A CLOSED LOOP REPLICATED VIRUS MODEL WITH EFFECTIVE DELAY

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ABSTRACT

We investigate some closed loops of a replicated virus model, to analyse a mathematical model for virus replication. A bifurcation analysis is performed to determine the ranges of parameter values that lead to a steady state. A Hopf bifurcation occurs of a critical value of the time delay for some ranges of parameters.

KEYWORDS: Steady state. Effective delay. Bifurcation. Free virus. infect

1. INTRODUCTION

With developing sciences. mathematics has always benefited from its involvement. Each successive interaction enhances the field. This has led mathematicians to attempt to construct mathematical model of biological principles to know how their processes work and predict what may pursue.

A population dynamics of the immune response was looked by Nowak & Bangham [1]. They developed three differential mathematical models to explain the relation between antiviral immune responses. virus load. and virus diversity. The model did not consider any time delay. Tam Juddy [2] was interested in Nowak & Bangham mathematical model and included a time delay somewhere. Here this research follows their mathematical form and adds an effective delay. Interestingly. as the time delay is increased chaotic behavior arises. The implications of this were pointed out by Murray [3] . It is known that a critical time delay may exist such that the steady state becomes linearly unstable. Therefore it is vital to investigate this new system analytically.

In this paper. we wish to study the effects of time delay on the mathematical model for a replicating virus. Our model differs from the others in that it has an explicit time delay. The model is introduced in Section 2.1. We identified two steady states of the model having no time delay. a washout state (0. 0. 0) and a non washout state (x_s, y_s, z_s). In section 2.2. putting time delay and doing the process of the linearized forms of the equations describing the model in which there is a time delay present are also given. For Section 2.3, we performed a bifurcation analysis using time delay as the bifurcation parameter. The purpose of performing the analysis is to obtain ranges of a bifurcation parameter. Finally. Section 3. we discuss and conclude.

2. METHOD

2.1 A Plentiful Virus

There are many intracellular parasites. Virus are dependent on these parasites for survival and replication. It is noteworthy that. many type of infection are caused by viruses. The abundance of the virus. the virus load. is always an important factor. For patients with HIV. the virus load is correlated with disease stage. pathogenic and progressive disease. In the real situation. Cytotoxic T Lymphocytes (CTL) is shown a critical part in antiviral defenses as it attacks

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virus infected cells. Physicians know that the rate of HIV nuclei determines the virus load. Nowak & Bangham [1, 4] showed that CTL responsiveness is an important concept.

We shall first introduce a simple model, which has no immune responses against infected cells, for the interaction between host cells and replicated virus. We use a modified model which depends on more realistic physiology associated with the effective time delay t ; The objective is to determine the possible existence of critical delay t

2.2 Mathematical Model for Replicated Virus

2.2.1 A Simple Model

A basic model of viral dynamics contains three variables that are based on the Nowak & Bangham [1] model. X : number of uninfected cells, Y : number of infected cells, Z : number of free virus particles, and all $a_i (i = 1, 2, \ldots, 6)$ are positive parameters.

$$\frac{dX}{dt} = a_1 - a_2 X - a_3 X Z \quad (1)$$

$$\frac{dY}{dt} = a_3 X Z - a_4 Y \quad (2)$$

$$\frac{dZ}{dt} = a_5 Y - a_6 Z \quad (3)$$

Numbers of uninfected cells are assumed to be generated at a constant rate a_1 with making from a pool of precursor cells, and can decline as uninfected cells and free virus particles at rate $a_3 X Z$. The rate of numbers of infected cells depends on uninfected cells and free virus particles and we produced rate $a_3 X Z$. A free virus is produced from infected cells at a rate $a_5 Y$. Finally, uninfected cells, infected cells and the free virus decline at the rate $a_2 X$, $a_4 Y$, and $a_6 Z$ respectively.

Thus the dynamical model is the described by the following system (1), (2) and (3). They are the simplest possible host cell dynamics in a steady state of host cells at $X_{s1} = \frac{a_1}{a_2}$, $Y_{s1} = 0$, and $Z_{s1} = 0$ and another steady state $X_{s2} = \frac{a_4 a_6}{a_3 a_5}$ $Y_{s2} = \frac{a_1}{a_4} - \frac{a_2 a_6}{a_3 a_5}$, and $Z_{s2} = \frac{a_1 a_5}{a_4 a_6} - \frac{a_2}{a_3}$. And $R = \frac{a_1 a_3 a_5}{a_2 a_4 a_6}$ (indicator as 1 by Nowak.M.A. & May. R.M.(1991). If $R < 1$ then presenting in the beginning of the infection each virus infects a cell. Suppose that the infection cannot spread, and fortunately the system returns to the uninfected state as can be seen from equation (1). However, in the case, when $R > 1$ the infected cell population will increase while the uninfected cell population will decline. The opportunity for the virus try to infect new cells, the system will then converge to a steady state given by (X_{s2}, Y_{s2}, Z_{s2})-that is spreading of the virus is limited at the steady state. Then, each infected cell will now produce, on average, exactly one newly infected cell. It is not necessary to evoke an immune response to attain a stable level of the virus in a persistent infection.

2.2.2 A replicated Virus Model with Time Delay

As the mathematical model pointed out, there is no lag in the time for virus replication in the absence of an immune response. Time delay should occur in the model because of certain biological phenomena. For sample, virus production may lag by an intracellular effective time delay t . firstly, between the emission of viral particles and the infection of a cell and secondly, before completed declining of infected cell – that is if a patient has more infected cells and a good environment for infected cells, the infected cell can respond after a time delay. We now use the term $Y(t - t)$, which denotes the density of infective stages at time $t - t$. Thus the factor that is accountable for the probability that infected cell decayed before starting to produce virus can be removed. Therefore , the system becomes (1) and

$$\frac{dY}{dt} = a_3 X Z - a_4 Y(t-\tau) \tag{4}$$

$$\frac{dZ}{dt} = a_5 Y(t-\tau) - a_6 Z \tag{5}$$

where τ, the effective time delay, is a positive parameter. These look like the delay model for the control of testosterone secretion presented by Murray [7].

System (1) - (3) and (1), (4) and (5) still have the same equilibrium state. We will now consider the linearized system of system (1), (4) and (5) at

$$x = X - \frac{a_1}{a_2}, \quad y = Y, \text{ and } z = Z \tag{6}$$

Then the system becomes

$$\frac{dx}{dt} = -a_2 x - \frac{a_1 a_3}{a_2} z \tag{7}$$

$$\frac{dy}{dt} = \frac{a_1 a_3}{a_2} z - a_4 y(t-\tau) \tag{8}$$

$$\frac{dz}{dt} = a_5 y(t-\tau) - a_6 z \tag{9}$$

For this system, we notice immediately that the real part of a certain eigenvalues are negative. This means that the stabling is the same as the case when $\tau = 0$.

We now consider the linearized system of (1), (4) and (5) by introducing

$$x = X - \frac{a_4 a_6}{a_3 a_5}, \quad y = Y - \left(\frac{a_1}{a_4} - \frac{a_2 a_6}{a_3 a_5}\right) \text{ and } z = Z - \left(\frac{a_1 a_5}{a_4 a_6} - \frac{a_2}{a_3}\right) \tag{10}$$

Then we get

$$\frac{dx}{dt} = -a_2 x - a_3 Z_{s2} x - a_3 X_{s2} z \tag{11}$$

$$\frac{dy}{dt} = a_3 Z_{s2} x - a_4 y(t-\tau) + a_3 X_{s2} z \tag{12}$$

$$\frac{dz}{dt} = a_5 y(t-\tau) - a_6 z \tag{13}$$

2.3 Bifurcation Analysis

It is well known that the steady state is stable if all eigenvalues of the exponential polynomial equation have negative real part and unstable if at least one root has a positive real part. A Hopf bifurcation occurs when the real part of a certain eigenvalues changes from negative to zero and then to positive (i.e. the steady state changes from one of stability to one of instability). This is usually caused by the delay. To find the solutions, we obtain

$$\begin{bmatrix} \dot{x}(t) \\ \dot{y}(t) \\ \dot{z}(t) \end{bmatrix} = \begin{bmatrix} -a_2 - a_3 Z_{s2} & 0 & -a_3 X_{s2} \\ a_3 Z_{s2} & -a_4 e^{-\lambda\tau} & a_3 X_{s2} \\ 0 & a_5 e^{-\lambda\tau} & -a_6 \end{bmatrix} \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix} \tag{14}$$

The characteristic equation associated with (14) is

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 = e^{-\lambda\tau}(q_1\lambda^2 + q_2\lambda + q_3) \tag{15}$$

where $p_1 = a_2 + a_3 Z_{s2} + a_6$, $p_2 = a_2 a_6 + a_3 a_6 Z_{s2}$, $p_3 = 0$, $q_1 = a_4$, $q_2 = a_2 a_4 + a_4 a_6 + a_3 a_4 Z_{s2} - a_3 a_5 X_{s2}$, and $q_3 = a_2 a_4 a_6 - a_2 a_3 a_5 X_{s2} + a_3 a_4 a_6 Z_{s2}$.

We treat the composite delay time τ as the bifurcation parameter. First, we look at (15) for $\tau = 0$, that is

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 = 0 \tag{16}$$

by the Routh-Hurwitz condition, all roots of equation (16) have negative real parts while $p_1 > 0$, $p_3 > 0$, and $p_1 p_2 - p_3 > 0$. Thus the steady state (X_s, Y_s, Z_s) is asymptotically stable.

Now for $t \neq 0$, we suppose that eginvalues of (15) are a pair of complex conjugates l_1 and l_2 i.e. $l_{1,2} = u(t) \pm iv(t)$ where u and v are constant. By continuity, we know that $u(t) < 0$ for sufficiently small t. Therefore, the steady state would remain stable for values of t such as $t < t_0$ for $t_0 > 0$. Suppose $u(t_0) = 0$ for a $\tau_0 > 0$, then u $(\tau) <$ 0 for $\tau \in [0, \tau_0)$. The stability of (x_s, y_s, z_s) will be lost at $\tau = \tau_0$ and we will have $\lambda = iv(\tau_0)$.

Obviously, iv, where $v > 0$, is a root of equation (15). Substituing $\lambda = iv$ into equation (15) gives

$$-iv^3 - p_1 v^2 + ip_2 v + p_3 = e^{-ivt}(-q_1 v^2 + q_2 iv + q_3) \quad (17)$$

Separating the real part and imaginary parts, we obtain

$$-p_1 v^2 + p_3 = (q_3 - q_1 v^2)\cos vt + q_2 v \sin vt \quad (18)$$

$$-v^3 + p_2 v = q_2 v \cos vt - (q_3 - q_1 v^2)\sin vt \quad (19)$$

Squaring both (18) and (19) and adding them, we have

$$v^6 + (p_1^2 - 2p_2 - q_1^2)v^4 + (p_2^2 - 2p_1 p_3 - q_2^2 + 2q_1 q_3)v^2 + (p_3^2 - q_3^2) = 0 \quad (20)$$

We find the root of (20) by reducing the power of v to the third degree. By letting $v^2 = s$, we have

$$Q(s) \equiv s^3 + ps^2 + qs + r = 0 \quad (21)$$

while $p = p_1^2 + 2p_2 - q_1^2$, $q = p_2^2 - 2p_1 p_3 - q_2^2 + 2q_1 q_3$, and $r = p_3^2 - q_3^2$

To find the roots of (21), we look at the following lemma.

Lemma Let $\eta = p^2 - 3q \quad (22)$

1.1 If $r < 0$ then equation (21) has at least one positive root.

1.2 If $r \geq 0$ and $\eta = p^2 - 3q \geq 0$ then equation has a positive root.

Proof 1.1 Now, letting $s = 0$ in equation (21) we get $Q(0) = r < 0$. As $\lim_{s \to \infty} Q(s) = \infty$, equation (21) must have a positive root where $Q = 0$, by the intermediate value theorem.

Proof 1.2

Let $\eta = p^2 - 3q \geq 0 \quad (23)$

And from (21) we have

$$\frac{dQ(s)}{ds} = 3s^2 + 2ps + q \quad (24)$$

The stationary point of $Q(s)$ is obtained by setting the RHS. equation (24). We get

$$s = \frac{-2p + \sqrt{4p^2 - 12q}}{6} = \frac{-p + \sqrt{\eta}}{3} \quad (25)$$

when $s > 0$. Thus, for $Q(s) < 0$ and $Q(0) = r \geq 0$, we know by the intermediate value theorem that Q must vanish somewhere between 0 and s.

Claim. Equation (20) has no positive real root if $r \geq 0$ and $\eta = p^2 - 3q < 0$

Proof

If $r \geq 0$ while $Q'(s) > 0$, Q is then an increasing function and does not vanish anywhere along the positive x-axis.

If $r \geq 0$ and $\eta = p^2 - 3q < 0$ which $\lambda = iv = i\sqrt{s}$, then there are all roots of the characteristic equation (15) having negative real parts for all $\tau \geq 0$. Therefore; the steady state (x_s, y_s, z_s) is always stable in this case.

On the other hand, if the condition in lemma 1 holds, then equation (21) has at least one positive real root. Without loss of generality, we may denote the three positive roots of equation (21) by $s_i, i = 1,2,3$. Then equation (21) has three positive roots

$$v_i = \sqrt{s_i}, i = 1,2,3 \tag{26}$$

Now, let $\tau_0 > 0$ be the minimum value for all the values of τ for which $\alpha(\tau_0) = 0$. After substituting v_i into (24), (25) and solving for τ, we get

$$\tau_i = \frac{1}{v_i}\left[\arctan\left(\frac{-v_i^3 + p_2 v_i}{-p_1 v_i^2 + p_3}\right)\right], i = 1,2,3 \tag{27}$$

Therefore, implying that τ_i can be considered as a function of $v_i, i = 1,2,3$, we choose

$$\tau_0 = \tau_{i_0} = \min_{i=1,2,3}\{\tau_i\} \tag{28}$$

Now we know all conditions for parameters that use time delay as the bifurcation parameter by considering the critical τ value of (27) as a function v. By claim and lemma, we obtain the following theorem

Theorem

Let τ_0 and v_0 be defined as (28), $s_0 = v_0^2$ and

$$Q(s) \equiv s^3 + (p_1^2 + 2p_2 - q_1^2)s^2 + (p_2^2 - 2p_1p_3 - q_2^2 + 2q_1q_3)s + (p_3^2 - q_3^2) = 0$$

Suppose that $p_1p_2 - p_3 > 0$

(i) If $r \geq 0$ and $\eta = p^2 - 3q < 0$ then the steady state (x_s, y_s, z_s) of the system (1), (4) and (5) is absolutely stable (i.e. asymptotically stable for $\tau \in [0, \infty)$)

(ii) If $r < 0$ or $r \geq 0, \exists s > 0$ and $Q(s) < 0$, then the steady state (x_s, y_s, z_s) of system (1), (4) and (5) is asymptotically stable for $\tau \in [0, \tau_0)$

(iii) If the condition of (ii) are satisfied, $\tau = \tau_0$, and $Q'(s) \neq 0$ then system (1), (4) and (5) will undergo a Hopf bifurcation at (x_s, y_s, z_s).

3. DISCUSSION AND CONCLUSION

A simple mathematical model for a virus presented by Nowak & Bangham (1996) was used here. The model included the effective delay. The effective time delay occurs somewhere between the emission of viral particles and the infection of cells. Our analysis aims to determine how the stability of the steady state of the system is affected by the length of the effective time delay. In order to perform a bifurcation analysis with time delays, we used the Hopf bifurcation theory. We can give a condition governing the parameter values of the model by the theorem. Depending on the suitable parameter values, we can generate curves resembling numerical or clinical data that we hope to look at in a later paper.

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