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Bifurcation analysis of macrophages infection model with delayed immune response☆

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ABSTRACT

Macrophages are capable of producing large amounts of both intracellular and extracellular infected cells without necessarily succumbing to the lethal effects of productive viral infection. In this manuscript, authors studied the macrophages infection by human immunodeficiency virus type 1 in the form of mathematical models along with two different types of delays. The asymptotic stability of the constructed model without time delay is proved by utilizing the roots of the characteristic quasi-polynomial which is obtained by applying Jacobian matrix method. Based on Routh–Hurwitz criterion, the dynamical properties of model with a delay is investigated. Instead of discrete time delay, the effect of distribution of delays in the immune activation is also analyzed by using linear chain trick technique. In particular, the model undergoes Hopf bifurcation depending on the critical value of single delay in the activation of immune response. Anti-retroviral treatments have been used to control the replication of HIV-1 virus in infected patients is investigated along with time delay. Moreover, it is proved that the existence of two different types of delays may cause the solutions of the model to become stable or unstable depending on the conditions of chosen bifurcation parameter. Numerical simulations are performed to validate the derived theoretical results.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is an retrovirus that preferentially targets $CD4^+$ helper T-cells, macrophages and dendritic cells. Due to infection of these cells by HIV-1 may induce devastating effects on patient's health. Infection with HIV-1 is the start of a progressive illness for most people that results in death due to the increasing occurrence of opportunistic infections. The ultimate cause is the progressive degradation of immune system by the virus may resulting in development of acquired immunodeficiency syndrome (AIDS) [4]. $CD4^+$ T cells count and plasma viral loads are the only two main factors involve in the clinical studies of the progression of HIV-1 infection. In the absence of anti-retroviral treatment, the regular patient response to HIV-1 infection has three main stages: (i) an initial primary infection, (ii) a long asymptomatic period and (iii) a final increase in viral load with a simultaneous collapse in healthy $CD4^+$T cell count during which AIDS appears, for more details see [5,8,14,26].

Whenever the host cell is infected by HIV-1, instantly immune response will be generated with two different types of functions. First, the humoral response forbids further infection from the same foreign agent and cellular immune response controls

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the infection of uninfected cells. Thus, impregnable cellular immune response could kill many virus-infected cells before production of new virus particles [18,39]. Even marginally less secure Cytotoxic T Lymphocytes (CTLs) response might obliterate many infected cells before they had produced their full accompaniment of virions. If the production of virus may reduced by the CTLs response, then the effect of measured life of infected cells would be minimal. The count of infected cells seems to vary with little over a range of $CD4^+$ T cell counts. So, it is clear that CTLs would control the level of virus reproduction according to the strength of the CTLs response. Small changes in these response activity cause large effects in virus production and plasma viral load [19,32].

In this work, the infection of macrophages by HIV-1 is discussed. Macrophages are large cells derived from monocytes, found within many tissues, which are invading micro-organisms also hunting various dead, damages cells and cellular debris. It ingests the foreign agent, then it traps that foreign agent and it fuses with lysosome (to digest the micro-organism). When the digestion is complete macrophage loads antigen and supplies it to a responding $CD4^+$ T cells. Macrophages together with Langerhans appear to be the first cell infected by HIV-1 to produce infected $CD4^+$ T cells. A number of clinical studies have been conducted to explore the role of macrophages in HIV infection as long-term reservoir [18,28]. A reservoir is a long-lived cell, which can have viral replication even after many years of anti-retroviral treatment. Furthermore, their numbers are maintained in HIV-1 disease both in vitro and in vivo. Monocyte/Macrophages are productively infected in the central nervous system of patients with AIDS dementia complex and vacuolar myelopathy [10]. Unlike lymphocytes, macrophages are capable of producing large amounts of both intracellular and extracellular infected cells without necessarily succumbing to the lethal effects of productive viral infection. If macrophage is infected by HIV-1 which produces cytokines that attracts immune cells and cause dilation of the local blood vessels. So, the infection of macrophages by HIV-1 play a crucial role in the study of HIV-1 virus, for details see [29].

The advent of anti-retroviral drugs (nucleoside/nucleotide, reverse transcriptase inhibitors, protease inhibitors, fusion or entry inhibitors, etc.,) has been considered as important breakthrough in HIV-1 treatment. Until today, different types of anti-retroviral drugs are used only to control the virus but there is always some difficulty to find an efficient therapy to eradicate these types of retroviruses. There are two types of anti-retroviral therapy used to control the production of newly infected cells such as reverse transcriptase therapy (RTI) and protease inhibitor (PI) with RTI blocks the translation of viral RNA to DNA which helps to incorporate the virus into host genomes, thus preventing the infection of new cells. Also, PI interfere with essential steps of protein cleavage in new virus, thus preventing infected cells from producing infectious viral particles. Once treatment is initiated three distinct viral decay phases are seen in patients [14,24]. The first phase is proportional to the death rate of infected cells, whereas the second phase is proportional to the death rate of long-lived infected cells such as macrophages.

A mathematical model may be used as a tool to analyze long term treatment options for HIV infection. A number of mathematical models have been proposed to examine some facets of HIV infection for more details, see [13] and references therein. These models explore the basic relation between $CD4^+$ T cells, infected $CD4^+$ T-cells, viral load, interaction between the immune response cells and HIV infected cells. Recently, the authors in [16] proposed a mathematical model by extending the standard virus-immune model including the effect of differentiation of CTL immune response which is specific to HIV-1 infection. Nowak and Bangham [27] constructed a mathematical model by describing the dynamics of the interaction between susceptible (uninfected) cells, infected cells and immune cells. Immune responses are made by cytotoxic T cells play a vital role in attacking the infected cells by producing suitable antigen and making an antiviral defense [7,17,35,36,38].

Several developed models have experimentally proved the existence and effects of time delays on the immune dynamics for more details, one can refer ([1,3,6,9,15,20–22,25,30,31,33,34,41,42]). Based on the literature review, there are lot of works available on the dynamical process such as efficacy of immune responses, the emergence of drug resistance from mutations in viral proteins, incidence rate and drug therapy [2,37] but only few works had done by researchers by considering and comparing the effect of both discrete and continuous time delays. Hence, in this present study, authors mathematically analyze and compare the effect of discrete and distributed type time delay in the immune activation.

In this paper, the method of bifurcation theory for delay differential equations is used to study full dynamics of the infection of macrophages by HIV-1 along with the effect of anti-retroviral therapy and immune response which needs to be activated against the infection. Stability analysis and existence of Hopf bifurcation for the appropriate model is investigated with and without time delays. The outline of the present work is as follows. In Section 2, authors proposed a mathematical model of macrophages infection by incorporating the anti-retroviral without time delay in the immune response. Section 3 discusses the steady states of the considered model with infection-free equilibrium and endemic equilibrium. In Section 4, the discrete time delay and continuous time delay are analyzed through two different subsections and find the boundary of Hopf bifurcation with respect to discrete type immune activation delay. Section 5 contains numerical explorations of the model and analysis of periodic solutions. The paper concludes in Section 6 with the discussion of results and an outlook.

2. Mathematical model

In this section, the following conceptual model (1) is proposed with population x denotes the density (μl^{-1}) of healthy macrophages at time t (days), y represents the density (μl^{-1}) of infected macrophages at time t (days), w denotes the density (μl^{-1}) of HIV-1 specific CTL effectors at time t (days), z represents the density (μl^{-1}) of HIV-1 specific CTL precursors at time t