Neural, Parallel, and Scientific Computations 23 (2015) 357-366

EFFECTS OF INTRACELLULAR DELAY AND IMMUNE RESPONSE DELAY IN HIV MODEL

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ABSTRACT. This article introduces a four species compartmental delayed differential HIV model assuming intracellular and immune response delay. The local stability analysis are performed to ascertain the local behaviour of solutions. The existence of Hopf bifurcation assuming the delay parameter as the bifurcation parameter is also discussed for this model and has been verified through numerical simulations. The model being non-linear in nature, should possess strange attractors and hence the existence of chaotic solutions are also explored through numerical simulations.

AMS (MOS) Subject Classification. 35K60, 35K57.

1. INTRODUCTION

The spread of HIV infection process is a very complex process but can be broadly described by three distinct phases viz. the acute infection phase followed by chronic infection phase and at last AIDS. Once a person get infected with HIV, the person remains in acute infection phase for the first few weeks. This phase is generally identified by flu-like symptoms. In this phase, HIV multiplies manifold thereby destroying the CD4+ T cells and wrecking havoc on the body's immune system [12]. The next stage is the Chronic Infection, also called the latency stage; during this stage the rapid progress of HIV is slowed down. Infected individuals may not exhibit HIV-related symptoms. This stage can last up to 10 to 12 years. The final stage of HIV infection is the AIDS (Acquired Immuno Deficiency Syndrome). During this period the body's immune response has plummeted and so its ability to fight the opportunistic infections reduces drastically. AIDS is said to be diagnosed when the count of CD4+ T cells falls below 200 cells mm^{-3}. Without treatment, people with AIDS can generally survive for 3 years. With treatment, the survival rate depends on the effectiveness of the drug being used and the response of the body to the treatment.

In HIV infection, various types of delay occurs but the most important delays that have been categorised are Intracellular Delay, Pharmacological Delay and Immunological Delay. In this particular study, a four dimensional delayed differential

Received September 15, 2015

equation model of HIV infection on human is proposed. The intracellular and immunological delay has been incorporated in this model. The proposed model has been studied in theoretical as well as numerical aspect. It has been proved in many references that delays can have very pronounced effects on stability of mathematical models [9, 16] and sometime can lead to very strange dynamics of the system. In literature, the delayed model of HIV infection on human are many [5, 6, 1, 14, 10]. It has been shown in many articles that delay can sometimes have no impact on the asymptotic stability of infected equilibrium state. The purpose of the present model is therefore to discuss a new delayed differential equation model of HIV infection where delay parameter plays a very important role in the overall dynamics of model.

2. MODEL DISCRIPTION

In mathematical modelling of HIV infection, the most important component of human body is CD4+T cell which are also known as helper T cell [4, 8, 18, 1, 2, 7, 13, 11, 15]. These cell are basically the backbone of human immune system. If T cell count falls below a threshold number, the person infected with HIV is said to be diagnosed as having AIDS. The effector cell is also another component in the body which governs the growth of T cell and virus. Assume that $u(t)$, $v(t)$, $w(t)$ and $x(t)$ denotes the density per unit volume of uninfected T cell, infected T cell, virus and effector cell respectively.

For a model of T cells in absence of virus, it is assumed that T cell is added to the body at a constant rate. It is also assumed that there is a constant natural death rate of T cell. In presence of virus, it is further assumed that interaction between T cell and HIV follows the law of mass action. Hence growth of healthy T cell is assumed to be governed by the following dynamical model

$$\frac{du}{dt} = s - du(t) - bu(t)w(t)$$

For the infected T Cell, intracellular delay, τ_1 which is the time span between the instant of interaction between the healthy T cell and virus and production of new virus particle by way of bursting of infected T cell is assumed. During this time lag, some of the T cell will actually die out and only those T cell which remains alive after this time from the instant of infection will take part in the dynamics of the infected T cell. In this time span, it is assumed that number of infected T cell follows exponential distribution i.e. if μ is the natural death rate of infected T cell then the total number of infected T cell at any time 't' is the sum of all the infected cell at previous time [3] i.e.

$$v(t) = \int_0^{\tau_1} be^{-\mu T} u\left(t-T\right) w\left(t-T\right) dT$$

For the dynamics of the virus, it is assumed that after infection, the helper T cell produces n copies of virus which will infect other helper T cells. The death rate of healthy T cell is equal to $e^{-\mu T}bu(t-T)w(t-T)$ and total number of virus produced with this death is

$$ne^{-\mu T}bu(t-T)w(t-T).$$

The natural mortality rate q of virus is assumed to be constant. The virus is also cleared by immune response at rate proportional to number of virus particle and immune response mechanism.

$$\frac{dw}{dt} = nbe^{-\mu T}u(t-\tau)w(t-\tau) - qw - b_1wx$$

The second lag of length τ_2 is assumed for immune response to get activated in the body. In literature, the effector cell growth has been assumed to be dependent on $u(t)$, $v(t)$ and $x(t)$ i.e. $f(u,v,x)$ where f represents the growth function. In this present model, immune response growth is assumed to be proportional to density of virus and effector cell density i.e. $f(w,x) = gw(t)x(t)$. The effector cells are also assumed to die out at a constant per capita rate c.

$$\frac{dx}{dt} = gw(t-\tau_2)x(t-\tau_2) - cx(t)$$

Hence overall dynamics of infection is assumed to be governed by the following coupled delay differential model

$$\begin{aligned} u'(t) &= s - du(t) - bu(t)w(t) \\ v'(t) &= bu(t)w(t) - be^{-\mu\tau_1}u(t-\tau_1)w(t-\tau_1) - \mu v(t), \\ w'(t) &= bne^{-\mu\tau_1}u(t-\tau_1)w(t-\tau_1) - b_1w(t)x(t) - qw(t) \\ x'(t) &= gw(t-\tau_2)x(t-\tau_2) - cx(t) \end{aligned} \tag{2.1}$$

where $n \geq 1$, $\tau = \max\{\tau_1, \tau_2\}$, $\tau \in (0,\infty)$, $s, b, b_1, d, c, g, q \in \mathbb{R}_+$ with initial conditions

$$\begin{aligned} u(0) &= \phi_1(\theta) \\ v(0) &= \int_{-\tau_1}^{0} be^{-\mu\phi}u_1(\phi)\,u_3(\phi)\,d\phi \\ w(0) &= \phi_2(\theta) \\ x(0) &= \phi_3(\theta) \end{aligned}$$

with $\phi_i(\theta) \in [0,\infty)$, $\theta \in [-\tau, 0]$, $\tau = \max\{\tau_1, \tau_2\}$ for $i = 1, 2, 3$. By the fundamental theorem of functional differential equations, it can be easily proved that there is a unique solution $(u(t), v(t), w(t), x(t))$ to the system (2.1) with initial conditions defined as above.

3. **Theoretical Analysis**

(a) Basic Properties of Model

The proposed model being a biological model should be positively invariant which can be stated as the following Lemma

Lemma 1. All solutions of the system (2.1) together with initial conditions stated above are positively invariant and ultimately bounded.

Proof. In order to prove positive invariance of the solutions, denote

$$U(t) = (u(t), v(t), w(t), x(t))^T \in \mathbb{R}^4$$

such that the original system can be put into the form

$$\dot{U(t)} = H(U(t)) \tag{3.1}$$

where

$$H(U(t)) = \begin{pmatrix} H_1(U(t)) \\ H_2(U(t)) \\ H_3(U(t)) \\ H_4(U(t)) \end{pmatrix} = \begin{pmatrix} s - du(t) - bu(t)w(t) \\ bu(t)w(t) - be^{-\mu\tau_1}u(t-\tau_1)w(t-\tau_1) - \mu v(t), \\ nbe^{-\mu\tau_1}u(t-\tau_1)w(t-\tau_1) - b_1w(t)x(t) - qw(t) \\ gw(t-\tau_2)x(t-\tau_2) - cx(t) \end{pmatrix}$$

Now if $\mathbb{R}^4_+ = [0,\infty)\times[0,\infty)\times[0,\infty)\times[0,\infty)$ with $H : \mathbb{R}^4_+ \to \mathbb{R}^4$, then it is clear that $H \in C^\infty(\mathbb{R}^4)$ and so H is locally Lipschitz and satisfies the conditions

$$H_i(U(t)) \geq 0 \text{ for all } u(t) = v(t) = w(t) = x(t) = 0$$

Hence applying Theorem A.4 on page 423 of [17], on the positivity of the solutions, all solutions with positives initial conditions remains positive for all time t. To prove boundedness of the solution, consider the non-negative function V defined by

$$V(t) = nu(t) + nv(t) + w(t) + \frac{b_1}{g}x(t+\tau_2).$$

Then, by simple differentiation,

$$\begin{aligned}
\frac{dV(t)}{dt} &= nu'(t) + nv'(t) + w'(t) + \frac{b_1}{g}x'(t+\tau_2) \\
&= n\left[s - du(t) - bu(t)w(t)\right] + n\left[bu(t)w(t) - be^{-\mu\tau_1}u(t-\tau_1)w(t-\tau_1) - \mu v(t)\right] \\
&\quad + \left[nbe^{-\mu\tau_1}u(t-\tau_1)w(t-\tau_1) - b_1w(t)x(t) - qw(t)\right] \\
&\quad + \left[b_1w(t)x(t) - \frac{b_1c}{g}x(t+\tau_2)\right] \\
&= ns - \left(ndu(t) + n\mu v(t) + qw(t) + \frac{b_1c}{g}x(t+\tau_2)\right)
\end{aligned}$$

Take $\delta = \min\{nd, n\mu, q, \frac{b_1c}{g}\}$, then above relation simplifies to

$$\frac{dV(t)}{dt} \leq ns - \delta V(t)$$

Which gives $0 \leq V(t) \leq ns/\delta$, i.e. $V(t)$ is ultimately bounded and so are the solutions $\{u(t), v(t), w(t), x(t)\}$ of the system (2.1) □

In the following section, the local stability analysis is performed to ascertain the local behaviour of the solutions.

(b) Local behaviour of the Solutions

The proposed system (2.1) permits three equilibrium points which are

1. $E_0 : (\overline{u}, 0, 0, 0) = \left(\frac{s}{d}, 0, 0, 0\right)$ exists for all values of parameters.
2. $E_1 : (\widetilde{u}, \widetilde{v}, \widetilde{w}, 0) = \left(\frac{qe^{\mu\tau_1}}{bn}, \frac{(1-e^{-\mu\tau_1})(bns - dqe^{\mu\tau_1})}{b\mu n}, \frac{bnse^{-\mu\tau_1} - dq}{bq}, 0\right)$ exists if

$$qd < bnse^{-\mu\tau_1}$$

3. $E_2 : (\widehat{u}, \widehat{v}, \widehat{w}, \widehat{x}) = \left(\frac{gs}{bc+dg}, \frac{bcs(1-e^{-\mu\tau_1})}{\mu(bc+dg)}, \frac{c}{g}, \frac{ngbse^{-\mu\tau_1}}{b_1(bc+dg)} - \frac{q}{b_1}\right)$ exists if

$$qd < bnse^{-\mu\tau_1} \text{ and } q(bc+dg) < bgnse^{-\mu\tau_1}$$

From these existence conditions, it is clear that existence of E_2 implies the existence of E_1 and existence of E_2 and E_1 depends on τ_1 only but not on τ_2 which is immune response delay. In order to determine the nature of solution around all these equilibrium points, the characteristic equation of Jacobian Matrix are needed.

Stability of Infection Free State

We have for E_0, the characteristic equation

$$(\lambda + c)(\lambda + d)(\lambda + \mu)\left(q - \frac{bnse^{-\mu\tau_1}}{d}e^{-\lambda\tau_1} + \lambda\right) = 0$$

On using stability switching criteria, the following theorem for stability behaviour of disease free equilibrium point can be stated.

Theorem 1. The disease free equilibrium $(\bar{u}_1, 0, 0, 0)$ is stable for all values of τ_1 if $q > \frac{nbs}{d}$.

Stability of Effector Free State

Again characteristic equation for E_1 is given by

$$(\lambda + \mu)\left(\lambda + \alpha_{11} + e^{-\lambda\tau_2}\beta_{11}\right)\left(\lambda^2 + \alpha_{21}\lambda + \alpha_{22} + e^{-\lambda\tau_1}(\beta_{21}\lambda + \beta_{22})\right) = 0$$

where coefficients are

$$\alpha_{11} = c,\ \beta_{11} = \frac{dg}{b} - \frac{gns}{q}e^{-\mu\tau_1}$$

$$\alpha_{21} = q + \frac{bns}{q}e^{-\mu\tau_1},\ \alpha_{22} = bnse^{-\mu\tau_1},\ \beta_{21} = -q,\ \beta_{22} = -dq$$

Therefore stability of E_1 dependent on the conditions that the transcendental equations

$$\begin{aligned} \lambda + \alpha_{11} + e^{-\lambda\tau_2}\beta_{11} &= 0 \\ \lambda^2 + \alpha_{21}\lambda + \alpha_{22} + e^{-\lambda\tau_1}(\beta_{21}\lambda + \beta_{22}) &= 0 \end{aligned} \tag{3.2}$$

have all roots with negative real parts. Since the coefficients of the above two equations explicitly depends upon the delay parameters τ_1, so it is impossible to obtain the stability conditions and hence critical value of the parameter τ_1 for Hopf bifurcation in usual way.

Stability of Endemic State

Finally the characteristic equation for E_2 can be calculated as

$$P_0 + e^{-\lambda\tau_1}P_1 + e^{-\lambda\tau_2}P_2 + e^{-\lambda(\tau_1+\tau_2)}P_3 = 0$$

and

$$\begin{aligned} P_0(\lambda, \tau_1) &= \lambda^3 + \alpha_1\lambda^2 + \alpha_2\lambda + \alpha_3 \\ P_1(\lambda, \tau_1) &= \beta_1\lambda^2 + \beta_2\lambda + \beta_3 \\ P_2(\lambda, \tau_1) &= \gamma_1\lambda^2 + \gamma_2\lambda + \gamma_3 \\ P_3(\lambda, \tau_1) &= \delta_1\lambda + \delta_2 \end{aligned}$$

where α_i, β_i, γ_i, $i = 1, 2, 3$ and δ_1, δ_2 depends upon the model parameters and delay parameter τ_1. The form of the characteristic equation is such that it is almost impossible to get analytical results on stability of nontrivial equilibrium points. Similar arguments holds for the case of Hopf Bifurcation analysis if τ_1 is chosen as bifurcation parameter. Although, the Hopf bifurcation point can be calculated if $\tau_2 = 0$ and in this case, the equation becomes somewhat simpler.

In this model, stability of the equilibrium point and bifurcation be can be easily verified using numerical simulation as can be seen in the next section. The other important nonlinear properties which are explored in this model are chaotic behaviour of the solutions.

4. **Numerical Simulations**

In this section, numerical simulations have been performed to ascertain local stability behaviour and periodic oscillation of the model. The following model parameters have been taken for this simulations wherever possible but to explore the chaotic behaviour of the solution, some parameters were randomly chosen.

In first set of figure, Figure 1(a)–(d) shows the stability behaviour of the endemic equilibrium point. In second set of figure, the unstable behaviour is obvious from Figure 2(a)–(d).

TABLE 1. Values of the Parameters

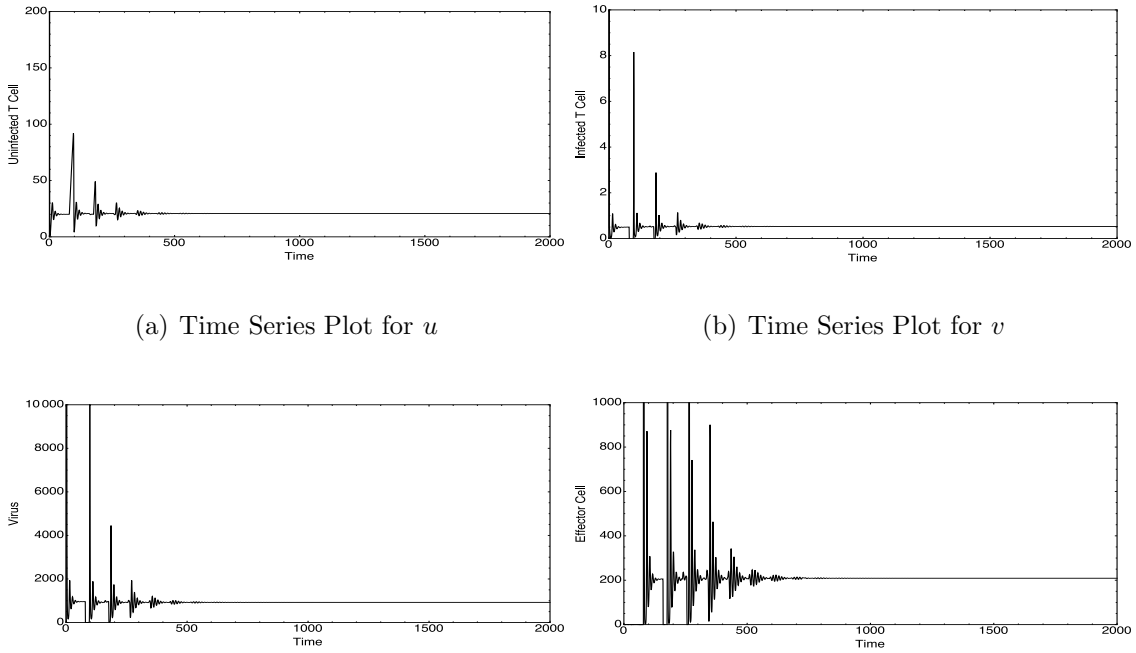
Parameters	**Descriptions**	**Value**
s	T Cell production rate	5 mm^{-3} day^{-1}
b	Rate of Infection of T Cell	0.00025 $mm^3 day^{-1}$
b_1	Virus Clearance Rate of due to Effector Cell	0.00025 $mm^3 day^{-1}$
d	Healthy T Cell Death Rate	0.01 day^{-1}
μ	Infected T Cell Death Rate	0.01 day^{-1}
q	Viral Death Rate	1.5 day^{-1}
n	Number of Virion Produced	300
c	Effector Cell death rate	28 day^{-1}
g	Activation rate of Effector Cell	12.0 $mm^3 day^{-1}$
τ_1	Intracellular Delay	0.11 days
τ_2	Immunological Delay	79.1 days

The third figure, Figure 3 depicts the chaotic behaviour of the solution. As can be seen in the figure that the solutions are very sensitive to initial perturbation, hence proving the existence of chaotic solution.

It has been observed in general, in HIV infection that the people show symptoms after about a year or so i.e. once latent period of the infection is over. The same behaviour of the infection is somewhat obvious in Figure 4 where number of helper cell initially maintaining a level which is regarded as latency phase. In this phase, the viral load remains minimum, but viral concentration gradually shoots up with the decrease in $CD4^+$ T cell count and keeps on oscillating. In this oscillation, there are times where $CD4^+$ cell count falls below 200 cells mm^{-3} which is a clear sign of full blown AIDS and the patient can succumb to HIV infection finally.

5. **Discussion**

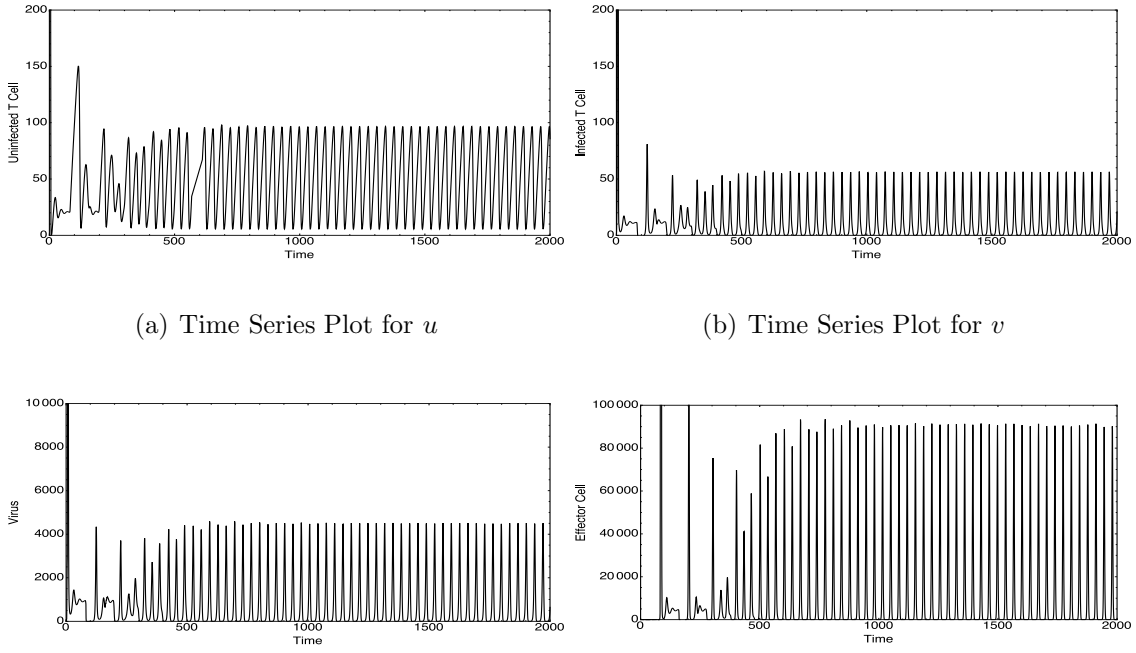
This article introduces a two delay model of HIV infection assuming the delay due to intracellular and immune response. The resulting model as a result posses three unique equilibrium points namely a disease free equilibrium point, effector cell free equilibrium point and an endemic equilibrium point. Analysis suggests that there exists a Hopf bifurcation w.r.t. delay parameters for effector free equilibrium point and endemic equilibrium points.The numerical simulation of this model suggest that the proposed model can give rise to a variety of dynamics which other model lacks. The proposed model also explains the emergence of AIDS in later phage of HIV cycle where helper T cell counts decreases to a value around 200 cells mm^{-3}.



(a) Time Series Plot for u (b) Time Series Plot for v

(c) Time Series Plot for w (d) Time Series Plot for x

FIGURE 1. Time Series Plot Showing Stability Behaviour



(a) Time Series Plot for u (b) Time Series Plot for v

(c) Time Series Plot for w (d) Time Series Plot for x

FIGURE 2. Time Series Showing Instability Behaviour

ACKNOWLEDGMENTS

Author greatly acknowledges the financial support given by the South Asian University, New Delhi through sanction order No. SAU/1/10/2010 dated 27/02/2015

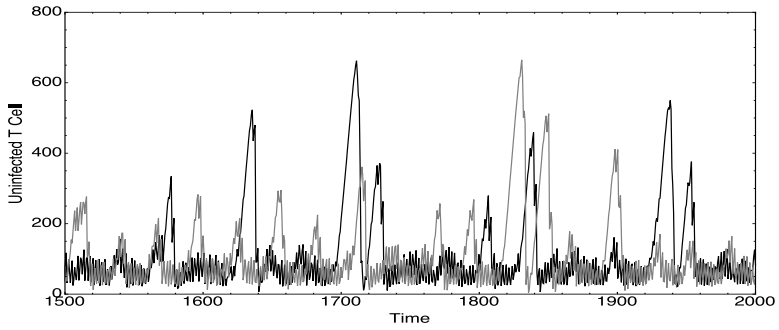
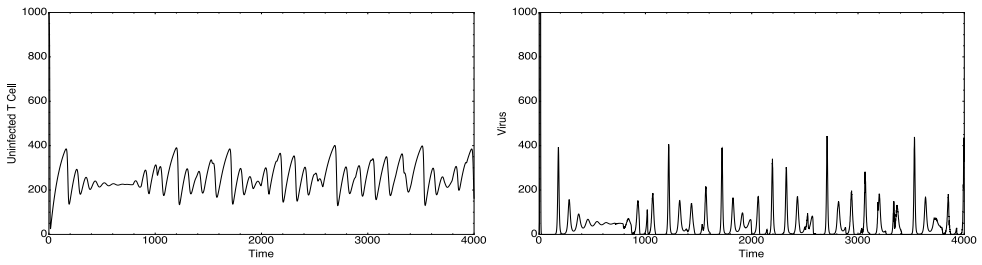


FIGURE 3. Sensitivity towards Initial Conditions



(a) (b)

FIGURE 4. Time Series Plot for u and w

for attending the 7th International Conference on Dynamic Systems and Applications & 5th International Conference on Neural, Parallel and Scientific Computations held during May 27–30, 2015 at Morehouse College, Atlanta, Georgia, USA. This work is the extended version of the paper presented in the above mentioned conference.

REFERENCES

[1] R. M. Anderson. Mathematical and statistical studies of the epidemiology of hiv. *Aids*, 3(6):333–346, 1989.

[2] J. J. Bailey, J. E. Fletcher, E. T. Chuck, and R. I. Shrager. A kinetic model of cd4+ lymphocytes with the human immunodeficiency virus (hiv). *BioSystems*, 26(3):177–183, 1992.

[3] E. Beretta and Y. Kuang. Modeling and analysis of a marine bacteriophage infection with latency period. *Nonlinear Analysis: Real World Applications*, 2(1):35–74, 2001.

[4] F. Brauer and C. Castillo-Chavez. *Mathematical models in population biology and epidemiology*, volume 1. Springer, 2001.

[5] R. V. Culshaw and S. Ruan. A delay-differential equation model of hiv infection of cd4+ t-cells. *Mathematical biosciences*, 165(1):27–39, 2000.

[6] R. V. Culshaw, S. Ruan, and G. Webb. A mathematical model of cell-to-cell spread of hiv-1 that includes a time delay. *Journal of mathematical biology*, 46(5):425–444, 2003.

[7] T. Hraba, J. Doležal, and S. čelikovský. Model-based analysis of cd4+ lymphocyte dynamics in hiv infected individuals. *Immunobiology*, 181(1):108–118, 1990.

[8] D. E. Kirschner and G. F. Webb. A mathematical model of combined drug therapy of hiv infection. *Computational and Mathematical Methods in Medicine*, 1(1):25–34, 1997.

[9] Y. Kuang. *Delay differential equations: with applications in population dynamics*. Academic Press, 1993.

[10] P. W. Nelson and A. S. Perelson. Mathematical analysis of delay differential equation models of hiv-1 infection. *Mathematical biosciences*, 179(1):73–94, 2002.

[11] M. A. Nowak and C. R. Bangham. Population dynamics of immune responses to persistent viruses. *Science*, 272(5258):74–79, 1996.

[12] A. S. Perelson and P. W. Nelson. Mathematical analysis of hiv-1 dynamics in vivo. *SIAM review*, 41(1):3–44, 1999.

[13] H. L. Smith and P. De Leenheer. Virus dynamics: a global analysis. *SIAM Journal on Applied Mathematics*, 63(4):1313–1327, 2003.

[14] X. Song and S. Cheng. A delay-differential equation model of hiv infection of cd4+ t-cells. *J. Korean Math. Soc*, 42(5):1071–1086, 2005.

[15] Y. C. Stafford, Max A, D. D. Ho, L. Corey, and A. S. Perelson. Modeling plasma virus concentration and cd4+ t cell kinetics during primary hiv infection, 1999. No. 99-05-036.

[16] Z. Sun, W. Xu, X. Yang, and T. Fang. Effects of time delays on bifurcation and chaos in a non-autonomous system with multiple time delays. *Chaos, Solitons & Fractals*, 31(1):39–53, 2007.

[17] H. R. Thieme. *Mathematics in Population Biology*. Princeton University Press, USA, 2003.

[18] L. Wang and M. Y. Li. Mathematical analysis of the global dynamics of a model for hiv infection of cd4+ t cells. *Mathematical Biosciences*, 200(1):44–57, 2006.