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# DYNAMICS ANALYSIS OF HIV-1 INFECTION MODEL WITH CTL IMMUNE RESPONSE AND DELAYS

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**Abstract.** In this paper, we rigorously analyze an HIV-1 infection model with CTL immune response and three time delays which represent the latent period, virus production period and immune response delay, respectively. We begin this model with proving the positivity and boundedness of the solution. For this model, the basic reproduction number $R_0$ and the immune reproduction number $R_1$ are identified. Moreover, we have shown that the model has three equilibria, namely the infection-free equilibrium $E_0$, the infectious equilibrium without immune response $E_1$ and the infectious equilibrium with immune response $E_2$. By applying fluctuation lemma and Lyapunov functionals, we have demonstrated that the global stability of $E_0$ and $E_1$ are only related to $R_0$ and $R_1$. The local stability of the third equilibrium is obtained under four situations. Further, we give the conditions for the existence of Hopf bifurcation. Finally, some numerical simulations are carried out for illustrating the theoretical results.

**Key words.** HIV-1, Delays, Stability, Hopf bifurcation, Lyapunov functionals.

## 1. Introduction

In the past few decades, many researchers and scientists focus on the study of simulating the interactions between pathogens and the host immune system. There is a convincing evidence that cytotoxic T lymphocyte (CTL) cells which attack infected cells are the main host immune factor that determines virus load [1–4]. Moreover, the Human Immunodeficiency Virus (HIV) models are crucial among the disease models since the Acquired Immune Deficiency Syndrome (AIDS) is mainly due to HIV and is still not curable today. Therefore, it makes sense to spend some time researching HIV-1 infection model with CTL immune response.

Based on some biological background in cellular immunology, Perelson and Nelson [5] established a four-dimensional ordinary differential system to study the dynamical behavior with cellular immune responses in 1999. The model is as follows:

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

where a dot denotes the differentiation with respect to time $t$, variables $x, y, v$ and $z$ represent the density of the healthy cells, the infected cells, the virus and CTL cells, respectively. Healthy cells are produced at rate $s$ and they died out naturally at rate $dx$. These cells may come into contact with the virus and become infected cells at rate $\beta xv$. Infected cells died out naturally at rate $ay$ and are removed by $z$ at rate $pyz$. From the infected cells, the viruses are replicated at rate $ky$ and they are cleared naturally at rate $uv$. CTL cells decay at a rate $hz$ and $f(x, y, z)$ has some different expressions according to the different assumptions. For example, the authors of [6, 7] supposed that the generation of CTL only depend on the infected

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cells, the researchers of [8] think that the emergence of CTL not only depend on the infected cells but also is related to the CTL cells. Based above analysis, the authors of [9] considered the formation of the CTL is also related to the healthy cells.

Most of the models discussed so far capture the CTL in a single population, $z$. However, when CTLs are stimulated by antigen, the population of CTL precursors (CTLp) expands. Upon contact with the virus during a subsequent infection, CTLp becomes CTL effectors (CTLe) which is again responsible for clearing away the invading virus [10–12]. Therefore, in order to describes the dynamics of CTL immune response more accurately, Wodarz [13] modified model (1) by assuming that the virus population is at a quasi-steady state, i.e. $v = (k/u)y$, and introduced $w$ (represents CTLp) and $z$ (represents CTLe) according to the action principle of CTL. Then, model (1) reduces to

$$(2) \qquad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)y(t), \\ \dot{y} = \beta x(t)y(t) - ay(t) - py(t)z(t), \\ \dot{w} = cy(t)w(t) - cqy(t)w(t) - bw(t), \\ \dot{z} = cqy(t)w(t) - hz(t). \end{cases}$$

Compared to model (1), healthy cells in this model become infected cells at rate $\beta xy$. CTLp emerges at rate $cyw$, becomes CTLe at rate $cqyw$ and decays at rate $bw$. Similarly, CTLe are created at rate $cqyw$ and cleared at rate $hz$. Chan and Yu [12] analyzed the stability of equilibria and bifurcation dynamics of model (2).

In order to model the immune system more precisely, Yu et al. [14] combined model (2) and the viruses to have the following 5-dimensional system :

$$(3) \qquad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)v(t), \\ \dot{y} = \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \dot{v} = ky(t) - uv(t), \\ \dot{w} = cy(t)w(t) - cqy(t)w(t) - bw(t), \\ \dot{z} = cqy(t)w(t) - hz(t). \end{cases}$$

The dynamical properties of model (3) (Fig. 1) have also been studied in [14].

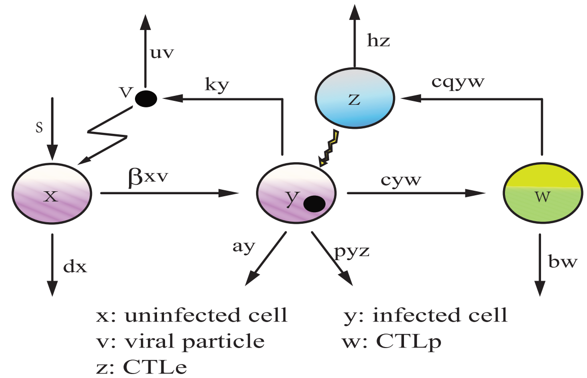


Figure 1. Model (3) with viral infection and immune response. Uninfected cell (healthy cell) $x$ is infected with viral particle $v$, becomes infected cell $y$; in order to clear away the infected cell, the immune system generates CTLp $w$ which has receptors specifically for detecting the virus form the previous infection. During a subsequent infection, CTLp differentiates CTLe $z$ which is again responsible for clearing away the invading virus.