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A grossman-type three-discrete-delay consolidated polynomial model of HIV-1 infection dynamics: Mathematical analysis and comparison with patients data

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ABSTRACT

In this paper, an HIV-1 infection dynamics model with three discrete delays is presented. This model takes into account delays contacted by the virus particles to achieve contamination. Using the Boubaker Polynomials Expansion Scheme BPES, it is proved that the consideration of these delays can have a positive effect on the asymptotically stable equilibrium. The main aim of the study is to identify model mechanisms that allow one to explain the trends observed in experimental clinical records, and hence to propose decision-making assistance for eventual drug therapeutic procedure and cure. The performed three-delay model provides better fits to patient data than zero-delay models.

KEYWORDS

$CD4^+$T cells;
Boubaker polynomials expansion scheme (BPES);
Delay differential equations;
Viral proliferation.

INTRODUCTION

In the last three decades, a tremendous amount of attention has been paid to mathematical models of Human Immuno-deficiency Virus type 1 (HIV-1) proliferation dynamics[1-8]. The standard infection process starts when HIV-1 enters its target T-cell and elaborates DNA copies of its viral RNA. Consequently, the viral DNA is inserted into the DNA of the infected cell, which will itself produce viral particles that can bud off the cell to infect other cells.

Throughout the world, already over 16 million deaths at the mean age of 43 years have been caused by this virus[2-4], bringing to attention an increasing need for understanding and studying its action and dynamics. Mathematical models have been proven valuable in understanding the dynamics of HIV infection[4-6].

One of the earliest models to primary infection with HIV is that developed by Perelson[7], which considered a standard four-population model involving uninfected CD4+ T cells, latently infected $CD4^+$ T cells, productively infected $CD4^+$ T cells and virus population.

In some recent studies[8-10], it has been outlined that time delays cannot be ignored in models for immune response, since antigenic stimulation generating CTLs and response efficiency both need a period of time. Based on several experimental records exhibiting irregular real time series data for randomly chosen patients[10,11], it has been found that such delays in activating immune response could lead to much unexpected dynamics.

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Many attempts have been performed in order to incorporate delays into the infection dynamics equations. Nelson *et al.*[12] added a discrete delay in the rise of productively infected CD4$^+$T-cells concentration and predicted rate of decline in plasma virus concentration depends on the length of this delay. Zhu *et al.*[13] proposed an extended model with two discrete delays. Nelson *et al.*[14] incorporated delays in both cell infection equation and virus replication. In a different context, Tam[15] and Culshaw *et al.*[16,17] introduced the notion of transient *infective oscillations* (or fluctuations) at early stages of infection, which are mainly attributed to intracellular delays.

Indeed, most models assumed that infection could occur instantaneously once a virus contacts a 'target cell'. It was also presumed that the number of target cells remains constant during an eventual therapy and that therapeutic action is always efficient.

To account for the time between viral entry into a target cell and the production of new virus particles, Herz *et al.*[18] included the fixed and discrete 'intracellular' delay by assuming that cells became productively infected only within a defined time after initial infection. They reported that the fact of including a delay changed the estimated value of the viral clearance rate, without altering productively infected CD4$^+$ T cell loss rate. In the same context, Mittler et al.[19] considered a continuous gamma-distributed intracellular delay. Results, along with experimental data fitting were guides for determining accurate viral clearance rate.

Grossman et al.[20] introduced a new type of delay in the cell death process. This type of delay introduced a gradual *n*-stage process. Production of virus was also supposed to be delayed from the time of initial infection.

In this paper, we extend the development of delay models of HIV-1 infection and treatment to the general case of three discrete delays. The rest of the paper is organized as follows. Section 2 gives an idea about the model and its governing equations along with the resolution protocol. In section 3, we discuss the obtained results in comparison with experimental records and precedent models. Section 4 summarizes the study and gives a global conclusion.

MATERIALS AND METHODS

Governing equations and general assumptions

Simple and standard classic models for HIV-1 proliferation dynamics[7,9-15] generally based on interacting features between three components: infected and uninfected CD4$^+$ T-cells along with virus population. The following equations describe the evolution of the system:

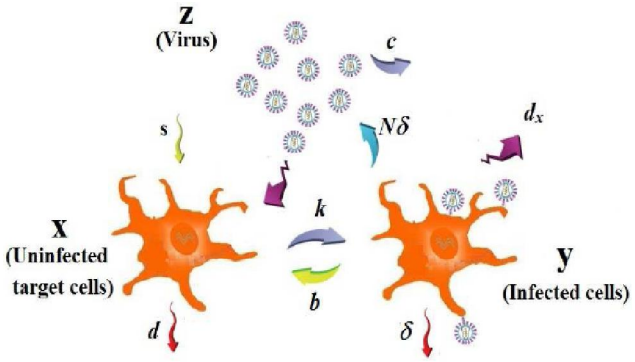

Figure 1 : A synopsis of model's dynamics

$$\begin{cases} \dot{x}(t) = s - kz(t)x(t) - dx(t) + by(t) \\ \dot{y}(t) = kz(t)x(t) - (bx(t) + \delta)y(t) \\ \dot{z}(t) = N\delta y(t) - cz(t) \\ \text{with B. C. :} \begin{cases} x(0) = x_0 \\ y(0) = y_0 \\ z(0) = z_0 \end{cases} \end{cases} \quad (1)$$

with:

x(t): Uninfected target CD4$^+$T-cells concentration; y(t): Productively infected CD4$^+$T-cells concentration; z(t): Free virus concentration in plasma; d: Death rate of target cells; s: Intrinsic rate of production of uninfected CD4$^+$T-cells; k: Intrinsic infection rate; b: Rate of return to uninfected state among infected cells; δ: Death rate of infected cells; K: Intrinsic infection rate; c: Death rate of virus; N: Average number of viral particles produced.

The second equation in the system (1) traduces antiretroviral effects in reference to eventual healing effects or entry in eclipse phase. It also expresses that the process of infection to the uninfected CD4$^+$ T-cells is in concordance with mass action principle under mixing homogeneity. In this case, the concentration of new infected cells is proportional to the product $x(t)y(t)$.

In the three-delay model that we present here, we call a productively infected cell, T, a cell that is producing virus. The correspondent immune delay τ_1 is not tangibly equal to the time needed for the adaptive immune response to emerge to control viral replication. We also

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consider Grossman-type delays[20] τ_2 and τ_3 for both uninfected and infected cells. System (1) is hence transformed to:

$$\begin{cases} \dot{x}(t) = s - kz(t-\tau_1)x(t) - dx(t-\tau_2) + by(t); & t > \sup(\tau_1,\tau_2) \\ \dot{y}(t) = kz(t-\tau_1)x(t) - by(t) + \delta y(t-\tau_3); & t > \sup(\tau_1,\tau_3) \\ \dot{z}(t) = N\delta y(t-\tau_3) - cz(t); & t > \tau_3 \end{cases} \quad (2)$$

where denotes the lag between contact and infection, and denote maturity delays for uninfected and infected cells, respectively.

It can be mentioned that the first delay includes, the phases of growth, successful attachment as well as penetration of virus into the target cell. The remaining delays correspond intrinsically, for a given class of cells, to a minimal maturity period before being recognized as such and hence exposed to outer effects.

Resolution technique

The resolution of system (2) along with boundary conditions has been achieved using the Boubaker Polynomials Expansion Scheme BPES[21-40]. This scheme is a resolution protocol which has been successfully applied to several applied-physics and mathematics problems. The BPES protocol ensures the validity of the related boundary conditions regardless of main equation features. The Boubaker Polynomials expansion scheme *BPES* is based on the Boubaker polynomials first derivatives properties:

$$\begin{cases} \sum_{q=1}^{N} B_{4q}(x)\Big|_{x=0} = -2N \neq 0; \\ \sum_{q=1}^{N} B_{4q}(x)\Big|_{x=r_q} = 0; \end{cases} \quad (3)$$

$$\begin{cases} \sum_{q=1}^{N} \frac{dB_{4q}(x)}{dx}\Big|_{x=0} = 0 \\ \sum_{q=1}^{N} \frac{dB_{4q}(x)}{dx}\Big|_{x=r_q} = \sum_{q=1}^{N} H_q \\ with: H_n = B'_{4n}(r_n) = \left(\frac{4r_n[2-r_n^2] \times \sum_{q=1}^{n} B_{4q}^2(r_n)}{B_{4(n+1)}(r_n)} + 4r_n^3 \right) \end{cases} \quad (4)$$

Several solutions have been proposed through the BPES in many fields such as numerical analysis[21-24], theoretical physics[24-27], mathematical algorithms[28], heat transfer[29], homodynamic[30-31], material characterization[32], fuzzy systems modeling[33-38] and biology[39,40].

Application

The resolution protocol is based on setting, and as estimators to the t-dependent variables, and, respectively:

$$\begin{cases} \tilde{x}(t) = \frac{1}{2N_0} \sum_{k=1}^{N_0} \xi_k^x \times B_{4k}(t \times r_k) \\ \tilde{y}(t) = \frac{1}{2N_0} \sum_{k=1}^{N_0} \xi_k^y \times B_{4k}(t \times r_k) \\ \tilde{z}(t) = \frac{1}{2N_0} \sum_{k=1}^{N_0} \xi_k^z \times B_{4k}(t \times r_k) \end{cases} \quad (5)$$

where are the 4k-order Boubaker polynomials[23-33], are minimal positive roots, is a prefixed integer, and are unknown pondering real coefficients.

The main advantage of this formulation is the verification of boundary conditions, expressed in Eq. (1), in advance to resolution process. In fact, thanks to the properties expressed in Eq. (3-4), these conditions are reduced to the inherently verified linear equations:

$$\begin{cases} \sum_{k=1}^{N_0} \xi_k^x = -N_0 x_0 \\ \sum_{k=1}^{N_0} \xi_k^y = -N_0 y_0 \\ \sum_{k=1}^{N_0} \xi_k^z = -N_0 z_0 \end{cases} \quad (6)$$

The BPES solution for Eq. (2) is obtained, according to the principles of the BPES, by determining the non-null set of coefficients that minimizes the absolute difference between left and right sides of the following equations:

$$\begin{cases} \sum_{k=1}^{N_0} (\xi_k^x + \xi_k^y) r_k \times \frac{dB_{4k}(t \times r_k)}{dt} = 2N_0 s - d\sum_{k=1}^{N_0} \xi_k^x r_k \times B_{4k}((t-\tau_2) \times r_k) x + \\ \qquad \frac{\delta}{2N_0} \sum_{k=1}^{N_0} \xi_k^y \times B_{4k}((t-\tau_3) \times r_k) \sum_{k=1}^{N_0} \xi_k^y \times B_{4k}(t \times r_k) \\ \sum_{k=1}^{N_0} \xi_k^z r_k \times \frac{dB_{4k}(t \times r_k)}{dt} = N\delta \sum_{k=1}^{N_0} \xi_k^y \times B_{4k}((t-\tau_3) \times r_k) - c\sum_{k=1}^{N_0} \xi_k^z \times B_{4k}(t \times r_k) \end{cases} \quad (7)$$

The final solution is hence:

$$\begin{cases} x_{sol.}(t) = \frac{1}{2N_0} \sum_{k=1}^{N_0} \xi_k^{x,sol.} \times B_{4k}(t \times r_k) \\ y_{sol.} = \frac{1}{2N_0} \sum_{k=1}^{N_0} \xi_k^{y,sol.} \times B_{4k}(t \times r_k) \\ z_{sol.} = \frac{1}{2N_0} \sum_{k=1}^{N_0} \xi_k^{z,sol.} \times B_{4k}(t \times r_k) \end{cases} \quad (8)$$

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RESULTS AND DISCUSSION

Solution plots

Plots of the solutions have been obtained for the parameter values gathered in TABLE 1;

Figure 2 gathers the result obtained for a non-delay model (). The observed evolution of both uninfected or infected cells and virus population is in good agreement with results related to the standard model[7-12]. Obvious

TABLE 1: Main parameters values

Parameter	Value	Unit
s	10^4	ml^{-1} day^{-1}
k	1.47	ml day^{-1}
b	0.32	day^{-1}
δ	0.30	day^{-1}
c	2.88	day^{-1}
N	480	$cell^{-1}$
x_0	5. 10^6	ml^{-1}
y_0	5. 10^6	ml^{-1}
z_0	4. 10^5	ml^{-1}

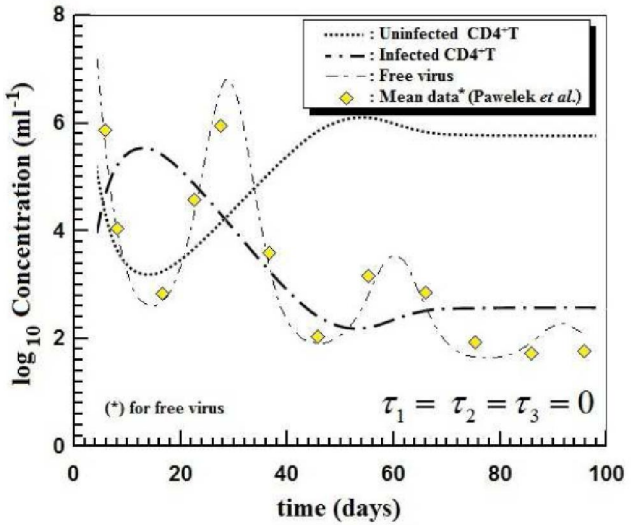

Figure 2 : Evolution of uninfected, productively infected CD4⁺T cellsand free virus concentration in plasma (case of: ($\tau_1 = \tau_2 = \tau_3 = 0$))

oscillations of the virus concentration are a characteristic to zero delay models[11,12].

Discussion and perspectives

Figures 2 and 4 show that, in the primary infection stage, a sharp decrease of CD4⁺T-cells concentration occurs because of the death of these cells. Nevertheless, the consideration of an exclusive delay between contact and infection (Figure 3) leads to a spectacular recovery in the uninfected cells population before reaching an asymptotically stable equilibrium. This phenomenon has been already reported by Arafa *et al.*[41], Wang *et al.*[42], Culshaw *et al.*[43] and Tuckwell *et al.*[44] in a standard model framework.

Tests on the values of the parameter *b* confirmed this trend. In fact, a high value of the parameter *b*, which is enabled by an increasing lag between virus attack and infection, results in an eventual expectable non-completion of reverse transcription during the delay period.

Moreover, and by examining Figures 3 and 4, we can notice that the duration of infection transient stage region appears to be unexpectedly shortened by considering delays in the maturity for both uninfected and infected cells. This paradox has been discussed by Nelson *et al.*[14]. It has been explained, in concordance with the results of Pellegrino *et al.*[45] and Kim *et al.*[46], by the fact that infected lymphocytes are unavoidably subjected to a time delay constrained by physical processes and hence are momentarily inactivated for a fixed period T_a. At this stage, comparison between Grossman-type delays[20], and T_a, the average lifespan of an infected cell from infection to death is needed. Moderate values of these delays must be taken into account in order to preserve model validity. Particularly, the condition: should be respected.

The recorded evolution of viral population was also in good agreement with the records of Pawelek *et al.*[47]. The observed oscillations (Figure 3-4) were simi-

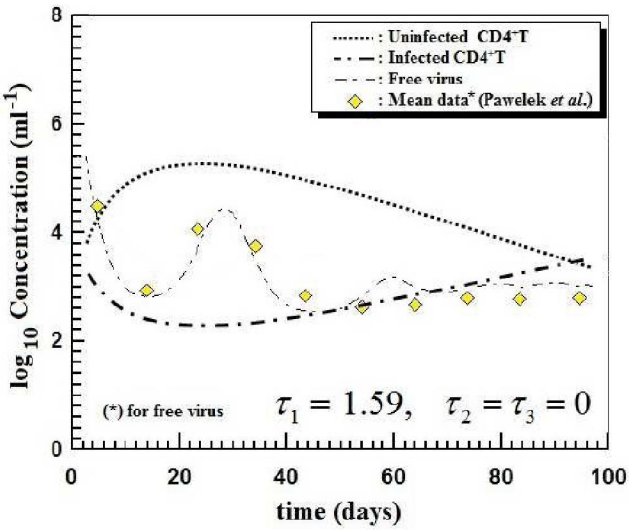

Figure 3 : Evolution of uninfected, productively infected CD4⁺T cells and free virus concentration in plasma (case of: ($\tau_1 = 1.59, \quad \tau_2 = \tau_3 = 0$))

lar to those reported by Tam[15] and Culshaw *et al.*[16,17].

In this paper we employed the Boubaker Polynomials Expansion Scheme BPES as protocol for studying the solution of human T-cell lymphotropic virus (HIV-I) infection of $CD4^+$T-cells with three discrete

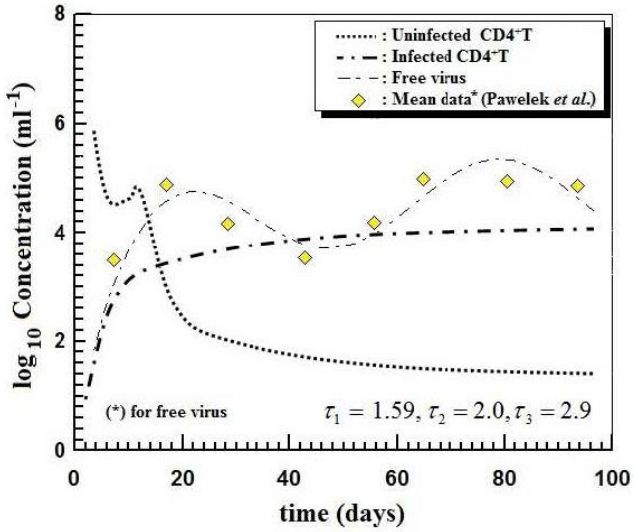

Figure 4 : Evolution of uninfected, productively infected $CD4^+$T cells and free virus concentration in plasma (case of: ($\tau_1 = 1.59,\ \tau_2 = 2.0,\ \tau_3 = 2.9$))

delays. From the obtained result, it was clear that perturbation may occur in the primary stage of the infection when the concentration of uninfected CD4+ T-cells is supposed to decrease. On the other hand, the number of the free HIV virus particles increased with some fluctuation as recorded elsewhere, and it was proved that if the consideration of Grossman-type discrete delays can have a positive effect asymptotically stable equilibrium.

Some features of the model have to be enhanced. Namely, the notion of free virus has to be revised since the virus-target link wasn't clearly defined in order to have the real status of a given viral particle.

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