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# Soluciones aproximadas de la dinámica de infección de VIH-1 con tasa de curación Approximate solutions for HIV-1 infection dynamics with cure rate 

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## Resumen

En este trabajo, se presentan dos soluciones aproximadas del modelo de la dinámica de infección de VIH-1 con tasa de curación. Las soluciones propuestas se obtienen usando el método de perturbación homotópica, por sus siglas en inglés (HPM) y el esquema de expansión polinomial de Boubaker por sus siglas en inglés (BPES). Al comparar las soluciones obtenidas vemos que HPM y BPES son herramientas muy potentes para resolver modelos no lineales de infecciones virales.

Palabras clave: Células CD4+T; Método de Perturbación Homotópica HPM; esquema de expansión polinomial de Boubaker BPES

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#### Abstract

In this paper, two approximate solutions of HIV-1 infection dynamics model with cure rate are presented. The proposed solutions are obtained using homotopy perturbation method (HPM) and Boubaker Polynomials expansion scheme (BPES). A comparison of obtained solutions shows that HPM and BPES are powerful tools to solve nonlinear host viral infection models.


Keywords: CD4+T cells; Homotopy Perturbation Method; Boubaker Polynomials expansion scheme BPES

## 1. Introduction:

In the last three decades, tremendous attention had been paid to establishing mathematical models to Human Immune-deficiency Virus type 1 (HIV-1) proliferation dynamics as AIDS (Acquired Immune Deficiency Syndrome) agent [1-15]. It has been recorded that the main target of HIV-1 infection is the population of $\mathrm{CD} 4^{+}$T-cells, a class of lymphocytes which are abundant white blood immunity cells in plasma.

It is commonly known that HIV-1 targets mainly $\mathrm{CD}^{+}$T-cells and causes their death. It decreases the body's ability to fight infections. The standard infection process starts when HIV-1 enters its target T-cell and elaborates DNA copies of its viral RNA, with the help of the reverse transcriptase enzyme RT. Consequently, the viral DNA is inserted into the DNA of the infected cell; which will produce, from itself, viral particles that can bud off the cell and infect other cells.

Throughout the world, already over 16 million deaths at average age of 43 years have been caused by this virus [2-4]; bringing into attention an increasing need to understand and study 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 the one developed by Perelson [7], which considered a standard four-population model involving uninfected CD4+ T cells, latently infected $\mathrm{CD} 4^{+} \mathrm{T}$ cells, productively infected $\mathrm{CD} 4^{+} \mathrm{T}$ cells, and virus population.

Unfortunately, the models for describing the dynamics of HIV infection for CD4+ cells are usually nonlinear differential equations with no known exact solution. Nonetheless, several methods are focused to find approximate solutions to nonlinear differential equations like: Homotopy perturbation method (HPM) [16-23], variational iteration method (VIM) [24-25], Boubaker Polynomials Expansion Scheme (BPES) [26-33], Homotopy Analysis Method (HAM) [34], Generalized Homotopy Method [35], among many others. Therefore, we propose a comparison between HPM and BPES methods by solving HIV-1 infection dynamics with cure rate [36].

The paper is organized as follows. Section 2 provides an idea about the model and its governing equations. We will describe the basic concepts of HPM in Section 3. Section 4 and Section 5 show the solution procedure for HIV using HPM and BPES, respectively. In Section 6, we
discuss the obtained results. Finally, Section 7 summarizes the study and provides a global conclusion.

## 2. Governing equations and general assumptions

Simple and standard classic models for HIV-1 proliferation dynamics [7,9-15] are generally based on interacting features between three components like: infected and uninfected CD4 ${ }^{+} \mathrm{T}$ cells along with virus population (Fig. 1).


Figure 1: A synopsis of model's dynamics

The following equations describe the evolution of the system [36]:

$$
\left\{\begin{array}{l}
\dot{x}(t)=s-d x(t)+a x(t)\left(1-\frac{x(t)}{T_{\max }}\right)-\beta x(t) z(t)+\rho y(t) \\
\dot{y}(t)=\beta x(t) z(t)-\delta y(t)-\rho y(t) \\
\dot{z}(t)=q y(t)-c z(t)  \tag{1}\\
\text { with boundaryconditions }\left\{\begin{array}{l}
x(0)=x_{0} \\
y(0)=y_{0} \\
z(0)=z_{0}
\end{array}\right.
\end{array}\right.
$$

with: $x(\mathrm{t}) \quad:$ Uninfected target $\mathrm{CD} 4^{+}$T-cells
$y(\mathrm{t}) \quad:$ Productively infected $\mathrm{CD} 4^{+}$T-cells
$z(\mathrm{t}) \quad$ : Viral load of the virons
$s \quad:$ Represents the rate at which new T cells are created from sources
a : Maximum proliferation rate of target cells
$T_{\max } \quad: \mathrm{T}$ population density at which proliferation shuts off
$d \quad$ : Death rate of T cells
$\beta \quad$ : Infection rate constant
$\delta \quad:$ Death rate of infected cells
$q \quad:$ Reproductively rate of the infected cells
c : Clearance rate constant of virions
$\rho \quad:$ The rate of "cure," i.e. noncytolytic loss of infected cells

The second equation in system (1) traduces anti-retroviral effects in reference to eventual healing effects or entry in eclipse phase. It also expresses that the process of infection to the uninfected $\mathrm{CD} 4^{+}$T-cells is in concordance to the mass action principle under mixing homogeneity. In this case, the concentration of new infected cells is proportional to the product $x(t)-y(t)$.

Table 1 Main parameters values [36]

| Parameter | Value | Unit |
| :---: | :---: | :---: |
| $s$ | 5 | day $^{-1} \mathrm{~mm}^{-3}$ |
| $d$ | 0.01 | day $^{-1}$ |
| $a$ | 0.5 | day $^{-1}$ |
| $T_{\max }$ | 1200 | $\mathrm{~mm}^{3} \mathrm{day}^{-1}$ |
| $\beta$ | 0.0002 | $\mathrm{~mm}^{-3}$ |

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| $\rho$ | 0.01 | day $^{-1}$ |
| :---: | :---: | :---: |
| $\boldsymbol{\delta}$ | 1 | day $^{-1}$ |
| $\boldsymbol{q}$ | $\mathbf{8 0 0}$ | $\mathrm{~mm}^{3}$ day $^{-1}$ |
| $\boldsymbol{c}$ | $\mathbf{5}$ | day $^{-1}$ |
| $x_{0}$ | $\mathbf{3 0}$ | $\mathrm{~mm}^{-3}$ |
| $y_{0}$ | 400 | $\mathrm{~mm}^{-3}$ |
| $z_{0}$ | $\mathbf{6 0 0}$ | $\mathrm{~mm}^{-3}$ |

## 3. Basic concept of HPM method

The HPM method can be considered as a combination of the classical perturbation technique [37,38] and the homotopy (whose origin is in the topology) [39-40], but not restricted to a small parameter like traditional perturbation methods. For instance, HPM requires neither small parameter nor linearization, but only few iterations to obtain accurate solutions.

To figure out how HPM method works, consider a general nonlinear equation in the form

$$
\begin{equation*}
A(u)-f(r)=0, \quad r \in \Omega \tag{2}
\end{equation*}
$$

with the following boundary conditions:
$B\left(u, \frac{\partial u}{\partial u}\right)=0, \quad r \in \Gamma$
where $A$ is a general differential operator, $B$ is a boundary operator, $f(r)$ a known analytical function, and $\Gamma$ is the domain boundary for $\Omega$. A can be divided into two operators $L$ and $N$, where $L$ is linear and $N$ nonlinear; from this last statement, (2) can be rewritten as

$$
\begin{equation*}
L(u)+N(u)-f(r)=0 . \tag{4}
\end{equation*}
$$

Generally, a homotopy can be constructed in the form [16-18,37]
$H(v, p)=(1-p)\left[L(v)-L\left(u_{0}\right)\right]+p[L(v)+N(v)-f(r)]=0, p \in[0,1], r \in \Omega$.
where $p$ is a homotopy parameter whose values are within the range of 0 and $1 ; u_{0}$ is the first approximation for the solution of (4) that satisfies boundary conditions.

When $p \rightarrow 0$, (5) is reduced to

$$
\begin{equation*}
L(v)-L\left(u_{0}\right)=0, \tag{6}
\end{equation*}
$$

where operator $L$ possesses trivial solution.
When $p \rightarrow 1$,(5) is reduced to the original problem

$$
\begin{equation*}
N(v)+L(v)-f(r)=0, \tag{7}
\end{equation*}
$$

Assuming that solution for (5) can be written as a power series of $p$

$$
\begin{equation*}
v=v_{0}+v_{1} p^{1}+v_{2} p^{2}+\cdots . \tag{8}
\end{equation*}
$$

Substituting (8) into (5) and equating identical powers of $p$ terms, there can be found values for the sequence $v_{0}, v_{1}, v_{2}, \ldots$

When $p \rightarrow 1$ in (8), it yields in the approximate solution for (4) in the form

$$
\begin{equation*}
u=\lim _{p \rightarrow 1}(v)=v_{0}+v_{1}+v_{3}+\cdots \tag{9}
\end{equation*}
$$

## 4. Solution by using HPM method

From (1) and (5), we establish the homotopy formulation

$$
\left\{\begin{array}{l}
H_{1}\left(v_{1}, v_{2}, v_{3}, p\right)=(1-p) \dot{v}_{1}+p\left(\dot{v}_{1}(t)-s+d v_{1}(t)-a v_{1}(t)\left(1-\frac{v_{1}(t)}{T_{\max }}\right)+\beta v_{1}(t) v_{3}(t)-\rho v_{2}(t)\right)=0,  \tag{10}\\
H_{2}\left(v_{1}, v_{2}, v_{3}, p\right)=(1-p) \dot{v}_{2}+p\left(\dot{v}_{2}(t)-\beta v_{1}(t) v_{3}(t)+\delta v_{2}(t)+\rho v_{2}(t)\right)=0, \\
H_{3}\left(v_{1}, v_{2}, v_{3}, p\right)=(1-p) \dot{v}_{3}+p\left(\dot{v}_{3}(t)-q v_{2}(t)+c v_{3}(t)\right)=0, \\
\text { with boundary conditions : }:\left\{\begin{array}{l}
v_{1}(0)=x_{0} \\
v_{2}(0)=y_{0} \\
v_{3}(0)=z_{0}
\end{array}\right.
\end{array}\right.
$$

From (8), we assume that solution for (10) can be written as a power series of $p$ as follows

$$
\begin{align*}
& v_{1}=\sum_{i=0}^{\infty} v_{1, i} p^{i} \\
& v_{2}=\sum_{i=0}^{\infty} v_{2, i} p^{i}  \tag{11}\\
& v_{3}=\sum_{i=0}^{\infty} v_{3, i} p^{i}
\end{align*}
$$

Where $v_{i, j}(i=1,2,3$, and $j=0,1,2, \ldots)$, are functions yet to be determined. Substituting (11) into (10), and rearranging the coefficients of $p$ powers, we have

$$
\begin{gather*}
\dot{v}_{1,0}+\left(\dot{v}_{1,1}-s+(d-a) v_{1,0}+\frac{a v_{1,0}^{2}}{T_{\max }}+\beta v_{3,0} v_{1,0}-\rho v_{2,0}\right) p+\cdots=0, \\
\dot{v}_{2,0}+\left(\dot{v}_{2,1}-\beta v_{3,0} v_{1,0}+(\rho+\delta) v_{2,0}\right) p+\cdots=0,  \tag{12}\\
\dot{v}_{3,0}+\left(\dot{v}_{3,1}-q v_{2,0}+c v_{3,0}\right) p+\cdots=0
\end{gather*}
$$

In addition, in order to fulfil the boundary conditions, we consider $v_{1,0}(0)=x_{0}, v_{2,0}(0)=y_{0}$ and $v_{3,0}(0)=z_{0}$. In order to obtain the unknown $v_{i, j}(i=1,2,3$, and $j=1,2,3, \ldots)$, we must construct and solve the following system of equations, considering initial conditions $v_{i, j}(0)=0$ ( $i=1,2,3$, and $j=1,2,3, \ldots$ )

$$
\begin{gather*}
\dot{v}_{1,0}=0 \\
\dot{v}_{1,1}-s+(d-a) v_{1,0}+\frac{a v_{1,0}^{2}}{T_{\max }}+\beta v_{3,0} v_{1,0}-\rho v_{2,0}=0 \\
\dot{v}_{2,0}=0  \tag{13}\\
\vdots \\
\dot{v}_{2,1}-\beta v_{3,0} v_{1,0}+(\rho+\delta) v_{2,0}=0, \\
\dot{v}_{3,0}=0 \\
\dot{v}_{3,1}-q v_{2,0}+c v_{3,0}=0, \\
\vdots
\end{gather*}
$$

Therefore,

$$
\begin{align*}
& v_{1,0}=x_{0}, \\
& v_{1,1}=\left(-\beta x_{0} z_{0}+\rho y_{0}+x_{0}(-d+a)+s-\frac{a x_{0}^{2}}{T_{\max }}\right) t, \\
& \vdots \\
& v_{2,0}=y_{0}, \\
& v_{2,1}=\left(\beta x_{0} z_{0}-\rho y_{0}-\delta y_{0}\right) t,  \tag{14}\\
& \vdots \\
& v_{3,0}=z_{0} \\
& v_{3,1}=\left(q y_{0}-c z_{0}\right) t,
\end{align*}
$$

$$
\vdots
$$

We obtained $v_{1,2}, v_{2,2}, v_{3,2}$, and succeeding terms; nevertheless, because they were too cumbersome, we skip them and use only the final results. Then, we obtain the 40 -th order approximation, considering $p \rightarrow 1$ yields the approximate solution for (1) as

$$
\begin{align*}
& x(t)=\lim _{p \rightarrow 1} v_{1}=\sum_{i=0}^{40} v_{1, i} \\
& y(t)=\lim _{p \rightarrow 1} v_{2}=\sum_{i=0}^{40} v_{2, i}  \tag{15}\\
& z(t)=\lim _{p \rightarrow 1} v_{3}=\sum_{i=0}^{40} v_{3, i}
\end{align*}
$$

We set the values of parameters and initial conditions $\left(x(0)=x_{0}, y(0)=y_{0}\right.$, and $\left.z(0)=z_{0}\right)$ as reported in Table 1 [41]. In order to increase the domain of convergence, we apply the Padé [20, 35] approximant to (15) and obtain approximations of order $x(t)_{[15 / 15]}, y(t)_{[14 / 15]}$, and $z(t)_{[14 / 15]}$.

## 5. Resolution using the Boubaker Polynomials Expansion Scheme BPES

The resolution of system (1) along with boundary conditions has been achieved using the Boubaker Polynomials Expansion Scheme (BPES) [26-33]. 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 protocol uses the Boubaker polynomials first derivatives properties:

$$
\left\{\begin{array}{l}
\left.\sum_{q=1}^{N} B_{4 q}(x)\right|_{x=0}=-2 N \neq 0  \tag{16}\\
\left.\sum_{q=1}^{N} B_{4 q}(x)\right|_{x=r_{q}}=0
\end{array}\right.
$$

and

$$
\left\{\begin{array}{l}
\sum_{q=1}^{N} d B_{4 q}(x) /\left.d x\right|_{x=0}=0  \tag{17}\\
\sum_{q=1}^{N} d B_{4 q}(x) /\left.d x\right|_{x=r_{q}}=\sum_{q=1}^{N} H_{q} \\
\text { with }: H_{n}=B_{4 n}^{\prime}\left(r_{n}\right)=\left(4 r_{n}\left[2-r_{n}^{2}\right] \times \sum_{q=1}^{n} B_{4 q}^{2}\left(r_{n}\right) / B_{4(n+1)}\left(r_{n}\right)+4 r_{n}^{3}\right)
\end{array}\right.
$$

Several solutions have been proposed using BPES in many fields such as numerical analysis, theoretical physics, mathematical algorithms, heat transfer, homodynamic, material characterization, fuzzy systems modelling, and biology [26-33].

The resolution protocol is based on setting $\tilde{x}(t), \tilde{y}(t)$, and $\tilde{z}(t)$ as estimators to the $t$-dependent variables $x(t), y(t)$, and $z(t)$, respectively

$$
\left\{\begin{array}{l}
\tilde{x}(t)=1 /\left(2 N_{0}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times B_{4 k}\left(t \times r_{k}\right) \\
\tilde{y}(t)=1 /\left(2 N_{0}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{y} \times B_{4 k}\left(t \times r_{k}\right)  \tag{18}\\
\tilde{z}(t)=1 /\left(2 N_{0}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{z} \times B_{4 k}\left(t \times r_{k}\right)
\end{array}\right.
$$

where $B_{4 k}$ are the 4 k -order Boubaker polynomials [29-30], $r_{k}$ are $B_{4 k}$ minimal positive roots, $N_{0}$ is a prefixed integer, and $\xi_{k}^{x}, \xi_{k}^{y},\left.\xi_{k}^{z}\right|_{k=1 . N_{0}}$ are unknown pondering real coefficients.

The main advantage of this formulation is the verification of boundary conditions, expressed in (1), in advance to the resolution process. In fact, thanks to the properties expressed in (16) and (17), these conditions are reduced to the inherently verified linear equations

$$
\left\{\begin{array}{l}
\sum_{k=1}^{N_{0}} \xi_{k}^{x}=-N_{0} x_{0}  \tag{19}\\
\sum_{k=1}^{N_{0}} \xi_{k}^{y}=-N_{0} y_{0} \\
\sum_{k=1}^{N_{0}} \xi_{k}^{z}=-N_{0} z_{0}
\end{array}\right.
$$

The BPES solution for (1) is obtained, according to the principles of the BPES, by determining the non-null set of coefficients $\xi_{k}^{x, \text { sol. }}, \xi_{k}^{y, \text { sol }},\left.\xi_{k}^{z, \text { sol }}\right|_{k=1 . . N_{0}}$ that minimizes the absolute difference between left and right sides of the following equations

$$
\left\{\begin{align*}
\frac{1}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times \frac{d B_{4 k}\left(t \times r_{k}\right)}{d t}= & s-\frac{d}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times B_{4 k}\left(t \times r_{k}\right) \\
& +\frac{a}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times B_{4 k}\left(t \times r_{k}\right)\left(1-\frac{\frac{1}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times B_{4 k}\left(t \times r_{k}\right)}{T_{\max }}\right) \\
& -\frac{\beta}{\left(2 N_{0}\right)^{2}} \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times \frac{d B_{4 k}\left(t \times r_{k}\right)}{d t} \sum_{k=1}^{N_{0}} \xi_{k}^{z} \times B_{4 k}\left(t \times r_{k}\right) \\
& +\frac{\rho}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{y} \times B_{4 k}\left(t \times r_{k}\right) \\
& -\frac{\delta}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{y} \times B_{4 k}\left(t \times r_{k}\right)-\frac{\rho}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{y} \times B_{4 k}\left(t \times r_{k}\right) \\
\frac{1}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{y} \times \frac{d B_{4 k}\left(t \times r_{k}\right)}{d t}= & \frac{\beta}{\left(2 N_{0}\right)^{2}} \sum_{k=1}^{N_{0}} \xi_{k}^{x} \times B_{4 k}\left(t \times r_{k}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{z} \times B_{4 k}\left(t \times r_{k}\right) \\
\frac{1}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{z} \times \frac{d B_{4 k}\left(t \times r_{k}\right)}{d t}= & \frac{q}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{y} \times B_{4 k}\left(t \times r_{k}\right)-\frac{c}{2 N_{0}} \sum_{k=1}^{N_{0}} \xi_{k}^{z} \times B_{4 k}\left(t \times r_{k}\right) \tag{20}
\end{align*}\right.
$$

The final solution is

$$
\left\{\begin{array}{l}
x_{\text {sol. }}(t)=1 /\left(2 N_{0}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{x, s o l .} \times B_{4 k}\left(t \times r_{k}\right) \\
y_{\text {sol. }}=1 /\left(2 N_{0}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{y, \text { sol. }} \times B_{4 k}\left(t \times r_{k}\right)  \tag{21}\\
z_{\text {sol. }}=1 /\left(2 N_{0}\right) \sum_{k=1}^{N_{0}} \xi_{k}^{z, \text { sol. }} \times B_{4 k}\left(t \times r_{k}\right)
\end{array}\right.
$$

## 6. Results and analysis

In order to provide a reference point, the obtained results were compared to the numerical solution obtained using the Fehlberg fourth-fifth order Runge-Kutta method with degree four interpolant (RKF45) [42,43] built-in routine from Maple 17 Software. The routine was configured using an absolute error of $10^{-7}$ and a relative error of $10^{-6}$. Figure 2 through 4 show the graphical comparison of the HPM (15), HPM-Padé and BPES (21) solutions. HPM and BPES solutions exhibit similar domains of convergence; the accuracy of both approximations decrease rapidly for $\mathrm{t}>0.4$ as depicted in figures $2-4$. Nonetheless, from the same figures, we can observe that the HPM-Pade solution possesses wider domain of convergence than BPES and standard HPM.

HPM-Padé technique is able to produce easy computable rational expression that exhibit a wide convergence region in comparison to polynomial solutions schemes. Nonetheless, further research is required in order to obtain solutions with even larger domain of convergence that can lead to a better understanding of the dynamics of the HIV infection and its relationship with the parameters of Table 1.


Figure 2. Approximate solutions for $x(t)$


Figure 3. Approximate solutions for $\mathrm{y}(\mathrm{t})$.


Figure 4. Approximate solutions for $\mathrm{z}(\mathrm{t})$.

## 7. Conclusion

In this paper, a comparison of HPM, HPM-Padé and BPES was studied by solving an HIV-1 infection dynamics model with cure rate. The HPM-Padé solution exhibited a wider domain of convergence than HPM and BPES, reaching a good agreement to the exact solution for range $t \in[0,2]$. Further research is required in order to obtain solution with larger domain of convergence that can lead to a better understanding of the dynamics of the HIV infection and the relationship with its parameters.

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