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Stability of a Class of Viral Dynamics with Two Delays

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Abstract–The local stability near a equilibrium of a viral dynamics with two delays is discussed in the paper. Taking one of the two delays as the control parameter, the stability is determined by checking the happens of stability switch through the critical delays. Numerical simulation is given for demonstration.

Keywords– two delays, virus, stability switch

1. Introduction

Infectious disease has always been a killer threatening to human's health. The black death in 1340, the Spanish flu in 1918, and cholera in the 19th century all caused a death of tens of millions of people. In order to prevent or even eliminate these infectious diseases, it is necessary to clarify the pathogenesis of these viruses. The mathematical modeling of HIV, SARS, HBV and Ebola and so on, helps much not only in understanding the virus's evolution and its dynamics mechanism, but also in finding possible strategies to prevent the virus's spread and to control progression of disease. Thus, many mathematical models have been proposed for studying the virus dynamics. One popular model, proposed by Nowak and co-authors [1][2][3], is described by the following group of differential equations

$$\begin{cases} \dot{x} = a - mx - \beta xv \\ \dot{y} = \beta xv - dy \\ \dot{v} = cy - bv \end{cases} \tag{1}$$

where x, y denote the uninfected/infected cell population respectively, and v is the virus load, a is the production rate of uninfected cells, and the positive numbers m, c and b are the fractional rates at which uninfected, infected cells and viral particles die, respectively. The problems such as how fast does virus reproduce, what kills productively the infected cells, and the curative effect of treatment, were discussed. Usually, the different kinds of virus co-exist in every organism peacefully until the number of some bad virus increases to a threshold. That is to say, virus usually has incubation period, which can be called delay effect. Thus, it is more reasonable to model the virus's dynamics with delay differential equations[4][5]. In [6], for example, two delays are introduced into Eq.(1) and the differential equations become

$$\begin{cases} \dot{x} = a - mx - \beta xv \\ \dot{y} = \beta xv - dy \\ \dot{v} = cy(t-\tau_1) - bv(t-\tau_2) \end{cases} \tag{2}$$

where τ_1 is the rate of virus produced after the dead of infected cell, τ_2 is the rate of virus eliminated after medical treatment (or from accepting medicine to kill virus). They are usually inevitable in the process of virus spreading. The global and local stability of equilibriums are discussed for three cases: $\tau_1 = \tau_2 = 0$; $\tau_1 = 0, \tau_2 > 0$; $\tau_1 > 0, \tau_2 = 0$ [6]; but no results are given for the more practical case: $\tau_1 > 0, \tau_2 > 0$. This motivates us to study the stability of this case.

This paper is organized as follows. Section 2 deals with some theoretical results about stability switch of dynamics with two delays. In section 3, the numerical simulation is demonstrated when reproductive rate satisfies $R_0 > 1$. Finally, section 4 concludes this paper..

2. Stability analysis of the equilibrium

For Eq. (2), the virus spreading is measured by effective reproductive rate of infected cells, defined by

$$R_0 = ac\beta / bdm$$

If $R_0 < 1$, the virus will not spread, Eq. (2) has exactly one infection-free equilibrium $E_0 = (a/m, 0, 0)$. When $R_0 > 1$, Eq. (2) has exactly one infection equilibrium $E_*(x_*, y_*, z_*)$, where

$$x_* = bd / \beta c$$
$$y_* = (a\beta c - bdm) / \beta cd$$
$$z_* = (a\beta c - bdm) / \beta bd$$

Both equilibriums don't depend on τ_1 or τ_2. The local dynamics near the equilibriums can be analyzed by using the method of stability switches in two steps: (i). To find the critical delay values at which the characteristic function has a pair of conjugate roots on the imaginary axis[7]; (ii). To determine the crossing direction of the branch of the characteristic root passing through the imaginary axis as the delay increases. The first step can be carried out in conventional routine, and the second step will be conducted by using the theorem proved by

Li and Ma[8], with which the crossing direction is determined by the sign of the Jacobi determinant of two auxiliary functions $E(\theta,\omega,\tau)$ and $K(\theta,\omega,\tau)$ associated with the characteristic function with two delays. In case of only one delay, if the parameters are independent of delay, the crossing direction is determined directly by the sign of the derivative of the function $F(\omega)$ deduced by Kuang[9], and if the parameters are dependent of delay, the crossing direction is determined by the sign of the Jacobi determinant of two auxiliary functions $F(\omega,\tau)$ and $G(\omega,\tau)$ defined by Wang [10][11] .

For simplicity, let us consider the case $\tau_2 = 2\tau_1$ only. This is a possible happen in reality[12], because the time of virus eliminated can be longer than virus produced when there are no special treatment for the virus. In this case, the corresponding characteristic equation reads

$$p(\lambda) = p_0 + p_1 e^{-\lambda\tau_1} + p_2 e^{-\lambda\tau_2} \tag{3}$$

Multiplying the two sides of Eq(3) by $\exp(\lambda\tau_1)$ gives

$$p(\lambda)e^{\lambda\tau_1} = p_0 e^{\lambda\tau_1} + p_1 + p_2 e^{-\lambda\tau_1} \tag{4}$$

Obviously $p(\lambda)e^{\lambda\tau_1} = 0$ if and only if $p(\lambda) = 0$. Let $\lambda = \pm i\omega\ (\omega > 0)$, by separating the real and imaginary parts of Eq. (4), the following functions give

$$\begin{cases} \cos(\omega\tau) = \dfrac{-p_0^r p_1^r + p_2^i p_1^i - p_0^i p_1^i + p_1^r p_2^r}{(p_0^i)^2 + (p_0^r)^2 - (p_2^i)^2 - (p_2^r)^2} \\ \sin(\omega\tau) = \dfrac{-p_0^r p_1^i - p_2^r p_1^i + p_0^i p_1^r + p_1^r p_2^i}{(p_0^i)^2 + (p_0^r)^2 - (p_2^i)^2 - (p_2^r)^2} \end{cases} \tag{5}$$

Where p_0^r, p_1^r, p_2^r are real parts of $p_0(i\omega)$, $p_1(i\omega)$ and $p_2(i\omega)$ respectively; p_0^i, p_1^i and p_2^i are imaginary parts of them. Based on trigonometric function, a function with respect to ω can be obtained

$$\cos^2(\omega\tau) + \sin^2(\omega\tau) = 1 \tag{6}$$

If Eq.(6) has the positive root ω, then purely imaginary roots of Eq.(3) exist, so stability switch may occur. According to the sign of $\sin(\omega\tau)$ and $\cos(\omega\tau)$, the critical delays are expressed by

$$\tau^* = \begin{cases} \dfrac{2k\pi + \arctan\theta}{\omega}, & \sin\theta > 0\ \cos\theta > 0 \\ \dfrac{2k\pi + \pi + \arctan\theta}{\omega}, & \sin\theta > 0\ \cos\theta < 0 \\ \dfrac{2k\pi + 2\pi + \arctan\theta}{\omega}, & \sin\theta < 0\ \cos\theta > 0 \\ \dfrac{2k\pi + \pi + \arctan\theta}{\omega}, & \sin\theta < 0\ \cos\theta < 0 \end{cases} \tag{7}$$

for $\theta = \omega\tau$ and $k = 0,1,2,\cdots$. By following the method in [7], the two auxiliary functions are of the form

$$\begin{cases} K(\theta,\omega) = (p_0^r + p_2^r)\cos\theta - (p_0^i - p_2^i)\sin\theta + p_1^r \\ E(\theta,\omega) = (p_0^i + p_2^i)\cos\theta + (p_0^r - p_2^r)\sin\theta + p_1^i \end{cases} \tag{8}$$

Then the direction of the characteristic root crossing through the imaginary axis is determined by

$$\operatorname{sgn}\left[\operatorname{Re}\left(\frac{d\lambda}{d\tau}\Big|_{\lambda=i\omega}\right)\right] = \operatorname{sgn}\left[-\begin{vmatrix} E_\omega' & E_\theta' \\ K_\omega' & K_\theta' \end{vmatrix}\right] \tag{9}$$

If the sign is positive (negative), then the crossing direction is from the left-half (right-half) complex plane to the right-half (left-half) complex plane, and one pair of conjugate characteristic roots with positive real part is increased (decreased) as the delay increases and passes through a critical value.

3.Numerical simulation

Let $a = 100, \beta = 0.2, m = 0.1, d = 3, b = 0.3$, and $c = 0.2$ [6], then effective reproductive rate of virus $R_0 = ac\beta / bdm > 1$, and the virus system has a non-zero equilibrium $E_*(x_*, y_*, z_*)$ with $x_* = 22.5, y_* = 32.58$ and $z_* = 21.72$ .When $\tau_1 = \tau_2 = 0$, the characteristic function is a polynomial and there is three roots with negative real part, so the equilibrium is locally asymptotically stable.

3.1 $\tau_1 \geq 0, \tau_2 = 0$

This is the case when the virus can be eliminated effectively and quickly. Then the characteristic function is

$$p_1(\lambda) = p_{10} + p_{11} e^{-\lambda\tau_1} \tag{10}$$

for

$$p_{10} = \lambda^3 + 7.74\lambda^2 + 15.7\lambda + 4$$
$$p_{11} = -(0.9\lambda + 0.09)$$

Let $\lambda = \pm i\omega (\omega > 0)$, then separating the real and imaginary parts of Eq.(10), the equation with respect to ω from Eq.(6) gives

$$0.81\omega^8 + 23.37\omega^6 + 145.7\omega^4 + 14.41\omega^2 + 0.13 = 0$$

The above equation doesn't have the positive real root. So stability switch doesn't occur and the equilibrium keeps stable. Pathologically, $\tau_2 = 0$ implies that the virus can be eliminated immediately once the virus was produced, the virus won't cause a wild spread, so the system keeps stable.

3.2 $\tau_1 = 0, \tau_2 \geq 0$

In this case, the characteristic function is of the form

$$p_2(\lambda) = p_{20} + p_{21} e^{-\lambda\tau_2} \tag{11}$$

where

$$p_{20} = \lambda^3 + 7.44\lambda^2 + 12.4\lambda - 0.09$$
$$p_{21} = 0.3\lambda^2 + 2.33\lambda + 4$$

Based on Eq.(6), the equation gives

$$\omega^{10} + 59.23\omega^8 + 1207\omega^6 + 9808\omega^4 + 26800\omega^2 = 2844$$

The only positive real root is $\omega_1 = 0.3198$, so the corresponding critical delay can be simulated

$$\tau_{1k}^{*} = \frac{2k\pi + \arctan 28.89}{0.3198} = 4.804, 24.45, \cdots$$

The auxiliary function $F(\omega)$ [9] can be shown

$$F(\omega) = \omega^6 + 30.46\omega^4 + 153.3\omega^2 - 16 \qquad (12)$$

The crossing direction of the characteristic root can be judged by the sign of the derivative of the auxiliary function $F(\omega)$

$$\operatorname{sgn}\left[\operatorname{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\Big|_{\lambda=i\omega}\right)\right] = \operatorname{sgn}\left[\frac{\mathrm{d}F}{\mathrm{d}\omega}\Big|_{\omega_1}\right] = 1$$

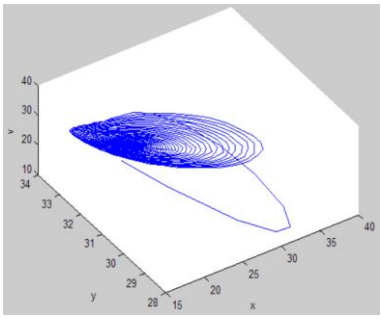

Figure1 The phase diagram when $\tau_1 = 0, \tau_2 = 4.7$

This implies the crossing direction is always from the left-half complex plane to the right-half complex plane, and one pair of conjugate characteristic roots with positive real part is increased as the delay increases and passes through a critical value. Then, stability switch does occur as the delay pass through the first critical value 4.804, and the number of characteristic roots with positive real parts in $(\tau_{1,0}, \tau_{1,1}), (\tau_{1,1}, \tau_{1,2}), (\tau_{1,2}, \tau_{1,3}), \cdots$ are $2, 4, 6, \cdots$ respectively. The equilibrium is asymptotically stable if and only if $0 < \tau < \tau_{1,0}$ .Then the stability switch doesn't occur any more and the system keeps unstable after τ_{10} (Figure2).

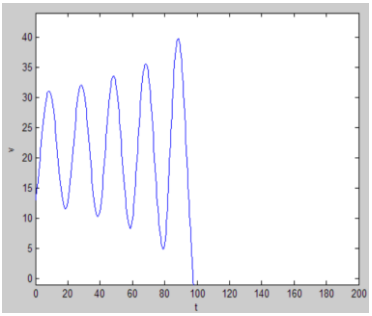

Figure2 The time history of v when $\tau_1 = 0, \tau_2 = 4.9$

3.3 When $\tau_2 = 2\tau_1$, the characteristic function becomes

$$p_3(\lambda) = p_{30} + p_{31}e^{-\lambda\tau_1} + p_{32}e^{-2\lambda\tau_1} \qquad (13)$$

where

$$p_{30} = \lambda^3 + 7.444\lambda^2 + 13.33\lambda$$

$$p_{31} = -0.9\lambda - 0.09$$

$$p_{32} = 0.3\lambda^2 + 2.333\lambda + 4$$

Let $\lambda = \pm i\omega\ (\omega > 0)$, the equation about ω gives

$$\omega^{12} + 57.33\omega^{10} + 1171\omega^8 + 9980\omega^6 + 29715\omega^4 - 5604\omega^2 = -255.9$$

The equation has two positive real roots $\omega_2 = 0.2940$, $\omega_3 = 0.3064$. So stability switch may occur, the critical delays τ_2^* and τ_3^* satisfy respectively

$$\tan(\omega_2\tau_2^{*}) = \frac{\sin(\omega_2\tau_2)}{\cos(\omega_2\tau_2)} = \frac{-0.7325}{-0.6850} = 1.069$$

$$\tan(\omega_3\tau_3^{*}) = \frac{\sin(\omega_3\tau_3)}{\cos(\omega_3\tau_3)} = \frac{0.6858}{0.7340} = 0.9343$$

They follow that

$$\tau_{2k}^{*} = \frac{2k\pi + \pi + \arctan 1.069}{0.2940} = 13.47, 34.84, 56.21, 77.58\cdots$$

$$\tau_{3k}^{*} = \frac{2k\pi + \arctan 0.9343}{0.3064} = 2.451, 22.96, 45.30, 66.67\cdots$$

Then the two groups of critical delays satisfy

$$\tau_{3,k} < \tau_{2,k} < \tau_{3,k+1}$$

for $k = 1, 2, \cdots 10$, and

$$\tau_{2,10} < \tau_{3,11} < \tau_{3,12} < \tau_{2,11}$$

The two auxiliary functions are of the form

$$\begin{cases} K(\theta,\omega) = (4 - 7.74\omega^2)\cos\theta + (\omega^3 - 11.1\omega)\sin\theta - 0.09 \\ E(\theta,\omega) = (15.6\omega - \omega^3)\cos\theta - (7.14\omega^2 + 4)\sin\theta - 0.9\omega \end{cases}$$

So the crossing direction is determined by

$$\operatorname{sgn}\left[\operatorname{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\Big|_{\lambda=i\omega_2}\right)\right] = \operatorname{sgn}(-185.7) = -1$$

$$\operatorname{sgn}\left[\operatorname{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\Big|_{\lambda=i\omega_3}\right)\right] = \operatorname{sgn}(189.0) = 1$$

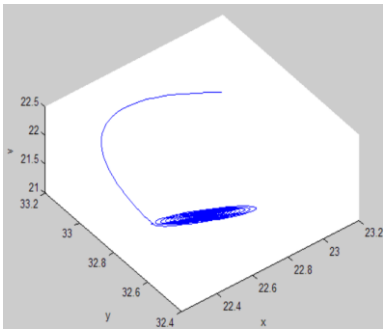

Figure3 The phase diagram $\tau_1 = 2.3$

It implies the first stability switch occurs as the delay increases and pass through $\tau_{3,0}$, and the system keeps unstable till the second stability switch occurs when the delay pass through $\tau_{2,0}$, then the system keep stable till

the stability switch occurs next time. Finally, stability switches don't occur any more after the delay pass through $\tau_{3,11}$, so the dynamics keeps unstable after $\tau_{3,11}$. Then the stable intervals are $(0,\tau_{3,0})\cup(\tau_{2,0},\tau_{3,1})\cup(\tau_{2,1},\tau_{3,2})\cup\cdots\cup(\tau_{2,10},\tau_{3,11})$, unstable intervals are $(\tau_{3,0},\tau_{2,0})\cup(\tau_{3,1},\tau_{2,1})\cup\cdots\cup(\tau_{3,10},\tau_{2,10})\cup(\tau_{3,11},+\infty)$. In fact, if the rate of virus eliminated is lower than that of virus produced, the disease is out of control. It is verified in Figure3-5, the original value is $(23,33,22)$, the time span is from 0 to 1000.

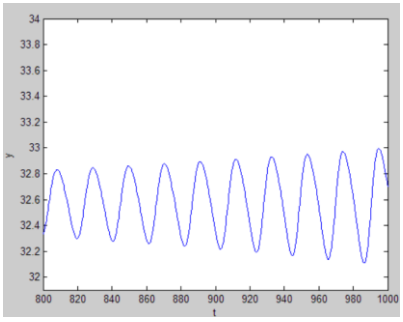

Figure4 The time history of y when $\tau_1 = 2.5$

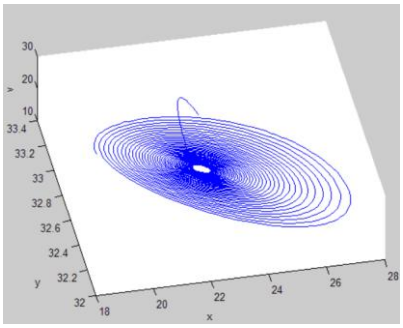

Figure5 The phase diagram $\tau_1 = 2.5$

4. Conclusion

The rate of virus produced after the dead of infected cell and the rate of virus eliminated after medical treatment (or from accepting medicine to kill virus) are two delays discussed in the paper. They play an important role in the stability of the viral dynamic system. With the increase of one of two delays from zero to infinity, the viral system undergoing a number of stability switches indicates the virus complex and uncontrolled, then the system keeps and it must be unstable ultimately.

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