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On the stability of a mathematical model for HIV(AIDS) — cancer dynamics

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In this work, we study an impulsive mathematical model proposed by Chavez et al. [1] to describe the dynamics of cancer growth and HIV infection, when chemotherapy and HIV treatment are combined. To better understand these complex biological phenomena, we study the stability of equilibrium points. To do this, we construct an appropriate Lyapunov function for the first equilibrium point while the indirect Lyapunov method is used for the second one. None of the equilibrium points obtained allow us to study the stability of the chemotherapeutic dynamics, we then propose a bifurcation of the model and make a study of the bifurcated system which contributes to a better understanding of the underlying biochemical processes which govern this highly active antiretroviral therapy. This shows that this mathematical model is sufficiently realistic to formulate the impact of this treatment.

Keywords: *equilibrium point, stability, HIV(AIDS)-cancer model, Lyapunov direct method.*

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1. Introduction

The body's natural defence system is called immune. It consists of antibodies, white blood cells, chemicals and proteins which attack and remove viruses and bacteria from the body. The $CD4^+T$ cells are blood cells (lymphocyte) whose role is to signal $CD8^+T$ cells to destroy bacteria and viruses [2]. HIV is a lentivirus which attacks and damages the immune system namely the $CD4^+T$ cells, that normally coordinate the adaptive T- and B-cell response to defend the body against intracellular pathogens [3]. It spreads through exchange of body fluids, including blood, semen, pre-seminal fluid, rectal fluid, vaginal fluids, and breast milk, from an infected person. Several tens of millions of cases of AIDS are recorded and almost 2 million people are affected each year, of which several hundred thousand die each year (see the web pages of WHO [4]). We can therefore understand the interest that researchers have in studying different models describing the evolution of this disease as well as the impact of different treatments.

Many proposals of mathematical models describing the dynamics of the AIDS pandemic are made by researchers to predict the evolution of the epidemic and study the most effective prevention strategies [2, 3, 5–7]. The need to evaluate intervention strategies for newly emerging and re-emerging pathogens has proven that the impact of mathematical modeling on public health is real.

In this work, we study an impulsive mathematical model proposed in Chavez et al. [1] to describe the dynamics of cancer growth and HIV infection, when chemotherapy and treatment for HIV, namely, highly active antiretroviral therapy (HAART) are included. This model presented in the form of a nonlinear partial differential equations system was solved numerically under a relevant set of a given boundary and initial conditions. The authors carried out a quantitative analysis from numerical results

using the values of the model parameters. However, the stability of the model has not been studied. Optimal control theory [6, 8–11] can be used to study the behavior of the system but it is important to be able to analyze the stability of a model without having to solve the differential equations.

To better understand this complex biological phenomena, we study the equilibrium points stability. To do this, we study the stability of certain points of equilibrium using a Lyapunov function [12], [13]. For other equilibrium points, where this technique does not allow us to conclude, we use the indirect Lyapunov method [14]. Stability analysis as performed in the present study contributes to a better understanding of the underlying biochemical processes that govern highly active antiretroviral therapy.

In addition, the study of stability analysis describes the potency of this mathematical model to be realistic enough to formulate the impact of this treatment.

2. The mathematical models

The body has defence system is called immune. It consists of antibodies, white blood cells, chemicals and proteins which attack and remove viruses and bacteria from the body. From [1],

$$\dot{x}_1(t) = r_1\left[1-\left(\frac{x_1}{c}\right)^{1/4}\right]x_1^{3/4} - k_1x_1x_2 - p_1(1-e^{-x_6})x_1, \tag{1}$$

$$\dot{x}_2(t) = s + x_2\left[r_2\left(1-\frac{x_1+x_2+x_4}{m}\right) - pk_1x_1 - k_2(1-\varepsilon_{RT})x_5 - p_2(1-e^{-x_6}) - \mu_2\right], \tag{2}$$

$$\dot{x}_3(t) = \xi k_2(1-\varepsilon_{RT})x_2x_5 - (a+\mu_3)x_3, \tag{3}$$

$$\dot{x}_4(t) = ax_3 + k_2(1-\xi)(1-\varepsilon_{RT})x_2x_5 - p_2(1-e^{-x_6})x_4 - \mu_4x_4, \tag{4}$$

$$\dot{x}_5(t) = N\mu_4(1-\varepsilon_{PI})x_4 - \mu_5x_5, \tag{5}$$

$$\dot{x}_6(t) = -dx_6. \tag{6}$$

Table 1. Symbols and values of the parameters used in system (1)–(6).

Symbol	Value	Parameter
r_1	0.18	Intrinsic growth rate of cancer cells
r_2	0.03	Intrinsic growth rate of healthy CD^+T cells
c	1.00×10^6	Maximum density of cancer cells
k_1	1.00×10^{-8}	Rate of cancer cells killed by immune system
k_2	2.40×10^{-7}	Infection rate of healthy $CD4^+T$ cells by HIV
p_1	0.90	Intrinsic killing rate of cancer cells by drug
p_2	0.60	Intrinsic killing rate of healthy $CD4^+T$ cells by drug
s	1.00×10^4	Growth rate of healthy $CD4^+T$ cells
m	1.50×10^6	Effective carrying capacity of the system
μ_2	0.02	Death rate of $CD4^+T$ cells
μ_3	0.05	Death rate of latent infected cells
μ_4	0.30	Death rate of infected cells
μ_5	3.00	Death rate of virus
d	0.90	Drug elimination rate
a	3.00×10^{-4}	Development rate of latent cells into infected cells
d_{IN}	2.40	Drug influx per injection
T_D	21	Period of drug application
p	0.10	Proportion of immune cells loss du to killing of cancer cells
ε_{RT}	0.75	RTI-based treatment efficacy
ε_{PI}	0.7	PI- based treatment efficacy
ξ	0.03	Proportion of healthy $CD4^+T$ cells moving to latent infected state
N	1.00×10^3	Bursting factor for virus growth

where $x_1(t)$ is cancer cells, $x_2(t)$ is Healthy $CD4^+T$ cells, $x_3(t)$ is latently infected $CD4^+T$ cells, $x_4(t)$ infected $CD4^+T$ cells, $x_5(t)$ is HIV, and $x_6(t)$ is chemotherapeutic dynamic, which modeled as follows. Drug's effectiveness is assumed to be bounded and limited to given phases of the cell cycles. Chemo is responsible for a proportion of $(1-e^{-x_6})$ of dead cells. The products $P_1(1-e^{-x_6})$ and $P_2(1-e^{-x_6})$ constitute the cell dose responses of the cancer, and of the healthy and infected x_2 cells.

The drug is eliminated with rate d. An expeditious drug distribution is considered in throughout the body, and with the impulsive control:

$$x_6(t^+) = d_{IN} + x_6(t^-), \quad t = nT_D, \quad n \in N. \tag{7}$$

All parameters of the system along their values are displayed in Table 1.

2.1. Stationary states

To study the local stability of system (1)–(6), we evaluate all equilibrium points of (1–(6) and use both Lyapunov direct method and the Lyapunov indirect method.

To evaluate the equilibrium points let $(x_1, \ldots, x_6)$ be a stationary state of system (1)–(6). Then it satisfies $\dot{x_i} = 0$ for $i = 1, 2, \ldots, 6$, that is to say

$$0 = r_1 \left[1 - \left(\frac{x_1}{c}\right)^{\frac{1}{4}}\right] x_1^{\frac{3}{4}} - k_1 x_2 x_1 - p_1(1 - e^{-x_6})x_1, \tag{8}$$

$$0 = s + x_2 \left[r_2 \left(1 - \frac{x_1 + x_2 + x_4}{m}\right) - pk_1 x_1 - k_2(1 - \varepsilon_{RT})x_5 - p_2(1 - e^{-x_6}) - \mu_2\right], \tag{9}$$

$$0 = \xi k_2(1 - \varepsilon_{RT})x_2 x_5 - ax_3 - \mu_3 x_3, \tag{10}$$

$$0 = ax_3 + k_2(1 - \xi)(1 - \varepsilon_{RT})x_2 x_5 - p_2(1 - e^{-x_6})x_4 - \mu_4 x_4, \tag{11}$$

$$0 = N\mu_4(1 - \varepsilon_{PI})x_4 - \mu_5 x_5, \tag{12}$$

$$0 = -dx_6. \tag{13}$$

From (13) $x_6 = 0$. Taking $x_5 = 0$ one can get from (12) that $x_4 = 0$, and (10) implies that $x_3 = 0$. Equation (8) implies two solutions $x_1 = 0$ or $x_1 \neq 0$. In the case of $x_1 = 0$, x_2 is obtained from (9) as the roots of the following polynomial of degree 2

$$ms - r_2 x_2^2 + (mr_2 - m\mu_2)x_2 = 0.$$

The roots of this polynomial are

$$\alpha = \frac{1}{2r_2} m \left(r_2 - \mu_2 - \sqrt{\frac{m\mu_2 r_2^2 + r_2 s}{m}}\right) \quad \text{and} \quad \beta = -\frac{1}{2r_2} m \left(-r_2 - \mu_2 + \sqrt{\frac{m\mu_2 r_2^2 + r_2 s}{m}}\right).$$

We get that $E_0 = (0, \alpha, 0, 0, 0, 0)$, $E_{01} = (0, \beta, 0, 0, 0, 0)$ are always steady states. Since β is negative then E_{01} biologically meaningless. The root $\alpha > 0$, thus E_0 is the only biologically significant trivial steady state, i.e. E_0 is the unique infection-free equilibrium.

Now when $x_1 \neq 0$ then $x_1 = \frac{r_1^4 c}{(r_1 + kc^{1/4}x_2)^4}$ and we obtain from (9) that x_2 is a root of the following equation of degree six

$$\frac{-k_1^4 c}{m} x_2^6 + (k_1^4 c r_2 - \frac{-4r_1 k_1^3 c^{3/4}}{m} - k_1 c\mu_2)x_2^5 + B_1 x_2^4 + B_2 x_2^3 + B_3 x_2^2 + B_4 x_2 + s r_1^4 = 0.$$

where

$$B_1 = k_1^4 cs + 4r_1 r_2 k_1^3 - \frac{6r_1^2 k_1^2 c^{1/2}}{m} - 4r_1 k_1^3 c^{3/4}\mu_2,$$

$$B_2 = 4r_1 k_1^3 c^{3/4} s + 6r_1^2 k_1^2 r_2 c^{1/2} - \frac{4r_1^3 k_1 c^{1/4}}{m} - 6r_1^2 k_1^2 c^{1/2},$$

$$B_3 = 6r_1^2 k_1^2 c^{1/2} s + 4r_1^3 r_2 k_1 c^{1/4} - \frac{r_1^4}{m} - 4r_1^3 k_1 c^{1/4}\mu_2,$$

$$B_4 = -r_1^4 - pk_1 - r_1^4 r_2 c + 4r_1^3 k_1 c^{1/4} s + r_1^4 r_2 - r_1^4 \mu_2.$$

The roots of this equation give rise to the following stationary states $E_j = (\delta_j, \varepsilon_j, 0, 0, 0, 0)$, $j = 1, \ldots, 6$, where

$$\delta_1 = \frac{r_1^4 c}{(r_1 + kc^{1/4}\varepsilon_3)^4}, \quad \varepsilon_1 = 166.6576446,$$

$$\delta_2 = \frac{r_1^4 c}{(r_1 + kc^{1/4}\varepsilon_4)^4}, \quad \varepsilon_2 = 49.24344613 + 124.7231338i,$$

$$\delta_3 = \frac{r_1^4 c}{(r_1 + kc^{1/4}\varepsilon_5)^4}, \quad \varepsilon_3 = -132.5722684 + 74.27706588i,$$

$$\delta_4 = \frac{r_1^4 c}{(r_1 + kc^{1/4}\varepsilon_6)^4}, \quad \varepsilon_4 = -2.277777778 \cdot 10^{22},$$
$$\delta_5 = \frac{r_1^4 c}{(r_1 + kc^{1/4}\varepsilon_7)^4}, \quad \varepsilon_5 = -132.5722684 - 74.27706588i,$$
$$\delta_6 = \frac{r_1^4 c}{(r_1 + kc^{1/4}\varepsilon_8)^4}, \quad \varepsilon_6 = 49.24344613 - 124.7231338i,$$

Since $(\varepsilon_j, \delta_j)$, $j = 2, \ldots, 6$ are negatives or complex we deduce that $E_j = (\delta_j, \varepsilon_j, 0, 0, 0, 0)$, $j = 2, \ldots, 6$ are biologically meaningless. The equilibrium point E_1 is the only biologically significant, since $(\varepsilon_1, \delta_1)$ are positives.

If $x_5 \neq 0$ from (12) it follows, that $N\mu_4(1 - \varepsilon_{PI})x_4 = \mu_5 x_5$, which gives

$$x_5 = \frac{N\mu_4(1 - \varepsilon_{PI})x_4}{\mu_5}. \tag{14}$$

From (10)

$$\xi k_2(1 - \varepsilon_{RT})x_2 x_5 = (a + \mu_3)x_3 \tag{15}$$

Substituting (15) in (11) implies

$$x_4 = \frac{\mu_3 x_3}{a + (1 - \xi)\mu_3}. \tag{16}$$

Combining (14), (16) and (15)

$$x_2(t) = \frac{(a + \mu_4)\mu_5}{Nk_2\xi(a + (1 - \xi)\mu_3)(1 - \varepsilon_{RT})(1 - \varepsilon_{PI})}. \tag{17}$$

Now substitute(17) in (9) we get

$$x_3 = \frac{\mu_5(ms + x_2[r_2(m - x_2^2) - \mu_2 m])}{x_2(\mu_5 r_2 + k(1 - \varepsilon_{RT})mN\mu_3(1 - \varepsilon_{PI}))}. \tag{18}$$

Taking $x_1 = 0$, one can get the first infection equilibrium $E_7 = (0, T_1, I_1, L_1, V_1, 0)$, where

$$T_1 = \frac{(a + \mu_4)\mu_5}{Nk_2\xi(a + (1 - \xi)\mu_3)(1 - \varepsilon_{RT})(1 - \varepsilon_{PI})}, \tag{19}$$
$$I_1 = \frac{\mu_5(ms + T_1[r_2(m - T_1^2) - \mu_2 m])}{T_1(\mu_5 r_2 + k(1 - \varepsilon_{RT})mN\mu_3(1 - \varepsilon_{PI}))}, \tag{20}$$
$$V_1 = \frac{N\mu_4(1 - \varepsilon_{PI})}{\mu_5} I_1, \tag{21}$$
$$L_1 = \frac{\mu_3}{a + (1 - \xi)\mu_3} I_1. \tag{22}$$

If $x_1 \neq 0$ then from equation (8)

$$x_1 = \frac{r_1^4 c}{(r_1 + kc^{1/4}x_2)^4}. \tag{23}$$

Equation (23) combined with equations (14)–(17) imply that the second infection equilibrium E_8 is given by $E_8 = (C_1, T_1, I_2, L_2, V_2, 0)$, where T_1 is given by equation (19),

$$C_1 = \frac{r_1^4 c}{((r_1 + k_1)T_1 c^{1/4})^4}, \qquad I_2 = \frac{\mu_5(ms + T_2[r_2(m - T_2 - C_1) - Pk_1 m\mu_5 - \mu_2 m])}{T_1(\mu_5 r_2 + k_2(1 - \varepsilon_{RT})mN\mu_4(1 - \varepsilon_{PI}))},$$
$$L_2 = \frac{\mu_3}{a + (1 - \xi)\mu_3} I_2, \qquad V_2 = \frac{N\mu_4(1 - \varepsilon_{PI})}{\mu_5} I_2.$$

To sum up, we have to study four stationary states E_0, E_1, E_7 and E_8.

2.2. Local stability of the equilibrium points

2.2.1. Lyapunov Stability

$$V(x_1, x_2, x_3, x_4, x_5, x_6) = \lambda_1 x_1^2 + \lambda_2 x_2^2 + \lambda_3 x_3^2 + \lambda_4 x_4^2 + \lambda_5 x_5^2 + \lambda_6 x_6^2.$$

For simplicity, suppose $\lambda_i = 1$ for $i = 1, 2, \ldots, 6$, then differentiating V with respect to t

$$\begin{aligned}
\dot{V}(x_1, x_2, x_3, x_4, x_5, x_6) &= 2[x_1\dot{x}_1 + x_2\dot{x}_2 + x_3\dot{x}_3 + x_4\dot{x}_4 + x_5\dot{x}_5 + x_6\dot{x}_6] \\
&= 2\Bigg[x_1\left(r_1\left[1 - \left(\frac{x_1}{c}\right)^{1/4}\right]x_1^{3/4}k_1x_2x_1 - p_1(1 - e^{-x_6})x_1\right) \\
&\quad + x_2\left(s + x_2\left[r_2\left(1 - \frac{x_1 + x_2 + x_4}{m}\right) - pk_1x_1 - k_2(1 - \varepsilon_{RT})x_5 - p_2(1 - e^{-x_6}) - \mu_2\right]\right) \\
&\quad + x_3\left(\xi k_2(1 - \varepsilon_{RT})x_2x_5 - ax_3 - \mu_3x_3\right) + x_4\big(ax_3 + k_2(1 - \xi)(1 - \varepsilon_{RT})x_2x_5 \\
&\quad - p_2(1 - e^{-x_6})x_4 - \mu_4x_4\big) + x_5(N\mu_4(1 - \varepsilon_{PI})x_4 - \mu_5x_5) + x_6(-dx_6)\Bigg]. \qquad (24)
\end{aligned}$$

Replacing E_0 in (24) we get that $\dot{V}(0, \alpha, 0, 0, 0, 0) \geqslant 0$, which imply that the infection-free equilibrium E_0 is unstable. The same conclusion can be made for E_7, indeed by replacing E_7 in (24) we get that $\dot{V}(0, T_1, I_1, L_1, V_1, 0) \geqslant 0$. This means that in this last case, the state of a person at early stage of HIV infection is unstable and may develop cancer. A person with no cancer infected with HIV, at the beginning of an illness, and did not develop cancer. But it is possible that he will develop cancer because the body begins to lose immunity due to the HIV virus.

Now for both equilibrium points E_1, E_8, since Lyapunov direct method is more complex to show that the both equilibrium points E_3, E_8 are positive or negative, we use Lyapunov Indirect method to study the stability.

2.2.2. Indirect method

In what follows, the system (1)–(6) will be linearized around its stationary states, and the characteristic equation for each case will be determined. Rewrite the system (1)–6) as a nonlinear sytem $\dot{x} = f(x)$, the corresponding linearized system at the equilibrium point $E_1 = (\varepsilon_1, \delta_1, 0, 0, 0, 0)$ is of the form

$$\begin{aligned}
\frac{\partial x_1}{\partial t} &= \left(\frac{3}{4}r_1\frac{1}{\varepsilon_1^{1/4}} - r_1\frac{1}{c^{1/4}} - k_1\delta_1\right)x_1 - k_1\varepsilon_1x_2 - p_1\varepsilon_1x_6, \\
\frac{\partial x_2}{\partial t} &= -\delta_1\left(\frac{r_2}{m} + pk_1\right)x_1 + r_2\left(1 - \frac{\varepsilon_1 + 2\delta_1}{m}\right)x_2 - \frac{\delta_1r_2}{m}x_4 - k_2(1 - \varepsilon_{RT})\delta_1x_5 - p_2\delta_2x_6, \\
\frac{\partial x_3}{\partial t} &= (-a - \mu_3)x_3 + \xi k_2(1 - \varepsilon)\delta_1x_5, \\
\frac{\partial x_4}{\partial t} &= ax_3 - \mu_4x_4 + k_2(1 - \xi)(1 - \varepsilon_{RT})\delta_1x_5, \\
\frac{\partial x_5}{\partial t} &= N\mu_4(1 - \varepsilon_{PI})x_4 - \mu_5x_5, \\
\frac{\partial x_6}{\partial t} &= -dx_6, \qquad (25)
\end{aligned}$$

Note that system (25) can be expressed in the following matrix form:

$$\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \\ \dot{x_3} \\ \dot{x_4} \\ \dot{x_5} \\ \dot{x_6} \end{pmatrix} = A_1 \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix} \qquad (26)$$

where A_1 is given by

$$A_1 = \begin{pmatrix} \frac{3}{4}r_1(\frac{1}{\varepsilon_1})^{1/4} - r_1(\frac{1}{c})^{1/4} - k_1\delta_1 & -k_1\varepsilon_1 & 0 & 0 & 0 & -p_1\varepsilon_1 \\ -\delta_1(\frac{r_2}{m} + pk_1) & r_2(1 - \frac{\varepsilon_1+2\delta_1}{m}) & 0 & -\frac{\delta_1 r_2}{m} & -k_2(1-\varepsilon_{RT})\delta_1 & -p_2\delta_2 \\ 0 & 0 & -a-\mu_3 & 0 & \xi k_2(1-\varepsilon_{RT})\delta_1 & 0 \\ 0 & 0 & a & -\mu_4 & k_2(1-\xi)(1-\varepsilon_{RT})\delta_1 & 0 \\ 0 & 0 & 0 & N\mu_4(1-\varepsilon_{PI}) & -\mu_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & -d \end{pmatrix}.$$

The matrix A_1 of this linear system is the Jacobian matrix $J(f)(E_1)$ of system (1)–(6) at the equilibrium point $E_1 = (\varepsilon_1, \delta_1, 0, 0, 0, 0)$. To use the indirect method we must study the eigenvalues of this matrix.

The characteristic equation of system (25) for the equilibrium point E_1 is given by

$$P(\lambda) = \det\left(J(f)(E_1) - \lambda I_6\right),$$

where I_6 is the identity matrix of order 6. The structure of the sparse matrix $J(f)(E_1)$ allows us an easy computation of $P(\lambda)$, that is,

$$P(\lambda) = \left(\frac{3}{4}r_1\frac{1}{\varepsilon_1^{1/4}} - r_1\frac{1}{c^{1/4}} - k_1\delta_1 - \lambda\right) \times \left(r_2\left(1 - \frac{\varepsilon_1 + 2\delta_1}{m}\right) - \lambda\right)(-a-\mu_4-\lambda)(-\mu_4-\lambda)(-\mu_5-\lambda)(-d-\lambda). \quad (27)$$

Then, the roots of this characteristic equation are:

$$\lambda_1 = r_1\left(\frac{3}{4}\frac{1}{\varepsilon_1^{1/4}} - \frac{1}{c^{1/4}}\right) - k_1\delta_1, \quad \lambda_2 = r_2\left(1 - \frac{\varepsilon_1+2\delta_1}{m}\right), \quad \lambda_3 = -(a+\mu_3),$$

$$\lambda_4 = -\mu_4, \quad \lambda_5 = -\mu_5, \quad \lambda_6 = -d.$$

From the parameters in Table 1, we have $r_1\frac{3}{4}(\frac{1}{\varepsilon_1^{1/4}} - \frac{1}{c^{1/4}}) < k_1\delta_1$ and $1 < \frac{\varepsilon_1+2\delta_1}{m}$ which imply that all roots of the characteristic equation (27) have negative real parts. Therefore, E_1 is locally asymptotically stable. This means that in this case, a patient who is not infected with HIV but has cancer cell which is at the beginning of a disease has immunity which helps disease to control the growth cancer cells and decrease the rate of death.

Consider the linearized system at the equilibrium point $E_8 = (C_1, T_1, I_2, L_2, V_2, 0)$:

$$\begin{aligned}
\frac{\partial x_1}{\partial t} &= A_{11}x_1 - k_1C_1x_2 - p_1C_1x_6, \\
\frac{\partial x_2}{\partial t} &= A_{21}x_1 + A_{22}x_2 - \frac{r_2T_1}{m}x_4 - A_{23}x_5 - p_2T_1x_6, \\
\frac{\partial x_3}{\partial t} &= A_{31}x_2 - (a+m_3)x_3 + A_{32}x_5, \\
\frac{\partial x_4}{\partial t} &= A_{41}x_2 - \mu_3x_3 + ax_4 + A_{42}x_5 - p_2I_2x_6, \\
\frac{\partial x_5}{\partial t} &= N\mu_4(1-\varepsilon_{PI})x_4 - \mu_5x_5, \\
\frac{\partial x_6}{\partial t} &= -dx_6, \qquad (28)
\end{aligned}$$

which can be written in matrix form as:

$$\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \\ \dot{x_3} \\ \dot{x_4} \\ \dot{x_5} \\ \dot{x6} \end{pmatrix} = \begin{pmatrix} A_{11} & -k_1C_1 & 0 & 0 & 0 & -p_1C_1 \\ A_{21} & A_{22} & 0 & -\frac{r_2T_1}{m} & -A_{23} & -p_2T_1 \\ 0 & A_{31} & -(a+\mu_3) & 0 & A_{32} & 0 \\ 0 & A_{41} & -\mu_3 & -a & A_{42} & -p_2I_2 \\ 0 & 0 & 0 & Nm_4(1-\varepsilon_{PI}) & -m_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & -d \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix}, \tag{29}$$

where

$$A_{11} = r_1\left(\frac{3}{4}C_1^{1/4} - \frac{1}{c^{1/4}}\right) - k_1T_1, \quad A_{21} = -T_1\left(\frac{r_2}{m} - pk_1\right),$$

$$A_{22} = r_2\left(1 - \frac{C_1+2T_1+I_2}{m}\right) - pk_1C_1 - k_2(1-\varepsilon_{RT})V_2 - \mu_2,$$

$$A_{23} = k_2(1-\varepsilon_{RT})T_1, \quad A_{31} = \xi k_2(1-\varepsilon_{RT})V_2, \quad A_{32} = \xi k_2(1-\varepsilon_{RT})T_1,$$

$$A_{41} = k_2(1-\varepsilon_{RT})(1-\xi)V_2, \quad A_{42} = k_2(1-\xi)(1-\varepsilon_{RT})T_1.$$

The matrix of this linear system is the Jacobian matrix $J(f)(E_8)$ of system(1)–(6) at the equilibrium point $E_8 = (C_1, T_1, I_2, L_2, V_2, 0)$.

Again, the structure of the sparse matrix $J(f)(E_8)$ allows us an easy computation of $P(\lambda)$, the characteristic equation of system (28):

$$\begin{aligned} P(\lambda) &= \det(J(f)(E_8) - \lambda I_6) \\ &= (A_{11}-\lambda)(A_{22}-\lambda)(-a-\mu_3-\lambda)(-a-\lambda)(-\mu_5-\lambda)(-d-\lambda). \end{aligned} \tag{30}$$

The roots of this characteristic equation are:

$$\lambda_1 = r_1\left(\frac{3}{4}C_1^{1/4} - \frac{1}{c^{1/4}}\right) - k_1T_1,$$

$$\lambda_2 = r_2\left(1 - \frac{C_1+2T_1+I_2}{m}\right) - pk_1C_1 - k_2(1-\varepsilon_{RT})V_2 - \mu_2, \quad \lambda_3 = -(a+\mu_3),$$

$$\lambda_4 = -a, \quad \lambda_5 = -\mu_5, \quad \lambda_6 = -d.$$

Some calculations using the values of the parameters and we end up with $r_1(\frac{3}{4}C_1^{1/4} - \frac{1}{c^{1/4}}) < k_1T_1$ and $r_2(1 - \frac{C_1+2T_1+I_2}{m}) < pk_1C_1 + k_2(1-\varepsilon_{RT})V_2 + \mu_2$. So, six roots λ_i, $i = 1, \ldots, 6$ are negatives and therefore, E_8 is locally asymptotically stable.

This means that a patient who is infected with HIV and has cancer cell which is at the beginning of a disease is in a stable condition in terms of the rate of cancer cells growth.

Note that, in all the equilibrium points of this system, the component representing the chemotherapeutic dynamic is zero. This does not make it possible to study the steady state around a positive value of this variable, i.e. after the start of chemotherapy treatment. In order to remedy this problem, we propose in the following section, based on the theory of bifurcation [15, 16], a study of stability by introducing a small perturbation of the variable representing the chemotherapeutic dynamic.

2.3. Bifurcation of the Mathematical model

Bifurcation theory refers to the study of qualitative changes to the state of a system as a parameter is varied. Otherwise the bifurcation of a differential equation is concerned with changes in the qualitative behavior of its phase portrait as a parameter (or set of parameters) varies.

Perturbation theory examines parameter dependence of solutions locally [15–17]. To present basic ideas simply, consider a one-parameter family of functions: for each x in a set R and real parameter ε in a punctured neighborhood of $\varepsilon = 0$, the values of the functions $f(x, \varepsilon)$ are in a metric space. The range is a metric space so that convergence of f as $\varepsilon \to 0$ can be discussed. $f(x, \varepsilon)$ is to be regarded as a solution of some set of equations containing ε as a parameter.

The equations are called a regularly perturbed problem if all solutions $f(x, \varepsilon)$ converge uniformly on $\mathbb{R}$ as $\varepsilon \to 0$.

If there is a solution which does not converge uniformly, the problem is called singularly perturbed.

Let us bifurcate the model (1)–(6) by adding a small parameter ε at the level of x_6, the variable representing the chemotherapeutic dynamic, which results in the following model,

$$\dot{x}_1 = r_1 \left[1 - \left(\frac{x_1}{c}\right)^{1/4}\right] x_1^{3/4} - k_1 x_1 x_2 - p_1(1 - e^{-x_6})x_1, \tag{31}$$

$$\dot{x}_2 = s + x_2 \left[r_2 \left(1 - \frac{x_1 + x_2 + x_4}{m}\right) - p k_1 x_1 - k_2(1 - \varepsilon_{RT})x_5 - p_2(1 - e^{-x_6}) - \mu_2\right], \tag{32}$$

$$\dot{x}_3 = \xi k_2(1 - \varepsilon_{RT})x_2 x_5 - (a + \mu_3)x_3, \tag{33}$$

$$\dot{x}_4 = a x_3 + k_2(1 - \xi)(1 - \varepsilon_{RT})x_2 x_5 - p_2(1 - e^{-x_6})x_4 - \mu_4 x_4, \tag{34}$$

$$\dot{x}_5 = N\mu_4(1 - \varepsilon_{PI})x_4 - \mu_5 x_5, \tag{35}$$

$$\dot{x}_6 = \varepsilon - d x_6. \tag{36}$$

As for the first model, we study the existence and the stability of the steady state for the bifurcated model. First, let's start by finding the stationary states of this system. Taking $\dot{x_i} = 0$ for $i = 1, 2, \ldots, 6$ in (31)–(36), then equation (36) implies that

$$x_6 = \frac{\varepsilon}{d}. \tag{37}$$

If $x_5 = 0$, then (35) implies that $x_4 = 0$, and (33) implies that $x_3 = 0$. The trivial case where equation (31) will be satisfied is $x_1 = 0$. In this case x_2 is obtained as a root of the second degree polynomial

$$ms - r_2 x_2^2 + m\big(r_2 - \mu_2 - p_2\big(1 - e^{\frac{-\varepsilon}{d}}\big)\big)x_2 = 0,$$

which gives rise to two points of equilibrium $E_{b0} = (0, \alpha_b, 0, 0, 0, \varepsilon/d)$, $E_{b01} = (0, \beta_b, 0, 0, 0, \varepsilon/d)$, where

$$\alpha_b = -\frac{1}{2r_2}\left(m\big(-r_2 + \mu_2 - P_1\big(1 - e^{\frac{-\varepsilon}{d}}\big)\big) + \sqrt{m^2\big(r_2 - \mu_2 - P_2\big(1 - e^{\frac{-\varepsilon}{d}}\big)\big)^2 - 4r_2 sm}\right),$$

$$\beta_b = -\frac{1}{2r_2}\left(m\big(-r_2 + \mu_2 - P_1\big(1 - e^{\frac{-\varepsilon}{d}}\big)\big) - \sqrt{m^2\big(r_2 - \mu_2 - P_2\big(1 - e^{\frac{-\varepsilon}{d}}\big)\big)^2 - 4r_2 sm}\right).$$

As β_b is negative, E_{b01} has no physical meaning, so we only retain E_{b0} as the equilibrium point representing the infection-free state.

If $x_1 \neq 0$, since x_2 is also non-zero, we obtain from (31) and (32) that $x_1 = \frac{r_1^4 c}{(r_1 + k c^{1/4} x_2)^4}$ and x_2 is a root of the following degree 6 polynomial equation:

$$\frac{A_2^4 r_2}{m}x_2^6 + A_3 x_2^5 + A_4 x_2^4 + A_5 x_2^3 + A_6 x_2^2 + A_7 x_2 + s A_1^4 = 0,$$

where,

$$A_1 = r_1\big(-1 + c^{1/4}\big) - P_1 c^{1/4}\big(1 - e^{\frac{-\varepsilon}{d}}\big),$$

$$A_2 = c^{1/4} k_1, \quad A_3 = \big(r_2 - P_2\big(1 - e^{\frac{-\varepsilon}{d}}\big) - \mu_2\big)A_2^4 - \frac{4r_2}{m}A_1 A_2^3,$$

$$A_4 = s A_2^4 - 4A_1 A_2^3\big(r_2 - P_2\big(1 - e^{\frac{-\varepsilon}{d}}\big) - \mu_2\big) + \frac{6r_2}{m}A_1^2 A_2^2,$$

$$A_5 = 6A_1^2A_2\big(-r_2 + P_2\big(1-e^{\frac{-\varepsilon}{d}}\big)+\mu_2\big) - 4sA_1A_2^3 - \frac{4r_2}{m}A_1^3A_2,$$

$$A_6 = 6sA_1^2A_2^2 - 4A_1^3A_2\big(r_2 - P_2\big(1-e^{\frac{-\varepsilon}{d}}\big)-\mu_2\big) - \frac{r_2}{m}A_1^4,$$

$$A_7 = A_1^4\big(r_2 - P_2\big(1-e^{\frac{-\varepsilon}{d}}\big)-\mu_2\big) - 4sA_1^3A_2.$$

Denoting these roots by ε_{bi}, $i=1,\dots,6$ we obtain 6 equilibrium points: $E_{bi}=(\delta_{bi},\varepsilon_{bi},0,0,0,\varepsilon/d)$, $i=1,\dots,6$, where

$$\varepsilon_{b1} = 1226.067470, \quad \delta_{b1} = \frac{r_1^4c}{(A_1-A_2\varepsilon_{b1})^4},$$

$$\delta_{b2} = \frac{r_1^4c}{(A_1-A_2\varepsilon_{b2})^4}, \quad \varepsilon_{b2} = 6.201000500\ 10^{26},$$

$$\delta_{b3} = \frac{r_1^4c}{(A_1-A_2\varepsilon_{b3})^4}, \quad \varepsilon_{b3} = 376.3119874 + 1148.012350i,$$

$$\delta_{b4} = \frac{r_1^4c}{(A_1-A_2\varepsilon_{b4})^4}, \quad \varepsilon_{b4} = -989.3457222 + 744.3816457i,$$

$$\delta_{b5} = \frac{r_1^4c}{(A_1-A_2\varepsilon_{b5})^4}, \quad \varepsilon_{b5} = -989.3457222 - 744.3816457i,$$

$$\delta_{b6} = \frac{r_1^4c}{(A_1-A_2\varepsilon_{b6})^4}, \quad \varepsilon_{b6} = 376.3119874 - 1148.012350i.$$

Since $(\varepsilon_{b3},\delta_{b3},\varepsilon_{b4},\delta_{b4},\varepsilon_{b5},\delta_{b5},\varepsilon_{b6},\delta_{b6})$ are complex, E_{b3}, E_{b4}, E_{b5} and E_{b6} do not have physical meaning, we therefore only retain E_{b1} and E_{b2}, as points of equilibrium requiring a study of stability.

In the case $x_5 \neq 0$ we get from (35)

$$x_5 = \frac{N\mu_4(1-\varepsilon_{PI})}{\mu_5}x_4. \tag{38}$$

Replacing x_5 in (33)

$$k_2(1-\varepsilon_{RT})x_2x_5 = \frac{(a+\mu_3)x_3}{\xi}. \tag{39}$$

This last equation combined with (34) leads to

$$x_3 = \frac{\xi\big[p_2\big(1-e^{\frac{-\varepsilon}{d}}\big)+\mu_4\big]x_4}{a+(1-\xi)\mu_3}. \tag{40}$$

By combining (40) and (38) with (39) we obtain

$$x_2 = \frac{\mu_5(a+\mu_3)\big[p_2\big(1-e^{-\frac{\varepsilon}{d}}\big)+\mu_4\big]}{k_2(1-\varepsilon_{RT})N\mu_4(1-\varepsilon_{PI})(a+(1-\xi)\mu_3)}. \tag{41}$$

Now equation (32) will be satisfied for two cases: in the trivial case $x_1=0$, the equation giving x_4 is obtained as a function of x_2 from equation (32)

$$x_4 = m\mu_4\frac{s+x_2\big[r_2\big(1-\frac{x_2}{m}\big)-p_2\big(1-e^{\frac{-\varepsilon}{d}}\big)-\mu_2\big]}{x_2r_2\mu_5+k_2m(1-\varepsilon_{RT})\mu_4N(1-\varepsilon_{PI})}.$$

In the non-trivial case $x_1\neq 0$, equation (31) gives x_1 as a function of x_2 as follows

$$x_1 = \frac{r_1^4c}{\big(r_1+c\big(k_1x_2-p_1\big(1-e^{-\frac{\varepsilon}{d}}\big)\big)\big)^4}.$$

Introducing this last equation with (41) in (32) implies

$$x_4 = m\mu_4 \frac{s + x_2\left[r_2\left(1 - \frac{x_1+x_2}{m}\right) - pk_1x_1 - p_2\left(1 - e^{\frac{-\varepsilon}{d}}\right) - \mu_2\right]}{x_2 r_2\mu_5 + k_2 m(1-\varepsilon_{RT})\mu_4 N(1-\varepsilon_{PI})}.$$

So, we get two equilibrium points $E_{b7} = (0, T_b, I_b, L_b, V_b, D_b)$ and $E_{b8} = (C, T, I, L, V, D)$, where

$$\begin{aligned}
T_b &= \frac{\mu_5(a+\mu_3)\left[p_2\left(1-e^{-\frac{\varepsilon}{d}}\right)+\mu_4\right]}{k_2(1-\varepsilon_{RT})N\mu_4(1-\varepsilon_{PI})(a+\mu_3-\xi\mu_3)},\\
I_b &= \frac{\xi\left[p_2\left(1-e^{\frac{-\varepsilon}{d}}\right)+\mu_4\right]L_b}{a+(1-\xi)\mu_3},\\
L_b &= m\mu_4\frac{s+T_b\left[r_2\left(1-\frac{T_b}{m}\right)-p_2\left(1-e^{\frac{-\varepsilon}{d}}\right)-\mu_2\right]}{T_b r_2\mu_5 + k_2 m(1-\varepsilon_{RT})\mu_4 N(1-\varepsilon_{PI})},\\
V_b &= \frac{N\mu_4(1-\varepsilon_{PI})}{\mu_5}L_b.\\
C &= \frac{r_1^4 c}{\left[r_1 + c^{1/4}\left(k_1 T - p_1\left(1-e^{-\varepsilon/d}\right)\right)\right]^4},\\
T &= \frac{\mu_5(a+\mu_3)\left[p_2\left(1-e^{-\frac{\varepsilon}{d}}\right)+\mu_4\right]}{k_2(1-\varepsilon_{RT})N\mu_4(1-\varepsilon_{PI})(a+\mu_3-\xi\mu_3)},\\
I &= \frac{\xi\left[p_2\left(1-e^{\frac{-\varepsilon}{d}}\right)+\mu_4\right]L}{a+(1-\xi)\mu_3},\\
L &= m\mu_4\frac{s+T\left[r_2\left(1-\frac{C+T}{m}\right)-pk_1C-p_2\left(1-e^{\frac{-\varepsilon}{d}}\right)-\mu_2\right]}{Tr_2\mu_5 + k_2 m(1-\varepsilon_{RT})\mu_4 N(1-\varepsilon_{PI})},\\
V &= \frac{N\mu_4(1-\varepsilon_{PI})}{\mu_5}L.
\end{aligned}$$

Let study the local stability for the equilibrium points. For the points E_{b0} and E_{b7} we use the Lyapunov direct method considering the Lyapunov function

$$V(x_1, x_2, x_3, x_4, x_5, x_6) = \sum_{i=1}^{6} x_i^2$$

for which the differential $\dot{V}$ is given by

$$\begin{aligned}
\dot{V}(x_1, x_2, x_3, x_4, x_5, x_6) &= 2\sum_{i=1}^{6} x_i\dot{x}_i\\
&= 2\Bigg[x_1\left(r_1\left[1-\left(\frac{x_1}{c}\right)^{1/4}\right]x_1^{3/4} - k_1x_1x_2 - p_1\left(1-e^{-x_6}\right)x_1\right)\\
&\quad + x_2\left(s + x_2\left[r_2(1-\frac{x_1+x_2+x_4}{m}) - pk_1x_1 - k_2(1-\varepsilon_{RT})x_5 - p_2\left(1-e^{-x_6}\right)-\mu_2\right]\right)\\
&\quad + x_3(\xi k_2(1-\varepsilon_{RT})x_2x_5 - (a+\mu_3)x_3)\\
&\quad + x_4\left(ax_3 + k_2(1-\xi)(1-\varepsilon_{RT})x_2x_5 - p_2\left(1-e^{-x_6}\right)x_4 - \mu_4x_4\right)\\
&\quad + x_5(N\mu_4(1-\varepsilon_{PI})x_4 - \mu_5x_5) + x_6(\varepsilon - dx_6)\Bigg]. \qquad (42)
\end{aligned}$$

Replacing E_{b0} in (42) we get also that $\dot{V}(x_1, x_2, x_3, x_4, x_5, x_6) > 0$, and in the same way if we replace E_{b7} we get also that $\dot{V}(x_1, x_2, x_3, x_4, x_5, x_6) > 0$. Thus, the system is unstable in these two equilibrium points.

Now, one can not obtain the sign of $\dot{V}$ by the application of the above technique to the equilibrium points E_{b1}, E_{b2} and E_{b8}. This is why we propose the use of the Lyapunov indirect method to study the stability of the system at these study states.

The corresponding linearized system at the equilibrium point $E_{b1} = (\varepsilon_{b1}, \delta_{b1}, 0, 0, 0, \varepsilon/d)$ is given by

$$\begin{aligned}
\frac{\partial x_1}{\partial t} &= C_{11}x_1 - k_1\varepsilon_{b1}x_2 - p_1\varepsilon_{b1}e^{-\varepsilon/d}x_6,\\
\frac{\partial x_2}{\partial t} &= C_{21}x_1 + C_{22}x_2 - \frac{r_2\delta_{b1}}{m}x_4 + C_{23}x_5 - p_2e^{-\varepsilon/d}\delta_{b1}x_6,\\
\frac{\partial x_3}{\partial t} &= -(a+m_3)x_3 + C_{31}x_5,\\
\frac{\partial x_4}{\partial t} &= ax_3 - C_{41}x_4 + C_{42}x_5,\\
\frac{\partial x_5}{\partial t} &= N\mu_4(1-\varepsilon_{PI})x_4 - \mu_5x_5,\\
\frac{\partial x_6}{\partial t} &= -dx_6,
\end{aligned} \tag{43}$$

where

$$C_{11} = \frac{3}{4}r_1(\varepsilon_{b1})^{-1/4} - r_1\frac{1}{c^{1/4}} - k_1\delta_{b1} - p_1\big(1-e^{-\varepsilon/d}\big), \quad C_{21} = -\left(\frac{r_2}{m} + Pk_1\right)\delta_{b1},$$

$$C_{22} = r_2\left(1 - \frac{\varepsilon_{b1}+2\delta_{b1}}{m}\right) - pk_1\varepsilon_{b1} - p_2\big(1-e^{-\varepsilon/d}\big) - \mu_2, \quad C_{23} = -k_2(1-\varepsilon_{RT})\delta_{b1},$$

$$C_{31} = \xi k_2(1-\varepsilon_{RT})\delta_{b1}, \quad C_{41} = p_2\big(1-e^{-\varepsilon/d}\big) + \mu_4, \quad C_{42} = k_2(1-\xi)(1-\varepsilon_{RT})\delta_{b1}.$$

This linear system can be written as:

$$\begin{pmatrix} \dot{x_1}\\ \dot{x_2}\\ \dot{x_3}\\ \dot{x_4}\\ \dot{x_5}\\ \dot{x_6} \end{pmatrix} = \begin{pmatrix} C_{11} & -k_1C & 0 & 0 & 0 & -p_1\varepsilon_{b1}e^{-\varepsilon/d}\\ C_{21} & C_{22} & 0 & \frac{r_2\delta_{b1}}{m} & C_{23} & -P_2e^{-\varepsilon/d}\delta_{b1}\\ 0 & 0 & -(a+m_3) & 0 & C_{31} & 0\\ 0 & 0 & a & C_{41} & C_{42} & 0\\ 0 & 0 & 0 & N\mu_4(1-\varepsilon_{PI}) & -\mu_5 & 0\\ 0 & 0 & 0 & 0 & 0 & -d \end{pmatrix} \begin{pmatrix} x_1\\ x_2\\ x_3\\ x_4\\ x_5\\ x_6 \end{pmatrix}. \tag{44}$$

The characteristic polynomial of this system is given by

$$\begin{aligned}
P(\lambda) &= \det(J(f)(E_{b1}) - \lambda I_6)\\
&= (C_{11}-\lambda)(C_{22}-\lambda)(-(a+m_3)-\lambda)\big(-\big(p_2\big(1-e^{-\varepsilon/d}\big)+\mu_4\big)-\lambda\big)(-m_5-\lambda)(-d-\lambda).
\end{aligned} \tag{45}$$

Therefore, roots of this characteristic equation are:

$$\lambda_1 = C_{11}, \quad \lambda_2 = C_{22}, \quad \lambda_3 = -(a+\mu_3),$$
$$\lambda_4 = -\big(p_2\big(1-e^{-\varepsilon/d}\big)+\mu_4\big), \quad \lambda_5 = -\mu_5, \quad \lambda_6 = -d.$$

It's easy to see that all these values are non-positive and thus the model is stable at the equilibrium point (E_{b1}). This means in this case that a patient with cancer, not infected with HIV, but who is treated with a chemotherapeutic dynamic, his disease can be controlled so that the cancer cells are reduced.

Let us consider the linearization of system (31)–(36) around the equilibrium point E_{b2}:

$$\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \\ \dot{x_3} \\ \dot{x_4} \\ \dot{x_5} \\ \dot{x_6} \end{pmatrix} = \begin{pmatrix} D_{11} & -k_1\varepsilon_{b2} & 0 & 0 & 0 & p_1\varepsilon_{b2}e^{-\varepsilon/d} \\ D_{21} & D_{22} & 0 & -\frac{r_2\delta_{b2}}{m} & D_{23} & -p_2e^{-\varepsilon/d}\delta_{b2} \\ 0 & 0 & -(a+m_3) & 0 & D_{31} & 0 \\ 0 & 0 & a & D_{41} & D_{42} & 0 \\ 0 & 0 & 0 & N\mu_4(1-\varepsilon_{PI}) & -\mu_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & -d \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix}, \tag{46}$$

where

$$D_{11} = \frac{3}{4}r_1(\varepsilon_{b2})^{-1/4} - r_1\frac{1}{c^{1/4}} - k_1\delta_{b2} - p_1\big(1-e^{-\varepsilon/d}\big), \quad D_{21} = -\left(\frac{r_2}{m} + pk_1\right)\delta_{b1},$$

$$D_{22} = r_2\left(1 - \frac{\varepsilon_{b2}+2\delta_{b2}}{m}\right) - pk_1\varepsilon_{b2} - p_2\big(1-e^{-\varepsilon/d}\big) - \mu_2, \quad D_{23} = -k_2(1-\varepsilon_{RT})\delta_{b2},$$

$$D_{31} = \xi k_2(1-\varepsilon_{RT})\delta_{b2}, \quad D_{41} = p_2(1-e^{-\varepsilon/d}) + \mu_4, \quad D_{42} = k_2(1-\xi)(1-\varepsilon_{RT})\delta_{b2}.$$

Once again, the structure of this matrix allows us to easily find an expression of the characteristic equation:

$$\begin{aligned} P(\lambda) &= \det\big(J(f)(E_{b2}) - \lambda I_6\big) \\ &= (D_{11}-\lambda)(D_{22}-\lambda)(-(a+m_3)-\lambda)\left(-\big(p_2\big(1-e^{-\varepsilon/d}\big)+\mu_4\big)-\lambda\right)(-m_5-\lambda)(-d-\lambda). \end{aligned} \tag{47}$$

The roots of this characteristic equation are:

$$\lambda_1 = D_{11}, \quad \lambda_2 = D_{22}, \quad \lambda_3 = -(a+\mu_3),$$

$$\lambda_4 = -\big(p_2\big(1-e^{-\varepsilon/d}\big)+\mu_4\big), \quad \lambda_5 = -\mu_5, \quad \lambda_6 = -d.$$

From parameters in Table 1, we show that D_{11} and D_{22} are negative, so six roots λ_i, $i = 1, \ldots, 6$ are negatives. Thus the model is stable. The same interpretation as for the previous case can be done.

In order to study the local stability of system (31)–(36) at the equilibrium point $E_{b8} = (C, T, I, L, V, D)$, the corresponding linearized system around this point is considered. This gives rise to the following system:

$$\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \\ \dot{x_3} \\ \dot{x_4} \\ \dot{x_5} \\ \dot{x_6} \end{pmatrix} = \begin{pmatrix} B_{11} & -k_1C & 0 & 0 & 0 & p_1Ce^{-D} \\ B_{21} & B_{22} & 0 & -\frac{r_2T}{m} & B_{23} & -p_2e^{-D}T \\ 0 & B_{31} & -(a+m_3) & 0 & B_{32} & 0 \\ 0 & B_{41} & a & B_{42} & B_{43} & -p_2e^{-D}I \\ 0 & 0 & 0 & N\mu_4(1-\varepsilon_{PI}) & -\mu_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & -d \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \end{pmatrix}, \tag{48}$$

where

$$B_{11} = \frac{3}{4}r_1C^{1/4} - r_1\frac{1}{c^{1/4}} - k_1T - p_1\big(1-e^{-D}\big), \quad B_{21} = -\left(\frac{r_2}{m} + pk_1\right)T,$$

$$B_{22} = r_2\left(1 - \frac{C+2T+I}{m}\right) - pk_1C - k_2(1-\varepsilon_{RT})V - p_2\big(1-e^{-D}\big) - \mu_2, \quad B_{23} = -k_2(1-\varepsilon_{RT})T,$$

$$B_{31} = \xi k_2(1-\varepsilon_{RT})V, \quad B_{32} = \xi k_2(1-\varepsilon_{RT})T, \quad B_{41} = k_2(1-\varepsilon_{RT})(1-\xi)V,$$

$$B_{42} = p_2\big(1-e^{-D}\big)+\mu_4) \quad B_{43} = k_2(1-\xi)(1-\varepsilon_{RT})T.$$

Then, the Characteristic polynomial is given by

$$\begin{aligned} P(\lambda) &= \det\big(J(f)(E_{b8}) - \lambda I_6\big) \\ &= (B_{11}-\lambda)(B_{22}-\lambda)(-(a+m_4)-\lambda)\left(-\big(p_2\big(1-e^{-D}\big)+\mu_4\big)-\lambda\right)(-m_5-\lambda)(-d-\lambda). \end{aligned} \tag{49}$$

From the last equation the eigenvalues of jaccobian equation $\mathrm{J}J(f)(E_{b8})$ are:

$$\lambda_1 = B_{11}, \quad \lambda_2 = B_{22}, \quad \lambda_3 = -(a + m_3), \quad \lambda_4 = -\big(p_2\big(1 - e^{-D}\big) + \mu_4\big), \quad \lambda_5 = -m_5, \quad \lambda_6 = -d.$$

We conclude from Table 1 that B_{11}, B_{22} negatives. This implies that six eigenvalues λ_i, $i = 1, \ldots, 6$ are negatives and thus the model is stable at E_{b8}. This means that the combination of the treatment and the chemotherapeutic dynamics of a patient with HIV and developing cancer allows stability in the course of the disease and the control of the growth of cancer cells which leads to a decrease in the death rate.

3. Conclusion

In this work, we present the study an impulsive mathematical model proposed in Chavez et al. [1] to describe the dynamics of cancer growth and HIV infection, when chemotherapy and HIV treatment are combined. We have considered a first approach for the study of this dynamic system which consists in looking for the points of equilibrium, that is to say the stationary solutions not showing the temporal evolution. We have studied the local stability of all these points of model equilibrium. To do this, we used both the direct Lyapunov method as well as the linearization technique called the indirect Lyapunov method. We have noticed that no point of equilibrium takes into account the chemotherapeutic dynamic, because in all cases the variable the representation is zero. To complete the study, we bifurcated the model by adding a small perturbation in the variable representing the chemotherapeutic dynamics, then we studied the stability of all the equilibrium points of the system obtained. Our next work, is to vary several system control parameters. We will then look at what becomes of the points of equilibrium, in particular those which were stable before modifying the parameters of the system. We will examine the possible bifurcations that appear. For the values of the parameters at which such qualitative changes appear, so-called bifurcation values, we will use tools adopted for construction of the phase portrait.

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Про стабільність математичної моделі ВІЛ (СНІД) — динаміка раку

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У цій роботі досліджується імпульсна математична модель, запропонована Чавесом та ін. [1] для опису динаміки росту раку та ВІЛ-інфекції, коли хіміотерапія поєднується з лікуванням ВІЛ. Щоб краще зрозуміти ці складні біологічні явища, вивчається стійкість точок рівноваги. Для цього будується відповідна функція Ляпунова для першої точки рівноваги, тоді як для другої використовується непрямий метод Ляпунова. Жодна з отриманих точок рівноваги не дозволяє дослідити стабільність хіміотерапевтичної динаміки, запропоновано роздвоєння моделі та дослідження роздвоєної системи, що сприяє кращому розумінню основних біохімічних процесів, які керують цією високоактивною антиретровірусною терапією. Це показує, що запропонована математична модель є достатньо реалістичною, щоб оцінити вплив такого лікування.

Ключові слова: *точка рівноваги, стабільність, модель рак-ВІЛ(СНІД), прямий метод Ляпунова.*