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Towards Modeling HIV Long Term Behavior ⋆

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Abstract: The precise mechanism that causes HIV infection to progress to AIDS is still unknown. This paper presents a mathematical model which is able to predict the entire trajectory of the HIV/AIDS dynamics, then a possible explanation for this progression is examined. A dynamical analysis of this model reveals a set of parameters which may produce two real equilibria in the model. One equilibrium is stable and represents those individuals who have been living with HIV for at least 7 to 9 years, and do not develop AIDS. The other one is unstable and represents those patients who developed AIDS in an average period of 10 years. However, further work is needed since the proposed model is sensitive to parameter variations.

Keywords: Biological Systems, Modeling, HIV

1. INTRODUCTION

Several mathematical models have been proposed to describe HIV dynamics since 1990, these present a basic relation between CD4+T cells, infected CD4+T cells and virus Nowak [2000], Kirschner [1996], Perelson [1999], Xia [2007]. These models give a good presentation of the initial peak infection and the asymptomatic stage. However, they are not able to describe the transition to the last stage of the disease AIDS (acquired immunodeficiency syndrome).

To obtain a more widely applicable model, some authors have tried to introduce other variables, taking into consideration other mechanisms by which HIV causes depletion of CD4+T cells. Numerous theories have been proposed, but none can fully explain all events observed to occur in practice. Recent studies Wang et al. [2000] have shown that HIV infection promotes apoptosis in resting CD4+T cells by the homing process. This mechanism was modeled in two compartments by Kirschner et al. [2000], in this study authors showed that therapeutic approaches involving inhibition of viral-induced homing and homing-induced apoptosis may prove beneficial for HIV patients. The role of the thymus in HIV-1 infection was considered by Kirschner et al. [1998]. The authors found that infection of the thymus can act as a source of both infectious virus and infected CD4+T cells. Significant effort has been developed in understanding the interaction of the immune system and HIV Campello [1999], Adams et al. [2004].

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One limitation of these mathematical models is that they do not reproduce the entire trajectory of HIV/AIDS dynamics. This trajectory consists of the early peak in the viral load; a long asymptomatic period and a final increase in viral load with a simultaneous collapse in healthy CD4+T cell count during which AIDS appears.

A number of studies have been conducted to explore the role of macrophages in HIV infection as long-term reservoir Oreinstein [2001]. A reservoir is a long-lived cell, which can have viral replication even after many years of drug treatment. Using this theory, Conejeros et al. [2007] proposed a deterministic model which describes the complete HIV/AIDS trajectory. Simulations results for that model emphasize the importance of macrophages in HIV infection and progression to AIDS, but no dynamical analysis is proposed.

In this paper, we present a simplification of Conejeros et al. [2007], in order to have the same behavior of HIV/AIDS, which permits us to understand and analyse the transition to AIDS. The model is discussed and compared with clinical data.

2. MODEL DESCRIPTION

The model proposed in this section is a simplification of Conejeros et al. [2007], and considers the following populations; T represents the uninfected CD4+T cells, T_i represents the infected CD4+ T cells, M represents uninfected macrophages, M_i represents the infected macrophages, and V represents the HIV population.

The mechanisms consider for this model are described by the next reactions;

A. Cell proliferation

The source of new CD4+T cells and macrophages from thymus, bone marrow, and other cell sources is considered constant.

$$\varnothing \xrightarrow{s_1} T \tag{1}$$

$$\varnothing \xrightarrow{s_2} M \tag{2}$$

s_1 and s_2 are the source terms and represent the generation rate of new CD4+T cells and macrophages. However, when pathogen is detected by the immune system, a signal is sent in order to become more aggressive, and then CD4+T cells and macrophages proliferate;

$$T + V \xrightarrow{k_1} (T + V) + T \tag{3}$$

$$M + V \xrightarrow{k_3} (M + V) + M \tag{4}$$

B. Infection cell

HIV can infect a number of different cells; activated CD4+T cells, resting CD4+T cells, quiescent CD4+T cells, macrophages and dentritic cells. For simplicity, just activated CD4+T cells and macrophages are considered viral hosts:

$$T + V \xrightarrow{k_2} T_i \tag{5}$$

$$M + V \xrightarrow{k_4} M_i \tag{6}$$

C. Virus proliferation

The viral proliferation is modeled as occurring in activated CD4+T cells and macrophages.

$$T_i \xrightarrow{k_5} V + T_i \tag{7}$$

$$M_i \xrightarrow{k_6} V + M_i \tag{8}$$

D. Natural death

Cells and virons have a finite lifespan. These losses are represented by the following reactions;

$$T \xrightarrow{\delta_1} \emptyset \tag{9}$$

$$T_i \xrightarrow{\delta_2} \emptyset \tag{10}$$

$$M \xrightarrow{\delta_3} \emptyset \tag{11}$$

$$M_i \xrightarrow{\delta_4} \emptyset \tag{12}$$

$$V \xrightarrow{\delta_5} \emptyset \tag{13}$$

Using reactions (1)-(13), we obtain the following model;

$$\begin{aligned} \dot{T} &= s_1 + k_1 TV - k_2 TV - \delta_1 T \\ \dot{T}_i &= k_2 TV - \delta_2 T_i \\ \dot{M} &= s_2 + k_3 MV - k_4 MV - \delta_3 M \\ \dot{M}_i &= k_4 MV - \delta_4 M_i \\ \dot{V} &= k_5 T_i + k_6 M_i - \delta_5 V \end{aligned} \tag{14}$$

The model implementation outlined in (14) will be conducted using MATLAB. Parameters and initial conditions were obtained from previous works in the area Perelson [1999], Xia [2007], Conejeros et al. [2007]. Using clinical data for the CD4+T cell counts Greenough [2000], Fauci et al. [1996], some parameters were adjusted, see Table 1, in order to obtain the best match with clinical data.

Table 1. Parameters Values

Parameter	Value	Value taken from:
s_1	10	Perelson [1999]
s_2	0.15	Perelson [1999]
k_1	2×10^{-3}	Fitted
k_2	3×10^{-3}	Fitted
k_3	7.45×10^{-4}	Conejeros et al. [2007]
k_4	5.22×10^{-4}	Conejeros et al. [2007]
k_5	5.37×10^{-1}	Conejeros et al. [2007]
k_6	2.85×10^{-1}	Conejeros et al. [2007]
δ_1	0.01	Conejeros et al. [2007]
δ_2	0.44	Fitted
δ_3	0.0066	Fitted
δ_4	0.0066	Fitted
δ_5	2.4	Xia [2007]

3. MODEL RESULTS

An infected HIV patient, in general, suffers a fast drop in healthy CD4+T cell count and at the same time a rapid increase in virus population. Then, the immune system responds to the virus by proliferating CD4+T cells and macrophages, this can be seen just after the dip during primary infection in Fig.1. During the next about 8 to

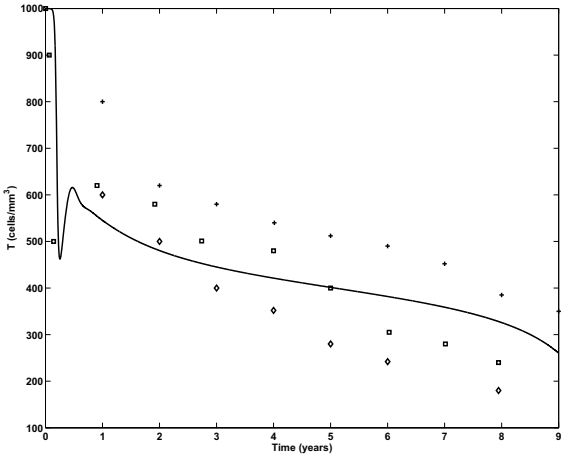

Fig. 1. CD4+ T cells dynamics. Comparison with clinical data taken from Greenough [2000] and Fauci et al. [1996]

10 years the patient experience an asymptomatic phase. On one hand, CD4+T cells experience a slow depletion but are with sufficient level to maintain most immune system functions. At the same time the virus population continues infecting healthy cells, therefore slowly advances in numbers, see Fig.2. At the end of asymptomatic period, constitutional symptoms appears when CD4+T cells are