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Stability and Hopf Bifurcation Analysis of a Viral Dynamic Model with Time Delay

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***Abstract*—In this paper, a new virus nonlinear dynamic model with time delay is proposed. Moreover, its stability, Hopf bifurcation and other dynamical behavior like chaos are studied. It is indicated that if the reproductive ratio is less than one, the infection-free equilibrium is partially asymptotically stable. Analytical and pictorial results show that if the reproductive ratio is greater than one, the combined effect of the reproductive ratio and the time delay is to create a rich dynamical behavior. Observing and analyzing the process from periodic oscillations to chaos can explain the different pathological feature of patients under different treatment stages. Finally, a simulation example is given to illustrate the correctness and assistance of the study on the virus dynamics research.**

Keywords—virus model; time delay; stability; Hopf bifurcation; uniform bounded

I INTRODUCTION

Over the past ten years, viral infectious disease dynamics [1] research has always been expected to be the key of overcoming all kinds of human infectious diseases. Considering that dynamic models [2] showed dynamic phenomena of rich variety, it's meaningful to establish an accurate mathematical model to control infectious diseases [3] and ultimately eliminating them.

Establishing a system model is no doubt the first step, and various function models have been used to simulate the condition in patient's body [4]. In order to be closer to realistic situation, time-delay systems [5] has become a research boom in recent years. Therefore, bringing the conception of time delay into the virus dynamics model boasts a lot of significance [6].

In this paper, the main contributions are as follows: 1) To satisfy the assumption that both the delay of the immune response and natural metabolism should be considered simultaneously, the new derived viral dynamic model with time delay is therefore more realistic. 2) We use nonlinear system stability theory and Center Manifold theory to precisely come up with the analysis basis and judgment result. 3) Several kinds of figures are demonstrated to clearly exhibit the stability character and complex dynamic behavior of system. The results extend the analysis on delay virus dynamics considered in the other papers and suggest useful methods to control virus infection.

II ESTABLISHMENT OF THE VIRUS MODEL

There has been much experience in mathematical modeling of traditional epidemic and viral dynamics [7,8] to learn from. Considering the fact that the rate viruses changing to infected cells is much higher than the reproductive ratio of the latter [9,10], namely the amount of free virus is simply proportional to the number of infected cells, a reasonable and bold hypothesis that the number of infected cells $y(t)$ can also be considered as a measure of virus load $v(t)$. Thus getting model as follows

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - \beta x(t)y(t) \\ \dot{y}(t) = \beta x(t)y(t) - ay(t) - py(t)z(t) \\ \dot{v}(t) = ky(t) - uv(t) \end{cases} \tag{1}$$

Considering that the immune cells work because of the stimulations of infected cells and viruses to the immune response, there will be a certain response time, so it will be more realistic to bring the time delay into this model. By the way, the natural immune cells metabolism will be delayed definitely at the same time. So the new viral time-delay dynamic model shows as follows

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - \beta x(t)y(t) \\ \dot{y}(t) = \beta x(t)y(t) - ay(t) - py(t)z(t) \\ \dot{z}(t) = cy(t-\tau) - bz(t-\tau) \end{cases} \tag{2}$$

where the model consists of the number of uninfected cells $x(t)$, the number of infected cells $y(t)$ and the number of immune cells $z(t)$. By the way, the uninfected cells are generated at a rate λ, die at a rate $dx(t)$ and become infected by the virus at a rate $\beta x(t)y(t)$. The infected cells are generated at a rate β, die at a rate $ay(t)$ and are killed by the immune cells at a rate $py(t)z(t)$. The immune cells are generated at a rate $cy(t-\tau)$, die at a rate $bz(t-\tau)$.

III STABILITY ANALYSIS AND EXISTENCE OF HOPF BIFURCATION

In this Section, the Lemma 1 shown in the reference [11] will be used, and another Lemma will be introduced at first.

Lemma 2 [12] (Transverse field conditions of Hopf bifurcation) Make $s(\tau)=\xi(\tau)+i\omega(\tau)$ the characteristic root of

$$\det(J-sI)=s^3+A_1s^2+A_2s+(B_1s^2+B_2s+B_3)e^{-s\tau}=0$$

the Hopf bifurcation exists if it meets $\xi(\tau_0)=0$ and $\omega(\tau_0)=\omega_0$ and its first differential of time delay τ based on characteristic root , namely

$$\mathrm{Re}\left(\frac{ds}{d\tau}\right)^{-1}\Big|_{\tau=\tau_k}\neq 0$$

In the following part. The existence of nonnegative equilibrium and local stability are going to be researched, and by the way, it is easy to verify that the solution of the system is uniformly and ultimately bounded. Two equilibriums can be derived through calculation.

$$E_0=\begin{pmatrix}\frac{\lambda}{d} & 0 & 0\end{pmatrix},\ E_1=\begin{pmatrix}x_1 & y_1 & z_1\end{pmatrix}$$

$$x_1=\frac{c\lambda}{cd+b\beta z_1},y_1=\frac{bz_1}{c},z_1=\frac{-(pcd+ab\beta)}{2bp\beta}+\frac{\sqrt{(pcd+ab\beta)^2-4bcp\beta(ad-\lambda\beta)}}{2bp\beta}$$

As for the target system, the virus reproductive ratio is $R=\frac{\lambda\beta}{ad}$. If $R<1$, E_0 , known as uninfected equilibrium point, will be the only positive one. If $R>1$, here comes a new equilibrium point, E_1 , known as the balanced infection equilibrium point, corresponding to a situation where virus and immune cells exist at the same time.

Theorem 3 If $R\leq 1$, the virus uninfected equilibrium point E_0 is partially asymptotically stable.

Proof. The Jacobian matrix of system at the equilibrium point E_0 can get us the eigenvalues equation.

$$D_{(\lambda)}=(d+\lambda)(be^{-\omega\tau}+\lambda)(-\frac{\lambda\beta}{d}+a+\lambda)$$

a) When reproductive ratio $R=\frac{\lambda\beta}{ad}\leq 1$, eigenvalues are given by

$$\lambda_1=-d<0\ ,\ \lambda_2=-be^{-\omega\tau}<0\ ,\ \lambda_3=\frac{\lambda\beta}{d}-a<0$$

It can be concluded that $E_0=\begin{pmatrix}\frac{\lambda}{d} & 0 & 0\end{pmatrix}$ is partially asymptotically stable.

b) When reproductive ratio $R=\frac{\lambda\beta}{ad}>1$, since there is at least one solution of characteristic equation greater than zero, the equilibrium E_0 is therefore a saddle point. It is concluded that snap through buckling happened here, namely when E_0 loses its stability, system jumps to another equilibrium point state. This completes the proof.

In the next part, let's define the coordinate transformation

$$x_*(t)=x(t)-x_1\ ,\ y_*(t)=y(t)-y_1\ ,\ z_*(t)=z(t)-z_1 \quad (4)$$

Note that equilibrium E_1 has been translated to the origin. The linearization of system translated to the origin is

$$\begin{cases}\dot{x}_*(t)=-(d+\beta y_1)x_*(t)-\beta x_1y_*(t)\\ \dot{y}_*(t)=\beta y_1x_*(t)-py_1z_*(t)\\ \dot{z}_*(t)=cy_*(t-\tau)-bz_*(t-\tau)\end{cases} \quad (5)$$

The characteristic equation can be described in the following form,

$$\det(J-sI)=s^3+A_1s^2+A_2s+(B_1s^2+B_2s+B_3)e^{-s\tau}=0 \quad (6)$$

also denoted as equation (3). Since the stability of system depends on how the roots of characteristic equation distribute, we will study the equation by means of Lemma 1. It is clear to find that conditions (i)–(v) of Lemma 1 are satisfied.

Through characteristic equation,

$$\tau_k^{(j)}=\frac{1}{\omega_k}[\arcsin\frac{A_1B_2\omega_k^3-(B_3-B_1\omega_k^2)(\omega_k^3-A_2\omega_k)}{B_2^2\omega_k^2+(B_3-B_1\omega_k^2)^2}+2j\pi] \quad (7)$$

where $k=1,2,3;\ j=0,1,....$,the $\pm\omega_k$ are a pair of pure imaginary root of Eq.(6) when $\tau=\tau_k^{(j)}$. The critical time delay parameter τ_k and the critical angle frequency ω_k satisfying (7) when $j=0$ are

$$\tau_k=\frac{1}{\omega_k}[\arcsin\frac{A_1B_2\omega_k^3-(B_3-B_1\omega_k^2)(\omega_k^3-A_2\omega_k)}{B_2^2\omega_k^2+(B_3-B_1\omega_k^2)^2}]\ ,\ \omega_k=\frac{-C_1-(\sqrt[3]{Y_1}+\sqrt[3]{Y_2})}{3} \quad (8)$$

where

$$Y_{1,2}=(C_1^2-3C_2)C_1+3(\frac{-(C_1C_2-9C_3)}{2}\pm\frac{\sqrt{(C_1C_2-9C_3)^2-4(C_1^2-3C_2)(C_2^2-3C_1C_3)}}{2})$$

At the same time, as for the equation in Lemma 1, we can verify the transversality condition below based on Lemma 2[11],

$$\mathrm{Re}\left(\frac{ds}{d\tau}\right)^{-1}\Big|_{\tau=\tau_k} \neq 0$$

Synthesizing all the Lemmas and Theorems above and Hopf bifurcation theory, we can obtain that,

Theorem 4 As for the system (2) in the case when reproductive ratio $R>1$.

(i) If $C_3 \geq 0$ and $\Delta \leq 0$, then Eq. $F(\omega)=0$ doesn't have any positive root, the infection equilibrium point E_1 is asymptotically stable when $\tau \geq 0$.

(ii) If $C_3 < 0$, then Eq. $F(\omega)=0$ has at least one positive root, and we can calculate critical time delay τ_k.

a) When $\tau \in [0, \tau_k)$, stability switches occur limited times.

b) When $\tau = \tau_k$, a Hopf bifurcation happens to equilibrium point E_1 of system, and periodic solution appears.

c) Stability switches occur as time delay increases, making system unstable if $\tau > \tau_k$.

IV SIMULATION

In order to study the stability characteristic as shown in Section 3, we perform simulation and verification based on different reproductive ratio and time delay parameters via Matlab. The standard configuration parameters are chosen as [7].

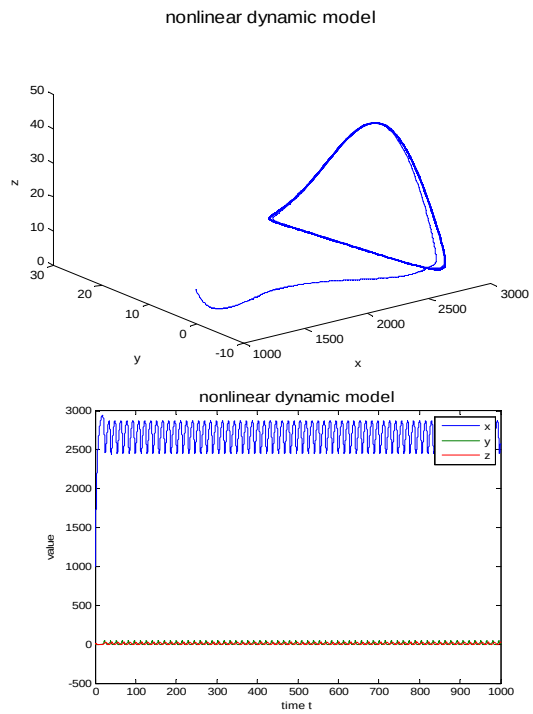


FIGURE I. TIME DELAY $\tau=\tau_k=2.22$, REPRODUCTIVE RATIO $R=1.2$

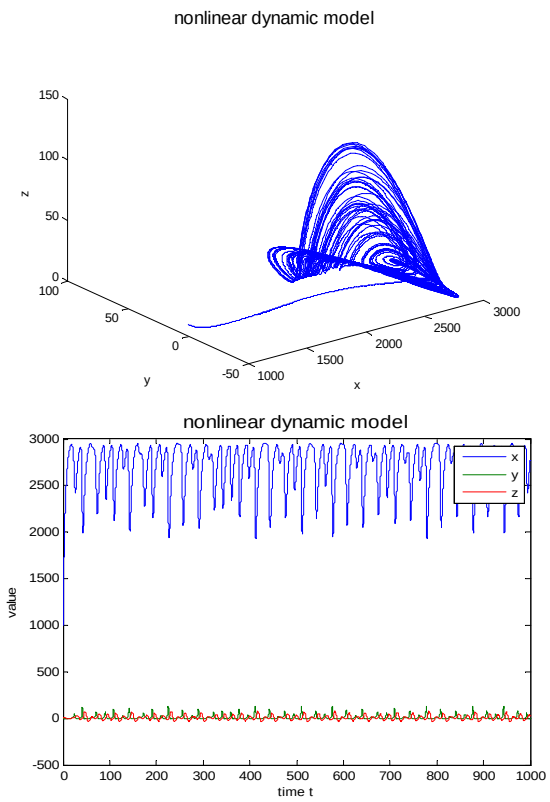
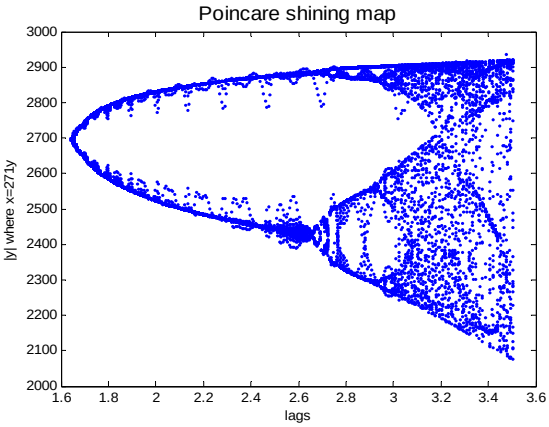
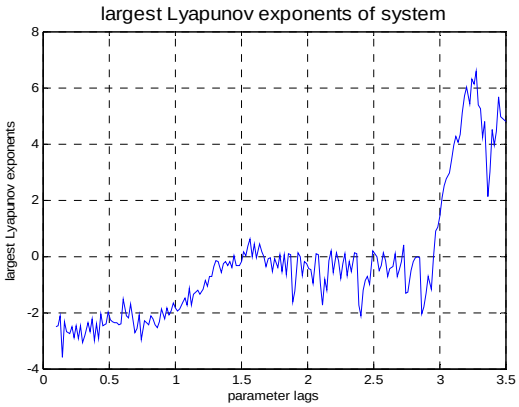


FIGURE II. TIME DELAY $\tau=3.5$, REPRODUCTIVE RATIO $R=1.2$

It can be calculated that $\tau_k = 2.22$, $\omega_k = 0.0097$. In the case when $\tau = \tau_k = 2.22$, Hopf bifurcation happens to virus infected equilibrium point E_1, as shown in Figure 1.



(a)



(b)

FIGURE III. REPRODUCTIVE RATIO $R = 1.2$. POINCARÈ SHINING MAP FIGURE 3.A, OF WHICH $\tau \in (1.6, 3.5)$. THE LARGEST LYAPUNOV EXPONENT FIGURE 3.B, OF WHICH $\tau \in (0, 3.5)$

In the period when $\tau > \tau_k = 2.22$, the virus infection equilibrium point E_1 is not stable, getting into chaotic state through period-doubling bifurcation, as shown in Figure 2.

From Poincarè shining map Figure 3.a and the largest Lyapunov exponent Figure 3.b, it is obvious to find that the state of equilibrium point has undergone a series of changes due to the increase of the time delay parameter, and it fits precisely the analysis results of the Section 3 in this article.

V CONCLUSIONS

In this article, a new virus nonlinear dynamic model with time delay which could be more realistic is proposed, and its stability, dynamical behavior like Hopf bifurcation. The research has clearly shown that adjusting the cells' reproductive ratio and time delay will affect viral infection. The analysis results will not only help us effectively grasp the complex dynamic behavior, but also provide the theory basis for treatment and operational plan in reality situation. Simulation example and lots of figures have verified the theoretical results given in this article. It is expected that the approach can be further used for the realistic treatment of the infectious diseases.

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