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Long term dynamics in a mathematical model of HIV-1 infection with delay in different variants of the basic drug therapy model

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ABSTRACT

Infection with HIV-1, degrading the human immune system and recent advances of drug therapy to arrest HIV-1 infection, has generated considerable research interest in the area. Bonhoeffer et al. (1997) [1], introduced a population model representing long term dynamics of HIV infection in response to available drug therapies. We consider a similar type of approximate model incorporating time delay in the process of infection on the healthy T cells which, in turn, implies inclusion of a similar delay in the process of viral replication. The model is studied both analytically and numerically. We also include a similar delay in the killing rate of infected $CD4^+$ T cells by Cytotoxic T-Lymphocyte (CTL) and in the stimulation of CTL and analyse two resulting models numerically.

The models with no time delay present have two equilibria: one where there is no infection and a non-trivial equilibrium where the infection can persist. If there is no time delay then the non-trivial equilibrium is locally asymptotically stable. Both our analytical results (for the first model) and our numerical results (for all three models) indicate that introduction of a time delay can destabilize the non-trivial equilibrium. The numerical results indicate that such destabilization occurs at realistic time delays and that there is a threshold time delay beneath which the equilibrium with infection present is locally asymptotically stable and above which this equilibrium is unstable and exhibits oscillatory solutions of increasing amplitude.

1. Introduction

Over the last two decades there has been extensive research on the area of HIV-1 infection invading the human immune system. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 37 million people worldwide are infected with HIV-1 today of whom 24 million are in developing countries. Though considerable knowledge has been gathered regarding the implications of genetic variation of immune cells, HIV-1 pathogenesis and probable therapies treating the infected individuals, nevertheless controlling HIV-1 infection continues to be a major challenge. HIV-1 infection is associated with an extremely vigorous virus-specific CTL response that declines with disease progression. There are several different HIV-1 vaccinations which include therapeutic vaccination (administered to those who are already infected) and prophylactic vaccination (administered prior to infection) [2,3].

Anti-retroviral therapy when given to an individual patient makes a portion of the immune cells toxic thereby introducing toxicity in the immune system of the individual. It is thus important to maintain an optimum controlled level of vaccine for

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an infected individual. Thus the use of vaccination at an optimum controlled level for HIV-1 in human infection may emerge that significantly increases the survival time of infected individuals. In particular, immunological escape and subsequent disease progression have been seen in several studies of vaccination therapy [4–6,3]. The main purpose of this study is to develop a mathematical framework that can be used to understand the bearing of drug response on the dynamical behaviour of the lymphocytic immune cells populations.

The main clinical indicators in the follow up of HIV-1 positive patients are both the viral load and the $CD4^+$ T cell count in blood plasma [7–10]. It has been observed clinically that patients infected with immunodeficiency virus type-1 (HIV-1), if treated with a combination of inhibitor drugs lamivudine and zidovudine show a 10–100 fold reduction of viral load and nearly 25% increase in the healthy $CD4^+$ T cells count. Survival of patients who receive such drugs is observed to be very substantially increased [1,11,12,2,4,3,13,14,8,9,15,16]. The longer survival is due to consequences of the diminishing rate of infections of the uninfected T cells. This obviously leads to the conjecture that the drug effectively drives the virus to a state of near extinction.

In this paper we propose and analyse a mathematical model of HIV-1 infection to $CD4^+$ T cells including the inhibitor drug mentioned above. The system responds to the drug-stimulation by generating CTL and this CTL in turn attacks the actively infected $CD4^+$ T cells and kills them. Note that there exists a finite time lag or delay in the process of disease transmission. Also it can be noted that there exists a finite time lag between a $CD4^+$ T cell getting actively infected and its subsequent death. Such a realistic time lag has been incorporated in the model under consideration. We have also considered the delay factor in the terms representing killing of virus-producing cells by CTL and in the stimulation of CTL. We analyse the dynamics of such a model in three different cases to understand how the HIV-1 infected immune system responds to varied levels of drugs applied under the systematic therapy procedure. The aim is to study and compare the dynamics of the proposed model including delay in three different cases to explore the crucial system parameters and their ranges in order to obtain different theoretical behaviours predicted from the interaction between infectible and infected $CD4^+$ T cells and also CTL response against virus infected cells.

Previous work

It is not possible to give a comprehensive review of mathematical models for the internal viral dynamics of HIV. There are too many of these and that is not the purpose of this paper. Instead we give some basic relevant models and their main results. Bonhoeffer et al. [1] consider two models. The first has viral dynamics of only infectible cells (x) and virus-producing cells (y)

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy, \\ \frac{dy}{dt} &= \beta xy - ay, \end{aligned} \tag{1.1}$$

where λ is the rate of immigration or creation of infectible cells, d is the natural death rate of infectible cells, a is the death rate of virus-producing cells and β is the rate of infection of uninfected cells. They examine the effect of reverse transcriptase inhibitors. They calculate R_0, the basic reproductive number both with and without treatment. R_0 is defined as the expected number of virus-producing cells caused by a single virus-producing cell entering the disease-free equilibrium (DFE)

$$R_0 = \frac{\beta\lambda}{ad}. \tag{1.2}$$

They show that for $R_0 \leq 1$ there is only the equilibrium with no virus-producing cells whereas for $R_0 > 1$ there is a unique equilibrium with both infectible cells and virus-producing cells. Simulations were performed to examine the dynamic behaviour of the model.

Later they introduce another variable z for the density of CTL responses against virus-infected cells. The extended model is

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy, \\ \frac{dy}{dt} &= \beta xy - ay - pyz, \\ \frac{dz}{dt} &= ky - bz. \end{aligned} \tag{1.3}$$

Here p is the killing rate of virus-producing cells by CTL, k is the rate of stimulation of CTL and b is the per capita death rate of CTL. For this model R_0 is still given by (1.2).

In another paper Bonhoeffer et al. [11] examine the dynamics of uninfected cells (x), infected cells (y) and virus (v). The equations are:

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xv, \\ \frac{dy}{dt} &= \beta xv - ay, \end{aligned} \tag{1.4}$$