

On the modeling of long-term HIV-1 infection dynamics

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Abstract

In this paper we propose and study models of long-term Human Immunodeficiency Virus (HIV-1) infection. Our aim is to identify model mechanisms that allow to explain the trends observed in clinical measurements of the number of CD4+ T-cells and virus throughout the long-term HIV-1 infection, from the acute phase until the onset of AIDS. To achieve our goal we apply some standard methods of modeling and analysis of dynamical systems. Among these methods are model development and validation processes such as parameter estimation, as well as Painleve and bifurcation analysis.

keywords: HIV dynamics, immune response, parameter estimation, dynamical systems

1 Introduction

It has been established that the HIV-1 is the etiologic agent of the AIDS. However, many of the corresponding host-pathogen interaction mechanisms are not yet completely understood. The mathematical modeling of the host-pathogen interactions has a growing importance as a tool to obtain insight into

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the dynamics of the cellular immune response to human immunodeficiency virus (HIV-1) infection. Efforts to model HIV-1 infection are ubiquitous, see for instance [1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12].

A basic model of virus dynamics was introduced by Nowak and May [8]. The Nowak-May model, among other models, has given feedback on the dynamics of HIV-1 infection; also, this model has served as a framework to build other models of HIV-1 infection. One of the consequences of the Nowak-May model is that nowadays is commonly accepted that a model of HIV-1 infection should have at least three classes of cells: healthy T-cells, infected T-cells and virus. On the other hand, the Nowak-May model uses only mass-action terms to account for the interaction of healthy T-cells and virus. This is adequate since the number of cells in the cellular immune system is large. However, according to the Painlevé Property (PP) test [15], the Nowak-May model is completely integrable. Therefore, it has “simple” dynamics as opposed to some trends commonly observed in the long-term HIV-1 infection. One of such trends, which is yet to be completely understood, is the slow depletion of healthy T-cells that ultimately leads to AIDS. Two possible explanations of this trend are i) direct HIV-1-mediated cell killing or ii) persistent activation of T-cells spared during the infection which progressively disrupts the functional organization of the immune system. Another key feature of HIV-1 infection is the ability of the HIV-1 to remain latent within the host and reactivate itself. Some authors support that virus reservoirs in resting infected T-cells may constitute a barrier to recovery [13]. Apparently, productively infected cells soon subside locally, and maintenance of the infection crucially depends on the activation of infected memory cells to spark new bursts of HIV-1.

In this paper we propose a class of models based on the Nowak-May model to study reactivation of resting infected T-cells T_r during long-term HIV-1 infection. These models incorporate classes of T_r cells and cytotoxic T-cells T_c . The term that accounts for reactivation T_r cells is general enough to prevent the proposed models from having the Painlevé Property (PP). The resulting models therefore, have a strong possibility of exhibiting chaotic behavior.

The paper is organized as follows: In section 2 are described the proposed models. In section 3 are shown some results of parameter estimation on one specific model using previously published data. The dynamical behavior of this model is further studied by applying continuation on selected parameters in a neighborhood of the unique stationary point on the non-negative hyper-quadrant. Finally, in section 4 we offer a discussion and conclusions.

2 Models Formulation

The Nowak-May model is given by

$$\frac{dT}{dt} = s_1 - d_1T - k_1TV, \quad (1)$$

$$\frac{dT_i}{dt} = k_1TV - d_2T_i, \quad (2)$$

$$\frac{dV}{dt} = k_9T_i - d_7V, \quad (3)$$

where T is the number of healthy T-cells at time t , T_i is the number of infected T-cells and V is the number of virus. This model has two stationary points. The stationary point $[T = \frac{s_1}{d_1}, T_i = 0, V = 0]$, which is a disease free steady state, is a saddle point if $s_1k_1k_9 < d_1d_2d_7$ and a global attractor if $s_1k_1k_9 > d_1d_2d_7$. The stationary point $[T = \frac{d_2d_7}{k_1k_9}, T_i = \frac{d_1d_2d_7 - s_1k_1k_9}{d_2k_1k_9}, V = \frac{d_1d_2d_7 - s_1k_1k_9}{d_2d_7k_1}]$, which is a chronic steady state, is a global attractor for $s_1k_1k_9 < d_1d_2d_7$ and a saddle point if $s_1k_1k_9 > d_1d_2d_7$. If parameters vary within a physically meaningful range the chronic steady state is a global attractor.

Based on the Nowak-May model we propose the following model that incorporates a compartment of resting infected T-cells T_r and a compartment of cytotoxic T-cells T_c . The inclusion of a class of T_c cells into the model allows to take into account the associated immune response.

$$\frac{dT}{dt} = s_1 - d_1T - k_1TV, \quad (4)$$

$$\frac{dT_i}{dt} = fk_1TV + \mathbf{g} - d_2T_i - k_3T_iT_c, \quad (5)$$

$$\frac{dT_r}{dt} = (1 - f)k_1TV - \mathbf{g} - d_3T_r, \quad (6)$$

$$\frac{dT_c}{dt} = s_3 + k_7T_iT_c - d_6T_c, \quad (7)$$

$$\frac{dV}{dt} = s_4 + k_9T_i - k_{11}TV - d_7V. \quad (8)$$

One fraction $1 - f$ of the T-cells become resting once infected. The term \mathbf{g} in equations (5) and (6) accounts for the reactivation of resting infected T-cells. The term $k_3T_iT_c$ in equation (5) signifies immune response of cytotoxic T-cells on infected T-cells. Immune response of T-cells on virus $k_{11}TV$ is incorporated in equation (8). Equation (7) considers the production and death of cytotoxic T-cells. Velasco *et. al* [14] claim that there is some compartmentalization of HIV-1-infected cells to lymphatic tissue, with a large number

of virus-producing cells residing there. The constant term s_4 in equation (8) accounts for the source of virus from the lymphatic tissue.

3 Model Analysis

In this section we apply three standard tools to examine the dynamics of model (4)-(8). First, we use the Painlevé Property (PP) test to choose the term \mathbf{g} that accounts for reactivation of T_r cells. Secondly, we conduct parameter estimation on the model with a specific example of the reactivation term \mathbf{g} . Finally, we examine the behavior of the unique steady state of the resulting model in a neighborhood of the estimated parameters.

3.1 Painlevé Property Test

We used the Painlevé Property (PP) test to obtain information on the dynamics of models (1)-(3) and (4)-(8). There is a conjecture that if a given system of ordinary differential equations does not have the PP then it is not completely integrable and has a strong possibility of exhibiting chaotic behavior. On the other hand, if the system has the PP then all the possible exact solutions can be found explicitly. We say that a system of nonlinear ordinary differential equations has the PP if all the movable singularities of all its solutions are poles.

Hone [15] proposes the following algorithm to test whether a system of ordinary differential equations has the PP. Let $y(z)$ denote the dependent variable

- Step 1: Identify all singularities of the form $y(z) = c_0(z - z_0)^\alpha$, where z_0 is arbitrary.
- Step 2: If all exponents α are integers, find positions where arbitrary constants can appear in the Laurent series (*resonances*).
- Step 3: If all resonances are integers, check compatibility conditions of the resonances in each Laurent expansion.
- Step 4: If no obstruction is found in steps 1-3 for every dominant singularity then the Painlevé Property (PP) test is satisfied.

If a given system of ordinary differential equations has the PP then its solutions must have local Laurent expansions around movable singularities. Further, if branching occurs then this can be detected by local singularity analysis (Step 3 in the above algorithm). Applying the PP test to the Nowak-May model (1)-(3) gives that the leading singularities have exponents $\alpha_1 = -1$, $\alpha_2 = -2$ and $\alpha_3 = -2$. The corresponding resonances are $r_1 = -1$, $r_2 = 2$ and $r_3 = 2$. The

compatibility condition at resonances $r = 2$ is $\frac{(d_1-d_2)(d_1-d_7)}{k_1k_9} = 0$. Therefore, the Nowak-May model has the PP. If we take $\mathbf{g} = \text{constant}$ in model (4)-(8), the PP test indicates that the leading singularities have exponents $\alpha_1 = -1$, $\alpha_2 = -1$, $\alpha_3 = -1$, $\alpha_4 = -1$ and $\alpha_5 = -1$. The corresponding resonances are $r_1 = -1$, $r_2 = 1$, $r_3 = 1$, $r_4 = 1$ and $r_5 = \frac{fk_7-k_{11}}{k_{11}}$. We conclude that the model (4)-(8) has the PP.

Apparently, maintenance of the infection crucially depends on the activation of infected memory cells to spark new bursts of HIV-1. Thus, it is interesting from a biological point of view to examine the dynamics of the model (4)-(8) with a non-constant \mathbf{g} . We propose the selection of a biologically meaningful reactivation term \mathbf{g} such that the resulting model does not have the PP. In order to achieve this, we suppose that the reactivation depends on the number of healthy T-cells, resting infected T-cells and virus.

Let us set $T = z^{p_1}$, $T_i = z^{p_2}$, $T_r = z^{p_3}$, $T_c = z^{p_4}$ and $V = z^{p_5}$ the state variables in the PP test. Let us suppose that \mathbf{g} is of the form

$$\mathbf{g} = g_1 T_r^N T^M V^k. \quad (9)$$

Our choice of the functional dependence of \mathbf{g} is based on the recommendation of several authors, see for instance [13]. The arising model does not have the PP if the equation

$$(L - M)p_1 + (1 - N)p_5 = 1 \quad (10)$$

has rational solutions for p_1 and p_5 . There are infinitely many solutions. We choose $N = 1$, $L = 3$ and $M = 1$ for the sake of simplicity. This leads to the following model

$$\frac{dT}{dt} = s_1 - d_1 T - k_1 TV, \quad (11)$$

$$\frac{dT_i}{dt} = f k_1 TV + g_1 T_r TV^3 - d_2 T_i - k_3 T_i T_c, \quad (12)$$

$$\frac{dT_r}{dt} = (1 - f) k_1 TV - g_1 T_r TV^3 - d_3 T_r, \quad (13)$$

$$\frac{dT_c}{dt} = s_3 + k_7 T_i T_c - d_6 T_c \quad (14)$$

$$\frac{dV}{dt} = s_4 + k_9 T_i - k_{11} TV - d_7 V. \quad (15)$$

We examine the dynamics of model (11)-(15) in the rest of this paper.

3.2 Parameter Estimation

Model (11)-(15) has the form

$$\dot{x} = \varphi(x, p), \quad (16)$$

$$x(t_0) = x_0, \quad (17)$$

where φ is the right hand side of the HIV-1 infection model, x are the state variables and p the parameters. Problem (16)-(17) defines a mapping $\Phi(p) = x$ from parameters p to state variables x , where $\Phi : R^m \rightarrow (L^2([0, T]))^n$. Also, there is a linear observation mapping from state variables to observed data $\Psi : (L^2([0, T]))^n \rightarrow R^{s \times k}$, where $s \leq n$ is the number of observed variables and k is the number of sample points.

Let z_δ denote the observed data, that is, the time series of the number of T-cells and virus. The parameter estimation problem can be formulated as

$$\min_{p \in R^m} \frac{1}{2} \|\Psi(x) - z_\delta\|^2 \quad (18)$$

such that

$$\dot{x} = \varphi(x, p) \quad (19)$$

$$x(t_0) = x_0 \quad (20)$$

We solved the parameter estimation problem (18)-(20) using data of the number of T-cells and virus throughout the HIV-1 infection published in Penisi [16] and the model (11)-(15), see Figure 1. Range values for most parameter appearing in this model are known from clinical data, for example, the mean life of virus or infected T-cells. Parameters for which no a priori information is available, e.g. k_3 or k_{11} , were estimated starting the Nelder-Mead algorithm [17] simultaneously at a random array of normally distributed points.

If an a priori estimate of the noise level in the data is available, then the parameters can be locally refined applying the Landweber iteration. The following implementation of the Landweber iteration is derived in [18].

Theorem 1 *The Landweber iteration*

$$p_{k+1} = p_k + F'(p_k)^*(F(p_k) - z_\delta) \quad (21)$$

can be written

$$p_{k+1} = p_k - \int_0^T \varphi_p(x_k(t), p_k)^* \lambda(t) dt \quad (22)$$

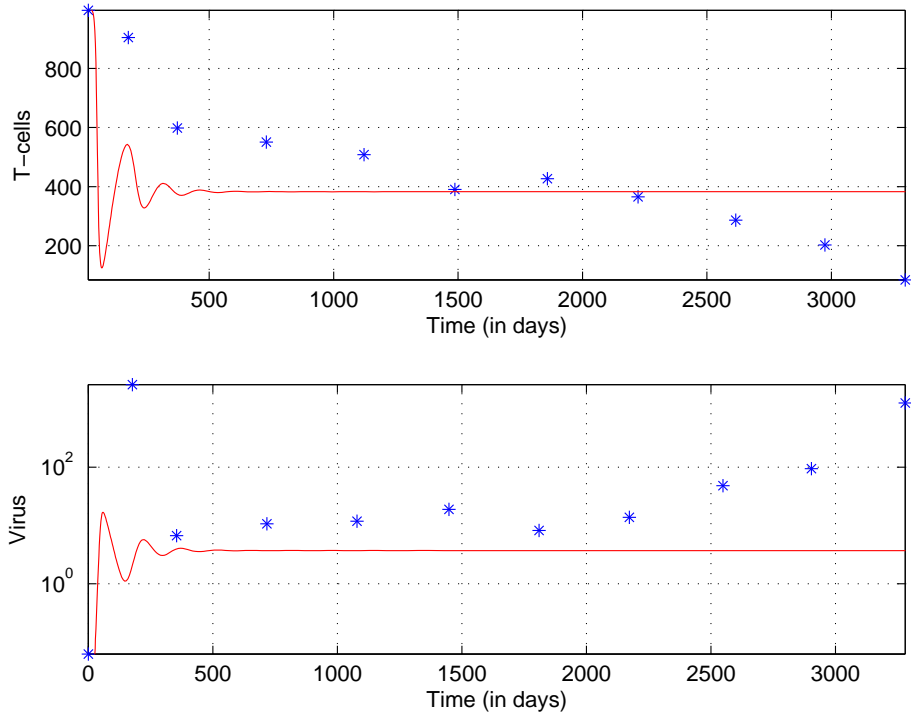


Fig. 1.

where $x_k(t) = \Phi(p_k)$ and $\lambda(t) \in (L^2([0, T]))^3$ is solution of the adjoint problem

$$\dot{\lambda} = -\varphi_x(x_k(t), p_k)^* \lambda + \Psi^*(F(p_k) - z_\delta(t)) \quad (23)$$

$$\lambda(T) = 0 \quad (24)$$

Remark 2 An approximate solution p_k can be refined evaluating $\Phi(p_k)$, $F(p_k)$, solving the adjoint problem (23)-(24) and updating the approximate solution according to (22).

The Landweber iteration yields a regularized solution of problem (18)-(20) only it is stopped at an appropriate step k_{final} . To stop the iteration we recommend the following a-posteriori stopping condition known as the discrepancy principle, see [19]. Choose k_{final} such that

$$\|F(p_{k_{\text{final}}}) - z_\delta\| \leq \tau \delta \leq \|F(p_k) - z_\delta\|, \quad k \leq k_{\text{final}}, \quad \tau > 2. \quad (25)$$

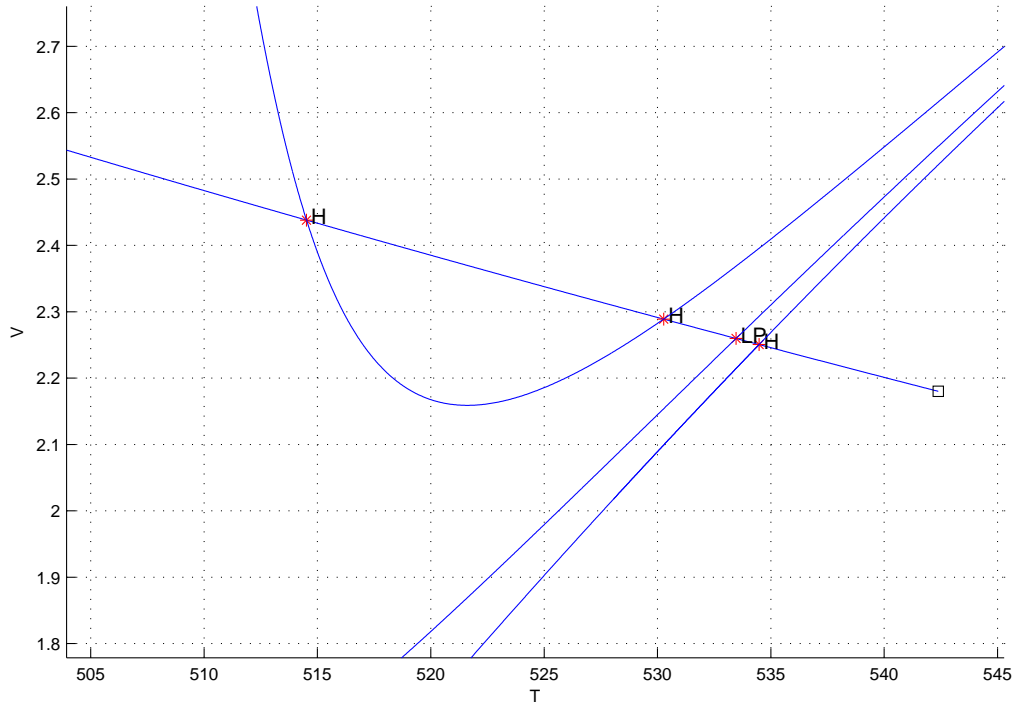


Fig. 2. The \square denotes the stationary point of model (11)-(15) with the estimated parameters. Applying continuation on g_1 are found three Hopf points and a limit-point, denoted by $*H$ and $*LP$ respectively. In this figure are is depicted continuation along the Hopf and limit points, taking g_1 and d_1 as free parameters.

3.3 Bifurcation Analysis

If we assume that all the parameters and state variables are non-negative, then the model (11)-(15) has only one stationary point. Using the estimated parameters this stationary point is an attractor. This point is depicted by a \square in Figure 2. We used *matcont* of Dhooge [20] to examine the dynamical behavior of the model by applying continuation on the parameters g_1 and d_1 . Varying g_1 in a neighborhood of the stationary point, there are four codimension-1 singularities, see Figure 2. These singularities are three Hopf bifurcation points and a limit-point, denoted by $*H$ and $*LP$ respectively. We applied continuation along the corresponding curves of Hopf and limit-points taking g_1 and d_1 as free parameters. The arising curves are also depicted in Figure 2.

4 Discussion and Conclusions

In this paper we propose a class of models to study reactivation of resting infected T-cells during long-term HIV-1 infection. By construction, the models have essentially different dynamics to the Nowak-May model.

We used reliable methods for model development and verification. First, the Painleve Property test was used to propose a class of models in order to study the nonlinearity of the reactivation term of resting infected T-cells. Later, we used standard verification tools such as parameter estimation. The obtained parameters served to numerically investigate the dynamics of a particular model considered as an example.

The aim of the proposed approach is to gain insight into the functioning of a class of models that might capture the dynamics of long term HIV-1 infection. Although the class of models developed in this paper may represent a niche to study HIV-1 infection dynamics, it is apparent that more insight from medicine practitioners is necessary.

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