, that is, on one side of the surface SN system (1.6) has not any positive equilibria; on the surface SN system (1.6) has only one positive equilibrium; on the other side of the surface SN system (1.6) has two positive equilibria. The detailed results will follow.

Next, we determine the stability of E_{11} and E_{12}. The Jacobian matrix at E_{11} is

$$\mathrm{J}_{E_{11}} = \begin{bmatrix} -d - \dfrac{\overline{y}_1^2}{1+\overline{y}_1^2} & -\dfrac{2\overline{x}_1\overline{y}_1}{\left(1+\overline{y}_1^2\right)^2} \\ \dfrac{\overline{y}_1^2}{1+\overline{y}_1^2} & -a + \dfrac{2\overline{x}_1\overline{y}_1}{\left(1+\overline{y}_1^2\right)^2} \end{bmatrix}. \tag{2.7}$$

After some calculations, we have

$$\det\left(\mathrm{J}_{E_{11}}\right) = -\frac{a(1+d)\left(4a^2d(1+d)+m\left(\sqrt{m^2-4a^2d(1+d)}-m\right)\right)}{2a^2(1+d)+m\left(m-\sqrt{m^2-4a^2d(1+d)}\right)}. \tag{2.8}$$

Since $m^2 > 4a^2d(1+d)$ in this case, $4a^2d(1+d)+m(\sqrt{m^2-4a^2d(1+d)}-m)) > 0$ is valid. Thus, $\det(\mathrm{J}_{E_{11}}) < 0$ and the equilibrium E_{11} is a saddle.

The Jacobian matrix at E_{12} is

$$\mathrm{J}_{E_{12}} = \begin{bmatrix} -d - \dfrac{\overline{y}_2^2}{1+\overline{y}_2^2} & -\dfrac{2\overline{x}_2\overline{y}_2}{\left(1+\overline{y}_2^2\right)^2} \\ \dfrac{\overline{y}_2^2}{1+\overline{y}_2^2} & -a + \dfrac{2\overline{x}_2\overline{y}_2}{\left(1+\overline{y}_2^2\right)^2} \end{bmatrix}. \tag{2.9}$$

By a similar argument as above, we can obtain that $\det(J_{E_{12}}) > 0$. Thus, the equilibrium E_{12} is a node, or a focus, or a center.

For the sake of simplicity, we denote

$$m_\varepsilon = 2a\sqrt{d(1+d)},$$
$$m_0 = \frac{a^2(1+2d)}{\sqrt{(a-d)(1+a+d)}}, \quad \text{if } a > 2d(1+d). \tag{2.10}$$

We have the following results on the stability of E_{12}.

Theorem 2.1. *Suppose that equilibrium E_{12} exists; that is, $m > m_\varepsilon$. Then E_{12} is always stable if $d \le a \le 2d(1+d)$. When $a > 2d(1+d)$, we have*

(i) *E_{12} is stable if $m > m_0$;*

(ii) *E_{12} is unstable if $m < m_0$;*

(iii) *E_{12} is a linear center if $m = m_0$.*

Proof. After some calculations, the matrix trace of $J_{E_{12}}$ is

$$\operatorname{tr}(J_{E_{12}}) = \frac{2a^3(1+d)(1+2d) - m(1+a+d)\left(m + \sqrt{m^2 - 4a^2d(1+d)}\right)}{2a^2(1+d) + m\left(m + \sqrt{m^2 - 4a^2d(1+d)}\right)}, \tag{2.11}$$

and its sign is determined by

$$F(m) \triangleq 2a^3(1+d)(1+2d) - m(1+a+d)\left(m + \sqrt{m^2 - 4a^2d(1+d)}\right). \tag{2.12}$$

Note that

$$F'(m) = -(1+a+d)\left(2m + \sqrt{m^2 - 4a^2d(1+d)} + \frac{m^2}{\sqrt{m^2 - 4a^2d(1+d)}}\right) < 0, \tag{2.13}$$

which means that $F(m)$ is a monotone decreasing function of variable m.

Clearly,

$$F(m_\varepsilon) = 2a^2(1+d)(a - 2d(1+d)) \begin{cases} > 0, & \text{if } a > 2d(1+d), \\ \le 0, & \text{if } a \le 2d(1+d). \end{cases} \tag{2.14}$$

Note that $F(m) = 0$ implies that

$$\frac{2a^3(1+d)(1+2d)}{m(1+a+d)} - m = \sqrt{m^2 - 4a^2d(1+d)}. \tag{2.15}$$

Squaring (2.15) we find that

$$\frac{4a^6(1+d)^2(1+2d)^2}{m^2(1+a+d)^2} - \frac{4a^3(1+d)(1+2d)}{1+a+d} + m^2 = m^2 - 4a^2d(1+d). \tag{2.16}$$

Thus,

$$\begin{aligned} \frac{a^4(1+d)(1+2d)^2}{m^2(1+a+d)^2} &= \frac{a(1+2d)}{1+a+d} - d = \frac{(a-d)(1+d)}{1+a+d}, \\ m &= \frac{a^2(1+2d)}{\sqrt{(a-d)(1+a+d)}}. \end{aligned} \tag{2.17}$$

This means that $F(m_0) = 0$. Thus, under the condition of $m > m_\varepsilon$ and the sign of $F(m)$, tr $(J_{E_{12}}) < 0$ is always valid if $a \leq 2d(1+d)$. When $a > 2d(1+d)$, $\mathrm{tr}(J_{E_{12}}) < 0$ if $m > m_0$, $\mathrm{tr}(J_{E_{12}}) > 0$ if $m < m_0$, and $\mathrm{tr}(J_{E_{12}}) = 0$ if $m = m_0$. □

For (1.6), its asymptotic behavior is determined by the stability of E_{12} if it does not have a limit cycle. Next, we begin to consider the nonexistence of limit cycle in (1.6).

Note that E_{11} is a saddle and E_{12} is a node, a focus, or a center. A limit cycle of (1.6) must include E_{12} and does not include E_{11}. Since the flow of (1.6) moves toward down on the line where $y = \overline{y}_1$ and $x < \overline{x}_1$ and moves towards up on the line where $y = \overline{y}_1$ and $x > \overline{x}_1$, it is easy to see that any potential limit cycle of (1.6) must lie in the region where $y > \overline{y}_1$. Take a Dulac function $D = (1+y^2)/y^2$, and denote the right-hand sides of (1.6) by P_1 and P_2, respectively. We have

$$\frac{\partial(DP_1)}{\partial x} + \frac{\partial(DP_2)}{\partial y} = -\frac{(1+a+d)y^2 - (a-d)}{y^2}, \tag{2.18}$$

which is negative if $y^2 > (a-d)/(1+a+d)$. Hence , we can obtain the following result.

Theorem 2.2. *There is no limit cycle in* (1.6) *if*

$$\overline{y}_1^2 > \frac{(a-d)}{(1+a+d)}. \tag{2.19}$$

Note that $\overline{y}_1 > 0$ as long as it exists. Thus, inequality (2.19) is always valid if $a = d$. When $a > d$, using the expression of $\overline{y}_1$ in (2.5), we have that inequality (2.19) that is equivalent to

$$\frac{2a^3(1+d)(1+2d)}{1+a+d} < m^2 < \frac{a^4(1+2d)^2}{(a-d)(1+a+d)}. \tag{2.20}$$

Indeed, since

$$\begin{aligned} \overline{y}_1^2 &= \frac{m^2}{2a^2(1+d)^2} - \frac{d}{1+d} - \frac{m\sqrt{m^2-4a^2d(1+d)}}{2a^2(1+d)^2}, \\ \frac{m^2}{2a^2(1+d)^2} - \frac{d}{1+d} - \frac{a-d}{1+a+d} &= \frac{m^2}{2a^2(1+d)^2} - \frac{a(1+2d)}{(1+d)(1+a+d)}, \end{aligned} \tag{2.21}$$

we have (2.19) that is equivalent to

$$\frac{m^2}{2a^2(1+d)^2} - \frac{a(1+2d)}{(1+d)(1+a+d)} > \frac{m\sqrt{m^2-4a^2d(1+d)}}{2a^2(1+d)^2}, \tag{2.22}$$

that is,

$$m^2 - \frac{2a^3(1+d)^2(1+2d)}{(1+d)(1+a+d)} > m\sqrt{m^2-4a^2d(1+d)}. \tag{2.23}$$

Thus,

$$m^2 > \frac{2a^3(1+d)^2(1+2d)}{(1+d)(1+a+d)}. \tag{2.24}$$

On the other hand, squaring (2.23) we find that

$$m^4 - \frac{4a^3(1+d)^2(1+2d)}{(1+d)(1+a+d)}m^2 + \frac{4a^6(1+d)^4(1+2d)^2}{(1+d)^2(1+a+d)^2} > m^4 - 4a^2d(1+d)m^2, \tag{2.25}$$

which is equivalent to

$$m^2 < \frac{a^4(1+2d)^2}{(a-d)(1+a+d)}. \tag{2.26}$$

The combination of (2.24) and (2.26) yields (2.20).

Furthermore,

$$4a^2d(1+d) < \frac{a^4(1+2d)^2}{(a-d)(1+a+d)} \tag{2.27}$$

is equivalent to $a \neq 2d(1+d)$, both

$$\begin{aligned} \frac{2a^3(1+d)(1+2d)}{1+a+d} &< \frac{a^4(1+2d)^2}{(a-d)(1+a+d)}, \\ \frac{2a^3(1+d)(1+2d)}{1+a+d} &< 4a^2d(1+d) \end{aligned} \tag{2.28}$$

are equivalent to $a < 2d(1+d)$. Consequently, we have the following.

Corollary 2.3. *There is no limit cycle in* (1.6) *if either of the following conditions hold:*

(i) $a = d$ *and* $m^2 > 4a^2d(1+d)$;

(ii) $d < a < 2d(1+d)$ *and* $4a^2d(1+d) < m^2 < a^4(1+2d)^2/(a-d)(1+a+d)$.

When $m^2 = 4a^2d(1+d)$, system (1.6) has a unique infection equilibrium E_1. The Jacobian matrix at E_1 is

$$\mathrm{J}_{E_1} = \begin{bmatrix} -d - \dfrac{y^{*2}}{1+y^{*2}} & -\dfrac{2x^*y^*}{\left(1+y^{*2}\right)^2} \\ \dfrac{y^{*2}}{1+y^{*2}} & -a + \dfrac{2x^*y^*}{\left(1+y^{*2}\right)^2} \end{bmatrix}. \tag{2.29}$$

The determinant of J_{E_1} is

$$\det\left(\mathrm{J}_{E_1}\right) = -\frac{a(1+d)\left(4a^2d(1+d) - m^2\right)}{m^2 + 4a^2(1+d)^2} = 0, \tag{2.30}$$

and the trace of J_{E_1} is

$$\mathrm{tr}\left(\mathrm{J}_{E_1}\right) = \frac{4a^2(1+d)(a-2d(1+d))}{m^2 + 4a^2(1+d)^2}. \tag{2.31}$$

Thus, E_1 is a degenerate singular point. Since its singularity, complex dynamic behaviors may occur, which will be studied in the next section.

3. Bifurcation Analysis

In this section, the Bogdanov-Takens bifurcation (for short, BT bifurcation) of system (1.6) is studied when there is a unique degenerate infection equilibrium E_1.

For simplicity of computation, we introduce the new time τ by $dt = (1+y^2)d\tau$, rewrite τ as t, and obtain

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= m - dx + my^2 - (1+d)xy^2, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= -ay + xy^2 - ay^3. \end{aligned} \tag{3.1}$$

Note that (3.1) and (1.6) are C^∞-equivalent; both systems have the same dynamics (only the time changes).

As the above mentioned, assume that

(H1) $m^2 = 4a^2d(1+d)$.

Then (3.1) admits a unique positive equilibrium $E_1 = (x^*, y^*)$, where

$$x^* = \frac{2a^2(1+2d)}{m}, \qquad y^* = \frac{m}{2a(1+d)}. \tag{3.2}$$

In order to translate the positive equilibrium E_1 to origin, we set $X = x - x^*$, $Y = y - y^*$ and obtain

$$\begin{aligned} \frac{\mathrm{d}X}{\mathrm{d}t} &= -2dX - 2aY - \frac{2a^2(1+d)}{m}Y^2 - \frac{m}{a}XY - (1+d)XY^2, \\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= \frac{d}{1+d}X + 2dY + \frac{m}{a(1+d)}XY + \frac{2a^2(1-d)}{m}Y^2 + XY^2 - aY^3. \end{aligned} \tag{3.3}$$

Since we are interested in codimension 2 bifurcation, we assume further that

(H2) $a = 2d(1+d)$.

Then, after some transformations, we have the following result.

Theorem 3.1. *The equilibrium E_1 of* (1.6) *is a cusp of codimension* 2 *if (H1) and (H2) hold; that is, it is a Bogdanov-Takens singularity.*

Proof. Under assumptions (H1) and (H2), it is clear that the linearized matrix of (3.3)

$$M = \begin{bmatrix} -2d & -2a \\ \dfrac{d}{1+d} & 2d \end{bmatrix} \tag{3.4}$$

has two zero eigenvalues. Let $x = X$, $y = -2dX - 2aY$. Since the parameters m, a, d satisfy the assumptions (H1) and (H2), after some algebraic calculations, (3.3) is transformed into

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= y + \frac{md}{2a^2}x^2 - \frac{1+d}{2m}y^2 + f_1(x,y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{md^2(2d+1)}{a^2}x^2 + \frac{2md^2}{a^2}xy + \frac{m(2d-1)}{4a^2}y^2 + f_2(x,y), \end{aligned} \tag{3.5}$$

where $f_i(x,y)$, $i = 1,2$, are smooth functions in variables (x,y) at least of the third order. Using an affine translation $u = x + y/2d$, $v = y$ to (3.5), we obtain

$$\begin{aligned}\frac{\mathrm{d}u}{\mathrm{d}t} &= v + \frac{m}{2a}u^2 - \frac{m}{a^2}uv + \tilde{f}_1(u,v),\\ \frac{\mathrm{d}v}{\mathrm{d}t} &= \frac{md^2(2d+1)}{a^2}u^2 - \frac{md}{a^2}uv + \tilde{f}_2(u,v),\end{aligned} \tag{3.6}$$

where $\tilde{f}_i(u,v)$, $i = 1,2$, are smooth functions in variables (u,v) at least of order three. To obtain the canonical normal forms, we perform the transformation of variables by

$$x = u + \frac{m}{2a^2}u^2, \qquad y = v + \frac{m}{2a}u^2. \tag{3.7}$$

Then, (3.6) becomes

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= y + F_1(x,y),\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{md^2(2d+1)}{a^2}x^2 + \frac{md(2d+1)}{a^2}xy + F_2(x,y),\end{aligned} \tag{3.8}$$

where $F_i(x,y)$, $i = 1,2$, are smooth functions in (x,y) at least of the third order.

Obviously,

$$\begin{aligned}\frac{md^2(2d+1)}{a^2} &> 0,\\ \frac{md(2d+1)}{a^2} &> 0.\end{aligned} \tag{3.9}$$

This implies that the origin of (3.3), that is, E_1 of (1.6), is a cusp of codimension 2 by in [25, Theorem 3, Section 2.11]. □

In the following we will investigate the approximating BT bifurcation curves. The parameters m and a are chosen as bifurcation parameters. Consider the following perturbed system:

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= m_0 + \lambda_1 - dx - \frac{xy^2}{1+y^2},\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{xy^2}{1+y^2} - (a_0 + \lambda_2)y,\end{aligned} \tag{3.10}$$

where m_0, a_0 and d are positive constants while (H1) and (H2) are satisfied. That is to say,

$$m_0^2 = 4a_0^2 d(1+d), \qquad a_0 = 2d(1+d). \tag{3.11}$$

λ_1 and λ_2 are in the small neighborhood of $(0,0)$; x and y are in the small neighborhood of (x^*, y^*), where

$$x^* = \frac{2a_0^2(1+2d)}{m_0}, \qquad y^* = \frac{m_0}{2a_0(1+d)}. \tag{3.12}$$

Clearly, if $\lambda_1 = \lambda_2 = 0$, (x^*, y^*) is the degenerate equilibrium E_1 of (1.6). Substituting $X = x - x^*$, $Y = y - y^*$ into (3.10) and using Taylor expansion, we obtain

$$\begin{aligned}
\frac{dX}{dt} &= \left(1+y^{*2}\right)\lambda_1 - \left(d + (1+d)y^{*2}\right)X - 2\left(a_0(1+2d) - (m_0+\lambda_1)y^*\right)Y \\
&\quad + (m_0 - (d+1)x^* + \lambda_1)Y^2 - \frac{m_0}{a_0}XY + f_1(X,Y,\lambda), \\
\frac{dY}{dt} &= -y^*\left(1+y^{*2}\right)\lambda_2 + y^{*2}X + \left(2x^*y^* - a_0\left(1+3y^{*2}\right) - \left(1+3y^{*2}\right)\lambda_2\right)Y \\
&\quad + 2y^*XY + \left(x^* - 3a_0y^* - 3y^*\lambda_2\right)Y^2 + f_2(X,Y,\lambda),
\end{aligned} \tag{3.13}$$

where $\lambda = (\lambda_1, \lambda_2)$, $f_i(X,Y,\lambda)$, $i = 1,2$, are smooth functions of X, Y and λ at least of order three in variables (X,Y). Making the change of variables $x = X$, $y = -2dX - 2(a_0 - y^*\lambda_1)Y$ to (3.13) and noting the conditions in (3.11) and expressions in (3.12), we have

$$\begin{aligned}
\frac{dx}{dt} &= \left(1+y^{*2}\right)\lambda_1 + y + \left(\frac{m_0 d}{2a_2^2} - \frac{d^2}{a_2^2}\lambda_1\right)x^2 + \frac{1}{4a_2^2}\left(\lambda_1 - \frac{m_0}{2d}\right)y^2 + \widetilde{f}_1(x,y,\lambda), \\
\frac{dy}{dt} &= \beta_0 + \beta_1 x + \beta_2 y + \beta_3 x^2 + \beta_4 xy + \beta_5 y^2 + \widetilde{f}_2(x,y,\lambda),
\end{aligned} \tag{3.14}$$

where

$$\begin{aligned}
a_2 &= a_0 - y^*\lambda_1, \\
\beta_0 &= -2d\left(1+y^{*2}\right)\lambda_1 + 2a_2y^*\left(1+y^{*2}\right)\lambda_2, \\
\beta_1 &= \frac{2d}{1+d}y^*\lambda_1 - 2d\left(1+3y^{*2}\right)\lambda_2, \\
\beta_2 &= -\left(1+3y^{*2}\right)\lambda_2, \\
\beta_3 &= \frac{m_0d^2(2d+1)}{a_0a_2} - \frac{4m_0d^2}{a_2(1+d)}\lambda_1 + \frac{6d^2y^*}{a_2}\lambda_2, \\
\beta_4 &= \frac{2m_0d^2}{a_0a_2} - \frac{2m_0d}{a_2(1+d)}\lambda_1 + \frac{6dy^*}{a_2}\lambda_2, \\
\beta_5 &= \frac{m_0(2d-1)}{4a_2a_0} + \frac{3y^*}{2a_2}\lambda_2.
\end{aligned} \tag{3.15}$$

$\widetilde{f}_i(u,v,\lambda)$, $i=1,2$, are smooth functions in variables (u,v) at least of the third order, and the coefficients depend smoothly on λ_1 and λ_2.

Let $X = x + y/2d$, $Y = y$. Using (3.11) and (3.12), after some algebraic calculations, we obtain

$$\begin{aligned}\frac{\mathrm{d}X}{\mathrm{d}t} &= c_0 + c_1X + c_2Y + c_3X^2 + c_4XY + F_1(X,Y,\lambda),\\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= e_0 + e_1X + e_2Y + e_3X^2 + e_4XY + F_2(X,Y,\lambda),\end{aligned} \tag{3.16}$$

where $F_i(X,Y,\lambda)$, $i=1,2$, are smooth functions of X, Y and λ at least of the third order in variables (X,Y),

$$\begin{aligned}c_0 &= \frac{1}{d}a_2y^*\left(1+y^{*2}\right)\lambda_2,\\ c_1 &= \frac{y^*}{1+d}\lambda_1 - \left(1+3y^{*2}\right)\lambda_2,\\ c_2 &= 1-\frac{y^*}{a_0}\lambda_1,\\ c_3 &= \frac{m_0}{a_0a_2}\left(d(1+d)+\frac{3d}{2(1+d)}\lambda_2-\frac{2a_0d}{1+d}\lambda_1\right),\\ c_4 &= \frac{m_0}{a_0a_2}(-1+2d\lambda_1),\\ e_0 &= -2d\left(1+y^{*2}\right)\lambda_1+2a_2y^*\left(1+y^{*2}\right)\lambda_2,\\ e_1 &= 2dc_1,\\ e_2 &= -\frac{y^*}{1+d}\lambda_1,\\ e_3 &= \frac{m_0d^2}{a_0a_2}\left(2d+1+\frac{3}{1+d}\lambda_2-\frac{4a_0}{1+d}\lambda_1\right),\\ e_4 &= \frac{m_0d}{a_0a_2}\left(-1+\frac{2a_0}{1+d}\lambda_1\right).\end{aligned} \tag{3.17}$$

Let $x = X$, $y = c_0 + c_1X + c_2Y + c_3X^2 + c_4XY + F_1(X,Y,\lambda)$. Then (3.16) becomes

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= y,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= b_0 + b_1x + b_2y + b_3x^2 + b_4xy + b_5y^2 + G(x,y,\lambda),\end{aligned} \tag{3.18}$$

where

$$\begin{aligned} b_0 &= c_2e_0 - c_0e_2, \\ b_1 &= c_2e_1 + c_4e_0 - c_1e_2 - c_0e_4, \\ b_2 &= c_1 - c_0\frac{c_4}{c_2} + e_2, \\ b_3 &= c_2e_3 + c_4e_1 - c_3e_2 - c_1e_4, \\ b_4 &= 2c_3 - c_1\frac{c_4}{c_2} + c_0\frac{c_4^2}{c_2^2} + e_4, \\ b_5 &= \frac{c_4}{c_2}. \end{aligned} \tag{3.19}$$

$G(x, y, \lambda)$ is smooth function in variables (x, y) at least of order three, and all the coefficients depend smoothly on λ_1 and λ_2.

By setting $X = x + b_2/b_4$, $Y = y$ to (3.18), we obtain

$$\begin{aligned} \frac{dX}{dt} &= Y, \\ \frac{dY}{dt} &= r_0 + r_1X + b_3X^2 + b_4XY + b_5Y^2 + G_1(X, Y, \lambda), \end{aligned} \tag{3.20}$$

where $G_1(X, Y, \lambda)$ is smooth function in variables (X, Y) at least of the third order and

$$\begin{aligned} r_0 &= \frac{b_0b_4^2 - b_1b_2b_4 + b_3b_2^2}{b_4^2}, \\ r_1 &= \frac{b_1b_4 - 2b_2b_3}{b_4}. \end{aligned} \tag{3.21}$$

Now, introducing a new time variable τ to (3.20), which satisfies $dt = (1 - b_5X)d\tau$, and still writing τ as t, we have

$$\begin{aligned} \frac{dX}{dt} &= Y(1 - b_5X), \\ \frac{dY}{dt} &= \left(r_0 + r_1X + b_3X^2 + b_4XY + b_5Y^2\right)(1 - b_5X) + G_2(X, Y, \lambda), \end{aligned} \tag{3.22}$$

where $G_2(X, Y, \lambda)$ is smooth function of X, Y and λ at least of three order in variables (X, Y). Setting $x = X$, $y = Y(1 - b_5 X)$ to (3.22), we obtain

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= y, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= r_0 + q_1 x + q_2 x^2 + b_4 xy + G_3(x, y, \lambda), \end{aligned} \tag{3.23}$$

where $G_3(x, y, \lambda)$ is smooth function of x, y and λ at least of order three in variables (x, y) and

$$\begin{aligned} q_1 &= r_1 - 2r_0 b_5, \\ q_2 &= r_0 b_5^2 - 2r_1 b_5 + b_3. \end{aligned} \tag{3.24}$$

If $\lambda_1 \to 0$ and $\lambda_2 \to 0$, it is easy to obtain the following results:

$$\begin{aligned} r_0 &\longrightarrow 0, \\ q_1 &\longrightarrow 0, \\ q_2 &\longrightarrow \frac{m_0 d^2 (2d+1)}{a_0^2} > 0 \\ b_4 &\longrightarrow \frac{m_0 d (2d+1)}{a_0^2} > 0. \end{aligned} \tag{3.25}$$

By setting $X = (b_4^2/q_2)x + q_1 b_4^2/2q_2^2$, $Y = b_4^3/q_2^2$ and $\tau = (q_2/b_4)t$, and rewriting (X, Y, τ) as (x, y, t), we obtain

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= y, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \mu_1 + \mu_2 y + x^2 + xy + G_4(x, y, \lambda), \end{aligned} \tag{3.26}$$

where

$$\begin{aligned} \mu_1 &= \frac{r_0 b_4^4}{q_2^3} - \frac{q_1^2 b_4^4}{4q_2^4}, \\ \mu_2 &= -\frac{q_1 b_4^2}{2q_2^2}, \end{aligned} \tag{3.27}$$

and $G_4(x, y, \lambda)$ is smooth function of x, y and λ at least of order three in variables (x, y).

By the theorem of Bogdanov in [26, 27] and the result of Perko in [25], we obtain the following local representations of bifurcation curves in a small neighborhood Δ of the origin (i.e., E_1 of (1.6)).

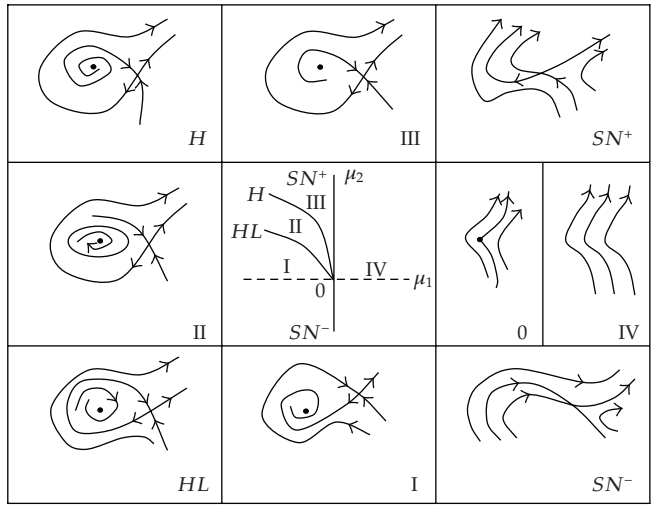

Figure 1: The bifurcation set and the corresponding phase portraits of system (3.26) at origin.

Theorem 3.2. *Let the assumptions (H1) and (H2) hold. Then* (1.6) *admits the following bifurcation behaviors:*

(i) *there is a saddle-node bifurcation curve* $\mathrm{SN}^{\pm} = \{(\lambda_1, \lambda_2) : \mu_1 = 0,\ \mu_2 > 0 \text{ or } \mu_2 < 0\}$;

(ii) *there is a Hopf bifurcation curve* $\mathrm{H} = \{(\lambda_1, \lambda_2) : \mu_1 = -\mu_2^2 + o(\|\lambda\|^2),\ q_1 < 0\}$;

(iii) *there is a homoclinic-loop bifurcation curve* $\mathrm{HL} = \{(\lambda_1, \lambda_2) : \mu_1 = -(49/25)\mu_2^2 + o(\|\lambda\|^2)\}$.

Concretely, as the statement in [28, Chapter 3], when $(\mu_1, \mu_2) \in \Delta$, the orbital topical structure of the system (3.26) at origin (corresponding system (1.6) at E_1) is shown in Figure 1.

4. Discussion

Note that most infection experiments suggest that the infection rate of microparasitic infections is an increasing function of the parasite dose, usually sigmoidal in shape. In this paper, we study a viral infection model with a type of nonlinear infection rate, which was introduced by Regoes et al. [11].

Qualitative analysis (Theorem 2.1) implies that infection equilibrium E_{12} is always stable if the virus is noncytopathic, $a = d$, or cytopathic in vivo but its cytopathic effect is less than or equal to an appropriate value, $a \leq 2d(1 + d)$. When the cytopathic effect of virus is greater than the threshold value, $a > 2d(1 + d)$, the stability of the infection equilibrium E_{12} depends on the value of parameter m, which is proportional to the birth rate of susceptible cells λ and is in inverse proportion to the infectious dose ID_{50}. The infection equilibrium is stable if $m > m_0$ and becomes unstable if $m < m_0$. When m gets to the critical value, $m = m_0$, the infection equilibrium is a linear center, so the oscillation behaviors may occur.

If our model (1.6) does not have a limit cycle (see Theorem 2.2 and Corollary 2.3), its asymptotic behavior is determined by the stability of E_{12}. When E_{12} is stable, there is a region outside which positive semiorbits tend to E_0 as t tends to infinity and inside

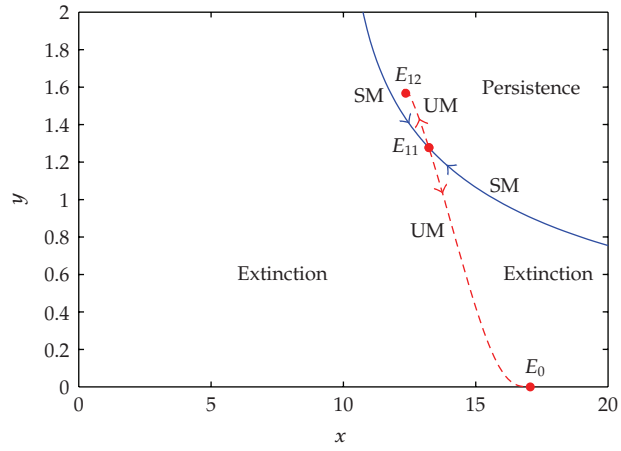

Figure 2: Illustrations of the Allee effect for (1.5). Here, $\lambda = 17.06$, $d = 1.0$, $a = 3.0$, $ID_{50} = 2$. $E_0 = (17.06, 0)$ is stable, $E_{11} = (13.2311, 1.2763)$ is a saddle point, $E_{12} = (12.3589, 1.567)$ is stable. Note that SM is the stable manifolds of E_{11} (solid line), UM is the unstable manifolds of E_{11} (dash line), and the phase portrait of (1.6) is divided into two domains of extinction and persistence of the virus by SM.

which positive semi-orbits tend to E_{12} as t tends to infinity; that is, the virus will persist if the initial position lies in the region and disappear if the initial position lies outside this region. Thus, besides the value of parameters, the initial concentration of the virus can also affect the result of invasion. An invasion threshold may exist in these cases, which is typical for the so-called *Allee effect* that occurs when the abundance or frequency of a species is positively correlated with its growth rate (see [11]). Consequently, the unrescaled model (1.5) can display an Allee effect (see Figure 2), which is an infrequent phenomenon in current viral infection models though it is reasonable and important in viral infection process.

Furthermore, when infection equilibrium becomes a degenerate singular point, we have shown that the dynamics of this model are very rich inside this region (see Theorems 3.1 and 3.2 and Figure 1). Static and dynamical bifurcations, including saddle-node bifurcation, Hopf bifurcation, homoclinic bifurcation, and bifurcation of cusp-type with codimension two (i.e., Bogdanov-Takens bifurcation), have been exhibited. Thus, besides the Allee effect, our model (1.6) shows that the viral oscillation behaviors can occur in the host based on the appropriate conditions, which was observed in chronic HBV or HCV carriers (see [29–31]). These results inform that the viral infection is very complex in the development of a better understanding of diseases. According to the analysis, we find that the cytopathic effect of virus and the birth rate of susceptible cells are both significant to induce the complex and interesting phenomena, which is helpful in the development of various drug therapy strategies against viral infection.

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