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A NONLINEAR DETERMINISTIC MODEL FOR HIV-INFECTION DYNAMICS WITH OPTIMAL CONTROL STRATEGY USING POWER SERIES METHOD

S. OLANIYI[1], B. GBADAMOSI AND I. A. OLOPADE

ABSTRACT. A non-linear deterministic model representing the interaction of a chronic retrovirus HIV and immune system of the human body is presented. The Optimal control of this model is explored using a power series method. We obtain the discritized control function $0 \leqslant u(t) \leqslant 1$ which maximizes the total count of CD_4^+T cells and minimizes the costs of the chemotherapy of HIV. Moreover, the numerical results are obtained using an iterative method by Runge-Kutta fourth order scheme.

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1. INTRODUCTION

Several mathematical models describing the interaction of the human immune-deficiency virus (HIV) with the immune system of the human body have been developed by researchers, see the references therein for examples. These models have become important tools for controlling the spread of the retrovirus HIV from developing into a full blown acquired immune-deficiency syndrome (AIDS).

The spread of HIV/AIDS epidemic continues around the world since its discovery in the early 1980's. HIV is a "retrovirus", a virus that is able to incorporate its own genome into the DNA of a cell that is infecting, thereby reversing the process of DNA replication [6]. In particular, the CD_4^+T (white blood cells) that HIV infects are the very ones that are necessary to ward off the invasion. The $CD4$ represents a protein marker on the surface of the CD_4^+T cell and the T in the CD_4^+T cell describes the connection to the thymus gland where the cells mature [2].

The count of CD_4^+T cells is a primary indicator used to measure progression of HIV infection. Whereas, in a normal person, the level

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[1]Corresponding author

of CD_4^+T cells in the peripheral blood is related at a level between 800 and 1200mm^{-3} [10]. Once the disease has progressed and the CD_4^+ count in the body falls below 200 cells, a person is diagnosed with AIDs, and immunity to infection is lost [9]. Due to the devastating effects HIV/AIDs epidemic has on lives and economic growth [8], control and preventive measures such as affinity hemodialysis of the infected blood [1] and the use of condoms [4] are proposed. However, in [4], it is shown that HIV may not be controlled using condoms alone in a population where the average number of HIV infected partners is large and preventability threshold is perhaps unattainable.

Thus, the therapeutic strategies appear promising for retarding the progression of HIV infection but because of the high cost and high risk of side effects (poisoning) of the therapeutic treatment, it is pertinent to use mathematical models in obtaining the optimal amount of medicine consumption in the control program of HIV. See [2,7,11,12] for some techniques used.

In this paper, we present a new system of ordinary differential equations modelling the interaction between the retrovirus HIV and the immune system of the human body. Unlike the previous techniques, we adopt a power series method to explore the optimal control of the formulated model.

2. MODEL FORMULATION

Let the concentration of the uninfected CD_4^+T cells be represented by $X(t)$ and let $Y(t)$ represent the concentration of latently infected CD_4^+T cells. $Z(t)$ denotes the concentration of actively infected T-cells and $V(t)$ represents the free virus particles concentration. With modification on [11,12],we obtain a new system of nonlinear equations as follows:

$$\frac{dX}{dt} = s + rX\left(1 - \frac{X+Y+Z}{N_{max}}\right) - \mu_1 X - k_1 VX \tag{2.1}$$

$$\frac{dY}{dt} = k_1 VX - \mu_2 Y - k_2 Y \tag{2.2}$$

$$\frac{dZ}{dt} = k_2 Y - \mu_3 Z + k_3 VY \tag{2.3}$$

$$\frac{dV}{dt} = \beta(1-u)\left(1 - \frac{Z}{L}\right) - \mu_4 V - k_3 VY \tag{2.4}$$

together with the initial conditions

$$X(0) = 820mm^{-3}, Y(0) = 0, Z(0) = 0, V(0) = 1mm^{-3}$$

Where s is a source term for uninfected cells produced from the bone marrow and represents the rate of generation of new CD_4^+T cells. r is the coefficient of the growth rate of uninfected CD_4^+T cells in the thymus gland, which is a logistic-type growth. This growth ensures that the uninfected CD_4^+T never grow larger than the maximum T-cells level denoted by N_{max}. $\mu_1, \mu_2, \mu_3, \mu_4$ with negative signs indicate the rate of normal death of uninfected CD_4^+T cells, latently infected CD_4^+T cells, actively infected CD_4^+T cells and free infectious virus respectively. k_1 is the rate that free virus infects T-cells, and k_2, rate latently infected T-cells convert to actively infected cells. In the chronic stage of infection, the term k_3VY emerges. This shows that the free virus is lost by connecting to already infected but latent cells at a rate k_3 and instantly boosts the actively infected cells population. Thus k_3VY is added to the population equation (2.3) describing the concentration of actively infected CD_4^+T cells. However, the actively infected CD_4^+T cells, $Z(t)$, enhances the increase of virus to a maximum level L at a rate β. Moreover, the optimal chemotherapy treatment is considered with the control $u(t)$ affecting the production of the free virus.

3. OPTIMAL CONTROL

For most HIV chemotherapy drugs, the length of treatment is less than 2 years. To prevent the transmission of uninfected CD_4^+T cells to infected ones and keep the side effects of the medicine therapy in low level, the following target function is used [2,7,11].

$$J(u) = \int_{t_0}^{t_1} \left(X(t) - \frac{B}{2} u(t)^2 \right) \tag{3.1}$$

The interest is to maximize (3.1). That is, maximizing the total count of CD_4^+T cells and minimizing the cost and high risk of the chemotherapy. The parameter $B > 0$ represents the desired weight on the benefit and cost. The control for the chemotherapy, $u(t)$, is chosen to be measurable functions defined on $[t_0, t_1]$, with the condition $0 \leqslant u(t) \leqslant 1$. The most drug efficacy is in the case $u = 1$, which means that CD_4^+T cells are not infected by viral load any more while $u = 0$ indicates that the drug does not change the disease progression.

4. POWER SERIES METHOD

In [3], theoretical considerations and applications of the power series method have been discussed. In the sequel, we use this method to

obtain the control $u(t)$, satisfying $0 \leqslant u(t) \leqslant 1$, for the chemotherapy of HIV. The procedure follows:
From initial conditions, the solution of (2.1) - (2.4) can be expressed as:

$$X(t) = 820 + a_1 t \tag{4.1}$$
$$Y(t) = b_1 t \tag{4.2}$$
$$Z(t) = c_1 t \tag{4.3}$$
$$V(t) = 1 + d_1 t \tag{4.4}$$

Substituting (4.1) - (4.4) into (2.1) - (2.4) and neglect high order term $O(t)$, we obtain

$a_1 = 4.73232, b_1 = 0.019680, c_1 = 0$ and $d_1 = -(6.76 + 0.24u)$.

We have used some of the following data [2, 11] in the process

$$\mu_1 = 0.02/d, \mu_2 = 0.03/d, \mu_3 = 0.24/d, \mu_4 = 7/d$$
$$k_1 = 0.000024mm^3/d, k_2 = 0.003/d, k_3 = 0.0002/d, r = 0.03/d$$
$$\beta = 0.24/d, L = 1200, N_{max} = 1500mm^{-3}, s = 10mm^{-3}$$

Next, suppose

$$X(t) = 820 + a_1 t + a_2 t^2 \tag{4.5}$$
$$Y(t) = b_1 t + b_2 t^2 \tag{4.6}$$
$$Z(t) = c_1 t + c_2 t^2 \tag{4.7}$$
$$V(t) = 1 + d_1 t + d_2 t^2 \tag{4.8}$$

On substitution into (2.1) - (2.4) and neglecting $O(t^2)$ yields

$$a_2 = 5.012351790 + 0.0023616u, b_2 = -(0.06652065 + 0.0023616u), c_2 = 0.00003148 \text{ and } d_2 = 23.77999803 + 0.72u.$$

Consequently, repeating the same procedure by extending the series solutions term by term we have

$$X(t) = 820 + a_1 t + a_2 t^2 + a_3 t^3 + a_4 t^4 + a_5 t^5 + a_6 t^6 + a_7 t^7 + ... \tag{4.9}$$
$$Y(t) = b_1 t + b_2 t^2 + b_3 t^3 + b_4 t^4 + b_5 t^5 + b_6 t^6 + b_7 t^7 + ... \tag{4.10}$$
$$Z(t) = c_1 t + c_2 t^2 + c_3 t^3 + c_4 t^4 + c_5 t^5 + c_6 t^6 + c_7 t^7 + ... \tag{4.11}$$
$$V(t) = 1 + d_1 t + d_2 t^2 + d_3 t^3 + d_4 t^4 + d_5 t^5 + d_6 t^7 + d_2 t^7 + ... \tag{4.12}$$

Where the values of the coefficients are given in the tables below:

Table 1. Values of the coefficients a_i of the power series.

i	a_i
3	3.139672051-0.00471917092u
4	$2.753 + 0.008654u + 3.4007 \times 10^{-9}u^2$
5	$1.6070 - 0.011872u - 1.3583 \times 10^{-8}u^2$
6	$2.10374 + 0.01401u + 3.8350 \times 10^{-8}u^2 - 4.5343 \times 10^{-16}u^3$
7	$0.9781 - 0.01389u - 8.3454 \times 10^{-8}u^2 - 5.0729 \times 10^{-15}u^3$

Table 2. Values of the coefficients b_i of the power series.

i	b_i
3	$0.1559 + 0.004719u$
4	$0 - .2723 - 0.008653u - 3.4007 \times 10^{-9}u^2$
5	$0.3814 + 0.01187u + 1.3490 \times 10^{-8}u^2$
6	$-0.4448 - 0.01401008264u - 3.8035 \times 10^{-8}u^2 + 4.5343$ $\times 10^{-16}u^3$
7	$0.4449 + 0.01389u + 8.2688 \times 10^{-8}u^2 + 4.8179 \times 10^{-15}u^3$

Table 3. Values of the coefficients c_i of the power series.

i	c_i
3	$-0.00008234 - 0.000002834u$
4	$0.0001756 + 0.00000625u + 2.8339 \times 10^{-8}u^2$
5	$-0.0003318 - 0.00001416u - 1.1468 \times 10^{-7}u^2$
6	$0.0005882 + 0.00002875u + 3.2562 \times 10^{-7}u^2 + 2.7206$ $\times^{-14}u^3 + 0.0005882$
7	$-0.0009898 - 0.00005378u - 7.1166 \times 10^{-7}u^2 - 1.61472$ $\times 10^{-13}u^3$

Table 4. Values of the coefficients d_i of the power series.

i	d_i
3	$-55.4067 - 1.7599u$
4	$97.0216 + 3.0199u - 2.8481 \times 10^{-8}u^2$
5	$-135.7821 - 4.2759u + 1.5344 \times 10^{-7}u^2 + 1.1336 \times 10^{-12}u^3$
6	$-135.7821 - 4.2759u + 1.5344 \times *10^{-7}u^2 + 1.1336 \times 10^{-12}u^3$
7	$-158.4169 - 4.9829u + 0.12018 \times 10^{-5}u^2 + 1.4636 \times 10^{-11}u^3$ $+7.7730 \times 10^{-19}u^4$

Now, since the therapeutic period requires that $t_1 - t_0 < 2$ years, it suffices to assume that the objective function (3.1) becomes

$$J(u) = \int_0^1 \left(X(t) - \frac{B}{2} u(t)^2 \right) \tag{4.13}$$

Applying (4.9) into (4.13) and differentiating $J(u)$ with respect to u, we have

$$J'(u) = -0.0003762 - 2.0967 \times 10^{-15} u^2 + (-1.307390475 \times 10^{-8} - B)u. \tag{4.14}$$

For $B = 30$ [2,12], the control u is obtained by setting $J'(u) = 0$ and since the second derivative $J''(u) < 0$, we show that $J(u)$ is maximized.

5. DISCUSSION OF RESULTS

Beside the power series method, numerical solutions for the CD_4^+T cells and virus concentrations are generated using an iterative method by Runge-Kutta fourth order scheme with Mapple 13 package. The graphical illustrations are presented hereunder:

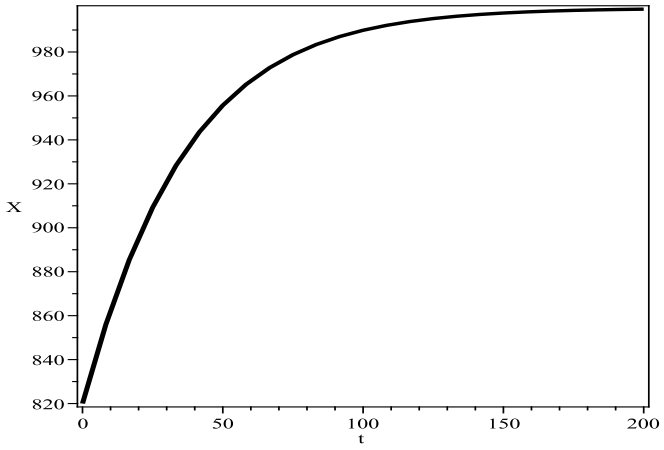

Fig. 1. Healthy cells behavior in the optimal control $B = 30$.

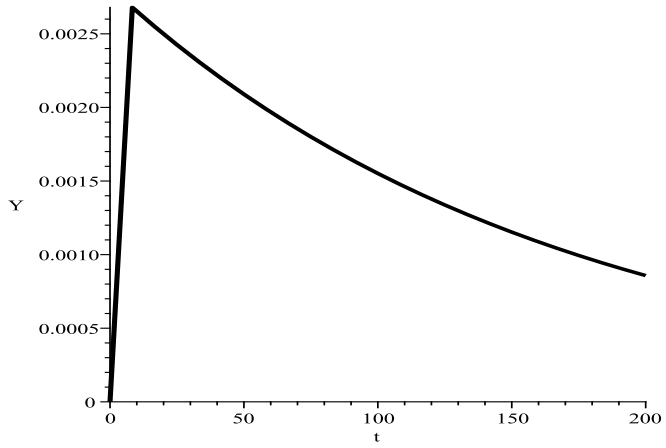

Fig. 2. Latently infected cells behavior in the optimal control $B = 30$.

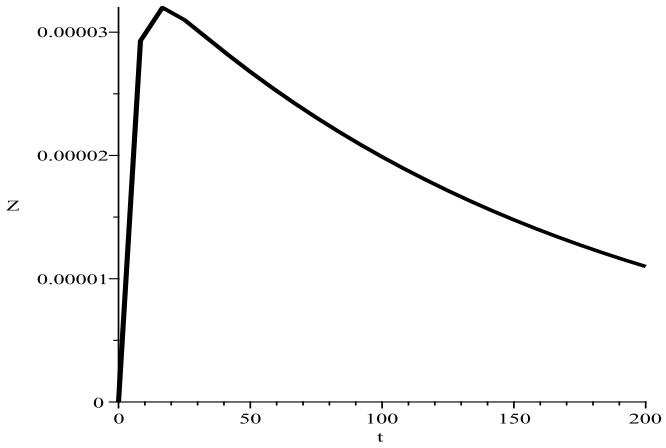

Fig. 3. Actively infected cells behavior in the optimal control $B = 30$.

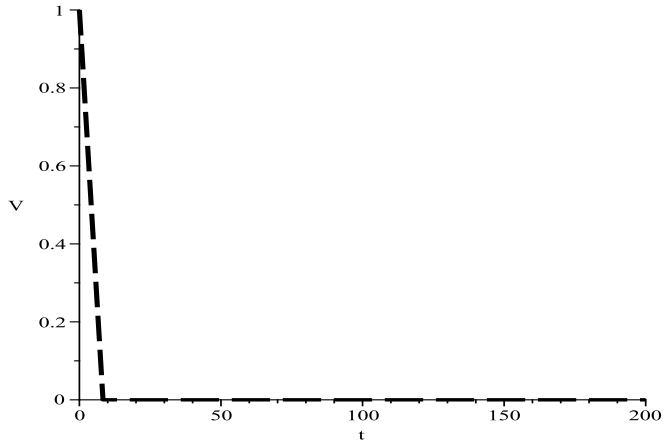

Fig. 4. Viral load behavior in the optimal control $B = 30$.

In Figure 1, the count of uninfected CD_4^+T cells is maximized by selecting proper amount of drugs for the control of HIV. In reality, the number of CD_4^+T cells experiences less decrease and later picks up during the therapeutic period. Figures 2 and 3 show the behavior of latently and actively infected cells as the cells grow due to the mutation of free virus particles but later reduce as a result of the therapeutic treatment.

Aslo in Figure 4, the viral load behavior experiences decrease during therapeutic period. Thus the control u, satisfying $0 \leqslant u(t) \leqslant 1$, ensures that the cost and risk of the medicine consumption for the treatment of HIV is minimized.

6. CONCLUDING REMARKS

We have presented a deterministic model which describes the interaction between HIV and CD_4^+T of the human body. We demonstrated how power series method could be used to generate control $0 \leqslant u(t) \leqslant 1$ that maximizes the count of the T-cells and minimizes the viral load with the side effects of the chemotherapy used for HIV positive patient.

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DEPARTMENT OF PURE AND APPLIED MATHEMATICS, LADOKE AKINTOLA UNIVERSITY OF TECHNOLOGY, P. M. B. 4000, OGBOMOSO, NIGERIA.
E-mail address: solaniyi@lautech.edu.ng

DEPARTMENT OF PURE AND APPLIED MATHEMATICS, LADOKE AKINTOLA UNIVERSITY OF TECHNOLOGY, P. M. B. 4000, OGBOMOSO, NIGERIA.
E-mail address: badmurs0@gmail.com

DEPARTMENT OF PURE AND APPLIED MATHEMATICS, LADOKE AKINTOLA UNIVERSITY OF TECHNOLOGY, P. M. B. 4000, OGBOMOSO, NIGERIA.
E-mail address: isaac.sola@yahoo.com