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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

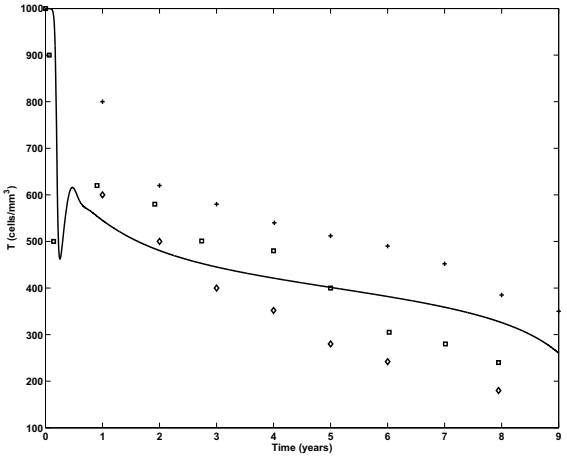

Fig. 1. CD4+ T cells dynamics. Comparison with clinical data taken from Greenough [2000] and Fauci et al. [1996]

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

below about 300 mm^{-3}. The last stage and the most dangerous for the patient is when CD4+T cells drop below 200 mm^{-3} and the viral explosion takes place, which is considered as AIDS. We can see in Fig.1 how the proposed model is able to represent all the stages of the infection and matches well clinical data.

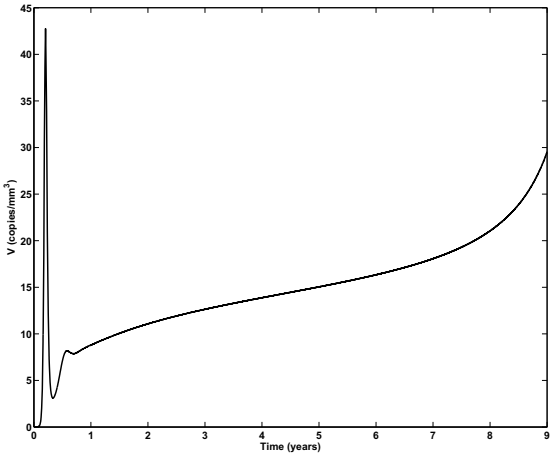

Fig. 2. Viral dynamics

Infected CD4+T cell behavior is structurally similar to the viral dynamics in the first years, see Fig.3. There is an initial peak of infected CD4+T cells, followed by a small increment but almost constant during the asymptomatic stage.

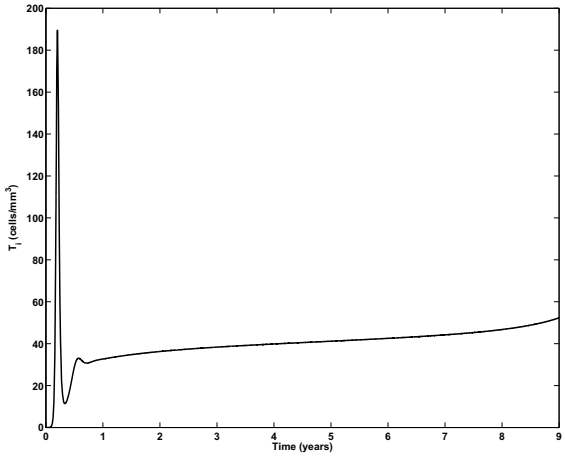

Fig. 3. Infected CD4+ T cell dynamics

Macrophages play a central role in this model of HIV infection. They are considered one of the first points of infection and then infected macrophages are long-lived virus reservoirs as is noted in Oreinstein [2001]. We may notice how the model is able to represent these facts. Fig.4 shows how macrophages climb over the years slowly trying to suppress the virus. This fact is consistent with previous works Conejeros et al. [2007], who suggest that macrophages may divide and become more aggressive.

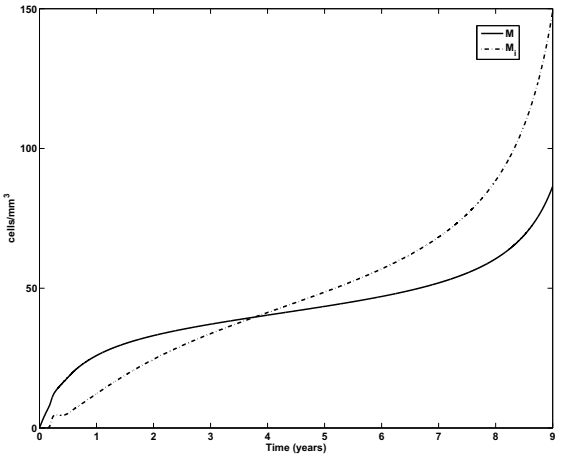

Fig. 4. Macrophages and infected macrophages dynamics

Infected macrophages increase slowly in number during the asymptomatic period, but when constitutional symptoms appear infected macrophages increase very rapidly as can be seen in Fig.4. This is consistent with the work of Igarashi et al. [2001], who argued that in the early infection the virus replication rate in macrophages is slower than replication rate in CD4+T cells, but over the period of years, the viral replication rate in macrophages is faster than early stages of infection.

4. AIDS TRANSITION

The model proposed by Conejeros et al. [2007] shows the complete HIV trajectory. However, they do not give a detailed explanation of the HIV/AIDS transition, since the model is difficult to analyze. For this reason, we propose some simplifying assumptions to allow analysis.

Assumption.1 Fast Viral Dynamics

Looking at the differential equations (14) and parameter values in Table 1, we notice that $\delta_5 >> 1$. In this case, the differential equation for the virus can be approximated by the next algebraic equation, as noted in Barao et al. [2007].

$$V = \frac{k_5}{\delta_5} T_i + \frac{k_6}{\delta_5} M_i \tag{15}$$

Assumption.2 Assume T_i is bounded

We note that in the asymptomatic period of infection (that is, after the initial transient, and before the final divergence associated with development of AIDS), the concentration of infected CD4+T cells is relatively constant. This assumption is also proposed in Astolfi et al. [2008]. Therefore the following assumption for infected CD4+T cells can be considered:

$$T_i(t) \approx \overline{T_i}, \forall t \geq t_0 \tag{16}$$

Then under (15), (16) can be reduced to

$$V(t) := c_1 M_i + V_{T_i} \tag{17}$$

where $V_{T_i} = \frac{k_5}{\delta_5}\overline{T_i}$ and $c_1 = \frac{k_6}{\delta_5}$. Note that if $\bar{T}_i$ is selected as an upper bound on T_i, then (17) represents an upper bound on $v(t)$. Therefore (17) describes the long asymptomatic period in the viral load dynamic. Using last assumptions in macrophages and infected macrophages equations, we have the following system

$$\dot{M} \approx s_2 - c_2 M + c_3 M M_i \tag{18}$$

$$\dot{M}_i \approx c_4 M + c_5 M M_i - \delta_4 M_i \tag{19}$$

where $c_2 = \delta_3 - (k_3 - k_4)V_{T_i}$, $c_3 = (k_3 - k_4)c_1$, $c_4 = k_4 V_{\overline{T_i}}$ and $c_5 = k_4 c_1$.

Assumption.3 M and M_i have an affine relation

Note that from (18) and (19), we expect that the bilinear terms are predominant for large M and M_i, then we may assume $\dot{M} \approx \frac{c_3}{c_5}\dot{M}_i$, which are rearranged in the next linear form;

$$M_i \approx c_6 M - c_7 \tag{20}$$

where $c_6 = \frac{c_2 c_5 + c_3 c_4}{c_3 \delta_4}$ and $c_7 = \frac{c_5 s_2}{c_3 \delta_4}$.

Proposition 1. Under Assumptions 1-3, the macrophage dynamics in an infected HIV patient are unstable with a finite time escape.

Proof: Substituting (20) in equation (18), we have a good approximation for the macrophage equation;

$$\dot{M} = s_2 + \alpha M^2 + \beta M \tag{21}$$

where
$\alpha = \frac{c_6 k_6 (k3 - k_4)}{\delta_5}$
$\beta = \frac{(k_3 - k_4)(k_5 \overline{T_i} - c_7 k_6)}{\delta_5} - \delta_3$
The solution of the differential equation (21) for $4\alpha s_2 \geq \beta^2$ is given by;

$$M = \frac{\beta}{2\alpha} + \frac{\sqrt{4\alpha s_2 - \beta^2}}{2\alpha} tan\left(\frac{\sqrt{4\alpha s_2 - \beta^2}}{2} t + \eta\right) \tag{22}$$

where η is a constant related to initial condition of macrophages given by;

$$\eta = tan^{-1}\left(\frac{2\alpha M_0 - \beta}{\sqrt{4\alpha s_2 - \beta^2}}\right) \tag{23}$$

In (22) there is a tangent function, which tends to ∞ when the argument tends to $\pi/2$, that is when;

$$t = T_\infty := \frac{\pi - 2\eta}{\sqrt{4\alpha s_2 - \beta^2}} \tag{24}$$

implies that there is a finite escape time.

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5. DYNAMICAL ANALYSIS

The structure of the system (14) can be decomposed in two feedbacks, see Fig.5; one is a fast negative feedback and the other is a slow positive feedback. The biological meaning of this is that feedback 1 is due to a fast CD4+T cell infection which is greater than the CD4+T cell proliferation. The feedback 2 is for a slow macrophages infection rate which is less than macrophage proliferation.

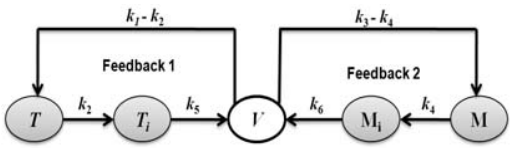

Fig. 5. HIV scheme

Using the system (14), we are able to get the equilibrium points analytically in the form;

$$T = \frac{s_1}{k_d V + \delta_1}, T_i = \frac{k_2 s_1}{\delta_2}\frac{V}{k_d V + \delta_1}$$
$$M = \frac{s_2}{k_n V + \delta_3}, M_i = \frac{k_4 s_2}{\delta_4}\frac{V}{k_n V + \delta_3}$$

where $k_d = k_2 - k_1$, $k_n = k_4 - k_3$ and the value of V is a solution of the polynomial.

$$aV^3 + bV^2 + cV = 0 \tag{25}$$

The equation (25) has three solutions, which are;

$$V^{(A)} = 0, V^{(B)} = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, V^{(C)} = \frac{-b - \sqrt{b^2 - 4ac}}{2a}$$

where;
$a = \delta_2 \delta_4 \delta_5 k_n k_d$
$b = \delta_2 \delta_3 \delta_4 \delta_5 k_d + \delta_1 \delta_2 \delta_4 \delta_5 k_n - \delta_4 k_2 k_n k_5 s_1 - \delta_2 k_4 k_d k_6 s_2$
$c = \delta_1 \delta_2 \delta_3 \delta_4 \delta_5 - \delta_3 \delta_4 k_2 k_5 s_1 - k_4 k_6 \delta_1 \delta_2 s_2$

Equilibrium A

$$T^{(A)} = \frac{s_1}{\delta_1},\ T_i^{(A)} = 0,\ M^{(A)} = \frac{s_2}{\delta_3},\ M_i^{(A)} = 0,\ V^{(A)} = 0$$

Equilibrium B,C

$$T^{(B,C)} = \frac{s_1}{k_1 V^{(B,C)} + \delta_1},\quad T_i^{(B,C)} = \frac{k_1 s_1}{\delta_2}\frac{V^{(B,C)}}{k_1 V^{(B,C)} + \delta_1}$$
$$M^{(B,C)} = \frac{s_2}{k_2 V^{(B,C)} + \delta_3},\quad M_i^{(B,C)} = \frac{k_2 s_2}{\delta_4}\frac{V^{(B,C)}}{k_2 V^{(B,C)} + \delta_3}$$

Equilibrium A represents an uninfected status. Using numerical values, the uninfected equilibrium is unstable, which is consistent with previous works Astolfi et al. [2008]. This could explain why it is difficult to revert a patient once infected, back to the HIV-free status. Using parameter set in Table 1, equilibria B and C take imaginary values since $b^2 \leq 4ac$, which are not important

for the biological case. This means that there is no stable point for the patient with this set of parameters, then the model will progress to AIDS status.

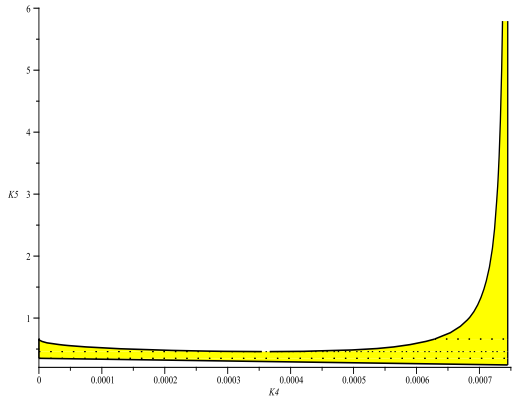

Fig. 6. Parameter space in terms of the number of equilibrium points: shaded region shows two equilibrium

5.1 Number of equilibrium points and parameter spaces

Using the recently developed symbolic real algebraic geometry methods we keep some parameters unfixed and get the number of equilibrium points for the unfixed parameter space. The method is called the discriminant variety method which was developed in Lazard et al. [2007], this is implemented in Maple as in-built packages called "Parametric" and "DV" Liang et al. [2009]. This method decomposes the parameter space into different cells such that the number of real roots is the same for any point in a given cell. We compute 2D parameter spaces below, for k_4 and k_5. In Fig. 6 the colored region shows the part of the parameter space in the $k_4 - k_5$ plane for which there are two equilibria in the system. All other parameters are set as in Table 1.

Remark 1. Using a built-in symbolic algebra routine we confirm that the number of equilibria with biological meaning and dynamic properties for the proposed model are equal to those in Conejeros et al. [2007].

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5.2 Bifurcation Analysis

Using the proposed model, there is a set of parameters which may produce real equilibria in B and C. If we solve for parameter δ_5, the change of stability is given by;

$$\delta_5 > \frac{\delta_2 k_5 k_d k_6 s_2 - \delta_4 k_2 k_n k_5 s_1}{(-\delta_1 k_n + k_d \delta_3)\delta_2 \delta_4} + \frac{2(-\delta_4 k_2 k_n k_5 s_1 \delta_2 k_4 k_d k_6 s_2)^{\frac{1}{2}}}{(-\delta_1 k_n + k_d \delta_3)\delta_2 \delta_4} \quad (26)$$

Increasing the value of δ_5 as in (26), the escape time may be delayed. This means that infected patients that are able to more rapidly clear the virus could postpone for many years the transition to AIDS. Furthermore, a change in the stability from unstable to stable is shown in Fig.7, that is the immune system would adapt to maintain a stable status in the patient.

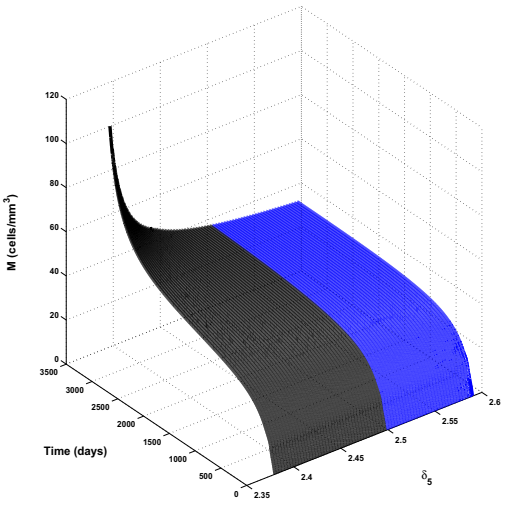

Fig. 7. Bifurcation using δ_5 (the black region is the unstable behavior and the blue region is stable)

Table 2. Bifurcation

Parameter	Critical Point
s_1	50.679
s_2	2.463
k_1	2.95×10^{-3}
k_2	3.33×10^{-3}
k_3	5.337×10^{-3}
k_4	5.648×10^{-4}
k_5	2.721
k_6	4.679
δ_1	1.178×10^{-2}
δ_2	4.732×10^{-1}
δ_3	6.99×10^{-3}
δ_4	7.4×10^{-3}
δ_5	2.497

Remark 2. Whilst the model reproduces known long term behavior, bifurcation analysis in Table 2 evidences an unusually high sensitivity. In particular, small relative changes in k_2, k_3, k_4, δ_1, δ_2, δ_3, or δ_5 give bifurcation to a qualitatively different behavior.

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5.3 Numerical Results

Choosing δ_5 as stated in condition (26), there are two real positive equilibria which are shown in Table 3. One point is called LTNP (Long Term Non Progressor), because it shows the characteristic of individuals who have been living with HIV around 7 to 12 years and have stable

CD4+T counts around 600 $cells/mm^3$ or more. The other point is called progressor; when CD4+T cell counts fall below 200 $cells/mm^3$, the patient is said to have AIDS.

We observe in Table 4 that LTNP point is stable and the progressor point is unstable. The model can represent adequately both phenomena as is presented in clinical studies. From the bifurcation analysis, it would appear that there are certain progressor patients who could become LNTP. However, it is unclear if this property would be preserved in more complete models, and clinical evidence for this seems weak.

Table 3. Equilibria

Points	V	T	T_i	M	M_i
LTNP	5.43	647.99	24.0	27.83	11.95
Progressor	21.31	319.3	46.40	81.22	136.92

Table 4. Eigenvalues for equilibria

LTNP	Progressor
-0.66	-0.66×10^{-2}
$-0.49 \times 10^{-1} + 0.14 \times 10^{-1} i$	0.286×10^{-2}
$-0.49 \times 10^{-1} - 0.14 \times 10^{-1} i$	-0.457×10^{-1}
-0.286	-0.238
-3.35	-3.19

6. CONCLUSIONS

The proposed model predicts the entire trajectory of the disease: initial viremia, latency, and the rapid increase of virus. Using this simplified model can be understood how HIV works in an infected patient; basically, the virus inhibits the CD4+T cell population while promotes the macrophages proliferation which are reservoir for virus replication. The long reservoir behavior of macrophages in an infected HIV patient is a possible explanation of why a patient progress to AIDS, and serve as recommendation for clinical study. However, we are concerned about the sensitivity of the model for some parameters, alternative mechanisms will be considered in future work.

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