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Full Length Research Paper

Presentation of a fast solution for solving HIV-infection dynamics and chemotherapy optimization based on fuzzy: AVK method

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The issue of including the most optimal amount of medicine consumption in the program of illness control program is important in the control of HIV because of its high cost and high risk of side effects (poisoning), so applying a mathematical model and modern technique are necessary in solving optimal control problem for prescribing optimal amount. In this paper two ordinary differential equations systems which models interaction between HIV viruses and human body immune system is used. In addition, A. V. Kamyad (AVK) discretization method is introduced and is used to solve the mathematical models. The results are then extended to the other domain points of the mathematical model by a fuzzy inference estimator.

Key words: A. V. Kamyad (AVK) method, fuzzy approximator, optimal control, HIV-infection dynamics.

INTRODUCTION

HIV has become a global problem. The humans suffering due to HIV and AIDS are enormous. AIDS is now the leading cause of death in Sub-saharan Africa. Many countries in this region have failed to bring the epidemic under control. It is said that nearly two thirds of the world's HIV positive people live in Sub-saharan Africa. There is a significant impact on African economies by HIV/AIDS as the number of people falling ill and subsequently dying from AIDS has a tremendous effect on demography, household, health, educational and economic aspects.

Various medicine therapies have been used for achieving an optimal solution for medicine therapy of HIV in people with HIV up to now. There is a question: What is the best medicine therapy for these patients knowing that therapeutic period is limited? The answer maybe an ordinary differential equation model which describes the interaction between HIV viruses and human body immune system and then applying a suitable optimal control on the system of equations using a suitable medicine program (Ledzewicz and Schattler, 2002; Fister et al., 1998).

During HIV infection, strong humoral immune responses and also HIV specific cellular immune are created, in spite of these patients's antiviral immunes responses encounters sustainable immune defect and illness development and HIV causes failure of almost all the immune system elements. Its main cause is the pollution of CD4+T cells by HIV viruses which finally results in body immune system failure. CD4+Ts are responsible in coordination of immune system responses and HIV reproduces through polluting them and immune system activation and weaken immune system. The main target of HIV is T cells with CD4 receptors, that is, CD4+T cells. In other words, existence of CD4 receptors is necessary for HIV is entering into a cell. In fact activation of T cells prepares condition for HIV reproduction in

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them (Radisavljevic-Gajic, 2009).

METHODOLOGY

At the beginning of the 1980s when AIDS became epidemic, many attempts were made for controlling this fatal illness by biologists and medical associations. Meanwhile mathematicians made a big contribution by making mathematical models which illustrate interaction among viruses and human body immune cells. When medical associations began their research on new medicines for preventing illness development in new therapeutical strategies, developed mathematical models were used in the experiments and these models were completed each year to provide better mathematical model.

Many mathematical models have been developed in order to understand the dynamics of HIV infection. In this paper, we first study a simple system of equations modelling interactions between blood cells, the immune system and the HIV/AIDs virus. More precisely, we study the following nonlinear system of ordinary differential equations (Nabendra and Robert, 2008):

$$\frac{dV}{dt} = aY - bV \quad (1)$$

$$\frac{dX}{dt} = c - dX - \beta XV \quad (2)$$

$$\frac{dY}{dt} = \beta XV - fV - \gamma YZ \quad (3)$$

$$\frac{dZ}{dt} = g - hZ \quad (4)$$

Where; V = Number of viruses in an organism; X =Number of uninfected target cells; Y =Number of infected cells; Z =Immune system response cells; a = Rate of viruses reproduction; b =Rate of death of viruses; c = Reproduction of uninfected cells; d =Death rate of uninfected cells; β =Multiplying constant to being infected; f =Death rate of infected cells; g = Reproduction rate of cells Z; h =Death rate of cells Z and γ =Multiplying constant to the elimination of infected cells.

The evolution process described by the equations (1) to (4) is as follows. The virus is replicated by the infected cells, so its rate of production is taken proportional to *Y* and dies at a specific rate *b.* The uninfected cells are constantly being produced by the organism at a rate *c*, they die at a rate *d* , and become infected by the virus at rate *βV* , thereby entering the *Y* class. Infected cells die at rate *f* = *e* + *d* where *d* is the natural death rate and *e* the additional death rate owing to the infection. The relationship between the virus and uninfected cells is analogous to that of predator and prey models (Ledzewicz and Schattler, 2002; Fister et al., 1998; Zadeh, 1989; Nabendra and Robert, 2008; Britton, 2003; Arrowsmith and Place, 1996; Ghiasi et al., 2011). Thus *βX* is a functional response of the virus to the uninfected cells. We refer the reader to other reference sources for more detailed models (Arrowsmith and Place, 1996; Ghiasi et al., 2011). This model have some weakness like we have never understanding about effect of drug so in this condition we can not planning any drug schedule for period of chemotherapy.

Now we introducing another mathematical model of HIV; the most important elements in this model include three types of CD4+Tcells: uninfected CD4+T cells which their condensation is illustrated by X(t) variable, latently infected CD4+T cells which their condensation is illustrated by Y(t) variable, actively infected CD4+T cells which their condensation is illustrated by Z(t) variable. V(t) shows the rate of condensation of free viruses and dynamic model of these four variables is modeled by following equations (Ledzewicz and Schattler, 2002):

$$\frac{dX}{dt} = \frac{s}{1+V(t)} - \mu_X X(t) - k_X V(t)X(t) + rX(t)\left(1 - \frac{X(t)+Y(t)+Z(t)}{N_{max}}\right) \quad (5)$$

$$\frac{dY}{dt} = k_X V(t)X(t) - \mu_Y Y(t) - K_Y Y(t) \quad (6)$$

$$\frac{dZ}{dt} = K_Y Y(t) - \mu_Z Z(t) \quad (7)$$

$$\frac{dV}{dt} = \left(1 - u(t)\right)L\mu_Z Z(t) - k_X V(t)X(t) - \mu_V V(t) \quad (8)$$

In these equations, expressions of μ_x, μ_y, μ_z, μ_v, with negative signs indicate the rate of natural death of uninfected CD4+T cells, latently infected CD4+T cells, actively infected CD4+T cells and free cells. $K_x V(t)X(t)$ expression is deducted from two equations of viruses populations (8) and healthy cells (5) and added to latently infected cells population Equation (6). K_y is the rate at which latently infected cells are converted to actively infected cells. Parameter of *r* shows the rate of population growth in CD4+T cells and *s* parameter shows source term for uninfected CD4+T. N_{max} indicates maximum CD4+T cells level and control variable *u(t)* shows amount of the effect of chemical medicines on system. $L\mu_Z Z(t)$ indicates the number of produced viruses by infected CD4+T cells with rate *L* and is added to virus population Equation (8) and deduced by a factor of *u(t)* which indicates effect of medicine during therapeutic period from viruses population Equation (8), (Ledzewicz and Schattler, 2002).

Optimal control of model

This control indicates a percentage of effect of medicine therapy on interaction between CD4+T and HIV viruses which is illustrated by *u(t)* , Although there are many side effects in medicine therapy and in wrong prescription of the amount of medicine for these causes virus resistance toward medicine or lead to poisoning. So therapeutic period must be limited (Ledzewicz and Schattler, 2002).

In most of medicine therapies therapeutic period is less than 2 years (Denise et al., 1997). For the aim of keeping the level of healthy CD4+T cells higher and keeping side effects of medicine therapy low, The following target function is used for maximizing above dynamics:

$$\int_{t_{start}}^{t_{final}} \left(X(t) - \frac{1}{2}Bu(t)^2\right)dt \quad (9)$$

where for most of a the HIV chemotherapy drugs:

$$t_{final} - t_{start} < 2years$$

The integrand *X* indicates that one wants to maximize the number of uninfected CD4+T cells. At the same time, the second term minimizes the negative effects of the chemotherapy where *B* > 0 represents a desired "weight" on the benefit and cost (Ledzewicz and Schattler, 2002; Fister et al., 1998). The model is a nonlinear

and solving the problem is difficult and there is no specific method for it. In next section, In addition to introducing AVK discretization method, we convert mentioned model to a problem of linear programming and use it is solve the model.

AVK method

The method is systematically described and will result in an approximate analytic solution for the strongly nonlinear ODEs. For linearization, we use relation below (Badakhshan et al., 2007):

$$f(x) \cong f(s) + (x - s)f'(s) \quad (10)$$

Suppose f' is not defined in *s*. we introduce weak differentiation for calculating differentiation in *s* we have:

$$f'(s) = \lim_{x \to s} \frac{f(x) - f(s)}{x - s} \quad (11)$$

Given $\varepsilon > 0$, for all $x \in (s - \varepsilon, s + \varepsilon)$, we define:

$$f'(s) = \lim_{x \to s} \frac{f(x) - f(s)}{x - s}, \qquad x \in (s - \varepsilon, s + \varepsilon) \quad (12)$$

We can extended above approach to *n* dimensional.

Theorem 1

Consider the nonlinear smooth function $f : [0, 1]^n \to R$. Then the optimal solution of the following optimization problem is the function $f'(x)$.

$$min_{p(.)} \int_0^1 \int_0^1 \dots \int_0^1 |f(x) - [f(s) + p(s).(x - s)]| dx_1 dx_2 \dots dx_n \quad (13)$$

where $s = (s_1, s_2, \dots, s_n) \in [0, 1]^n$ is an arbitrary point and *p(.)* is a vector of the form $(p_1(.), p_2(.), \dots, p_n(.))$.
Proof (Vaziri et al., Unpublished).

Now based on theorem (1) the following definition may be stated for nonsmooth functions.

Definition

Let $f: [0, 1]^n \to R$ is a non-smooth function. The global weak differentiation with respect to *x* in the sense of l_1 space is defined as the *p(.)* the optimal solution of the minimization problem which is shown in (13).

In the case that $n = 1$, we may obtain differentiation of *f(x)* on *[0, 1]* by partitioning interval *[0, 1]* to *n* subinterval of *[xi−1, xi]* such that $x_i = \frac{i}{n}$ for all $i = 1, 2, \dots, n$. Let s_i be a point in $[\frac{i-1}{n}, \frac{i}{n}]$. We show differentiation of *f(x)* at $x = s$ by *p(s)*. We may obtain values of *p(s)*, by solving the following problem:

$$min \sum_{i=1}^{n} \int_{x_{i-1}}^{x_i} |f(x) - f(s_i) - (x - s).p(s_i)| dx \times \frac{1}{n} \quad (14)$$

where $x_i = \frac{i}{n}$ and $s_i \in (x_{i-1}, x_i)$ is an arbitrary point for all *i = 1, 2, . . . , n*. (note: we may define $s_i = \frac{2i-1}{2n}$ for all *i = 1, 2, . . . , n*)

Using fuzzy estimator for extension AVK method

Fuzzy Logic, which was developed in early 1960s, provides a tool to deal with uncertainty and human reasoning (Zadeh, 1989).

Here, we propose a fuzzy estimator. In previous section we introduced AVK method. This method is very useful in finding a discrete proximate solution but this method has a weakness due to the proximate solution is limited on special points and we do not have any information about other domain points. This fuzzy inference engine can help us to find an approximate solution without resolving NLP problems for other points.

RESULTS

Applying a fast and parsimonious solution in solving the simple model of HIV/AIDs

A fast and parsimonious solution will be applied to approximate solving the nonlinear system of ordinary differential equations by using the proposed method discussed earlier. We can renovate the Equations (1) to (4) equal as:

$$\frac{dV}{dt} - aY + bV = 0 \quad (15)$$

$$\frac{dX}{dt} - c + dX + \beta XV = 0 \quad (16)$$

$$\frac{dY}{dt} - \beta XV + fV + \gamma YZ = 0 \quad (17)$$

$$\frac{dZ}{dt} - g + hZ = 0 \quad (18)$$

we can assume the integral span from 0 to 1 and following (13):

$$G(v_1, v_2, \dots, v_n, x_1, x_2, \dots, x_n, y_1, y_2, \dots, y_n, z_1, z_2, \dots, z_n) = min \sum_{i=1}^{5} \int_{\frac{i+1}{5}}^{\frac{i}{5}} (V' - aY + bV)^2 + (X' - c + dX + \beta XV)^2 + (Y' - \beta XV + fV + \gamma YZ)^2 + (Z' - g + hZ)^2 dt \times \frac{1}{5} \quad (19)$$

for V' and X', Y', Z' we have (10), using Equations (19), for $x = 0.2$.

Now our nonlinear equation simply converted to a linear programming problem and it's very easy to solve. Finally we will extend it to the other domain points of

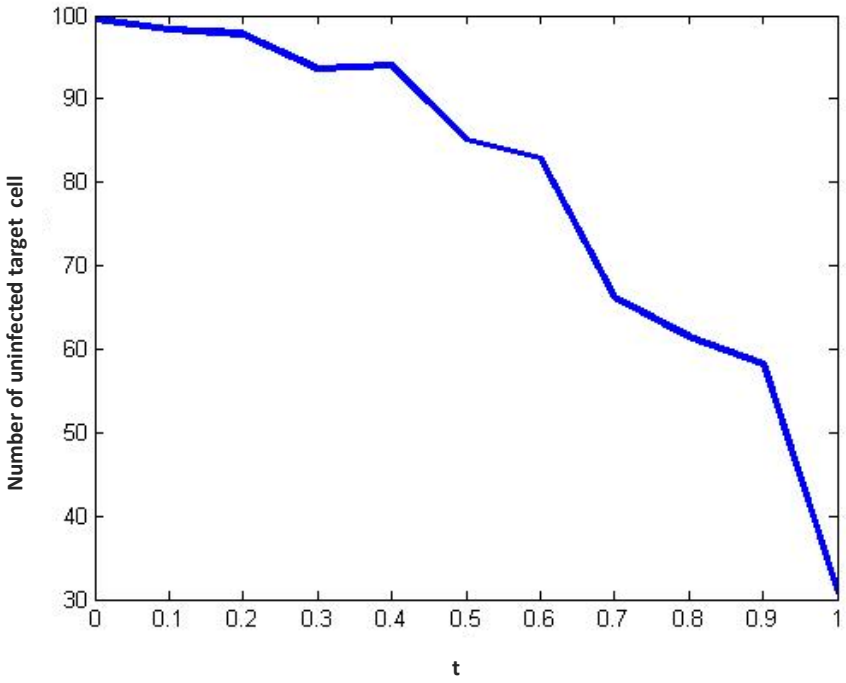

Figure 1. *X* cells behavior.

equation by a fuzzy inference estimator (Ghiasi et al., 2011).

We solve equation (19) in our proposed method and get answers of the unknowns of the problem according to Figures 1 and 2. In solving equation (19) we use following values for constants of the problem and initials conditions (Ledzewicz and Schattler, 2002):

These values were used for the constants in numerical calculations:

1. β=0.015: Rate at which uninfected cells becomes infected.
2. ^{a}=224.06: Rate of virus reproduction.
3. b=2.4: Rate of death of viruses.
4. c=6: Reproduction of uninfected cells.
5. d=0.1:Death rate of uninfected cells.
6. f=0.4:Death rate of infected cells.
7. x=100: initial x.
8. y=0: Initial y.
9. v=4 initial v.

Applying AVK method in solving optimal control model

Since therapeutic period must be less than 2 years, we assumed the HIV chemotherapy drugs period is:

$$t_{final} - t_{start} < 600\ days$$

We can assume the integral span from 0 to 20 and with resolving of this integral you can find the efficient monthly amount of drug and the level of CD4+T cells and viruses in every 30 days of treatment.

We assume equation (9) as the objective function for solving optimal control model and assume equations (5) to (8) as objective functions constraints and solve them by using AVK method. By placing equations (9) in (13) we can find:

$$min \sum_{i=1}^{n} \int_{0}^{20} [X(t) - \frac{1}{2} Bu(t)^2] dt \times \frac{1}{n} \quad (20)$$

For objective functions constraints, Equations (5) to (8) are placed in (13) as above. Thus the problem is converted to a linear programming problem which is solved easily. We solve equation (20) in AVK method and get answers of the unknowns of the problem according to Figures 3 to 5. In solving equation (20) we use following values for constants of the problem and initials conditions (Fister et al., 1998):

X_0 =820 $/mm^3$
V_0=1 $/mm^3$

These values were used for the constants in numerical calculations:

1. $^{\mu_x}$ = 0.02/d: Death rate of uninfected and latently

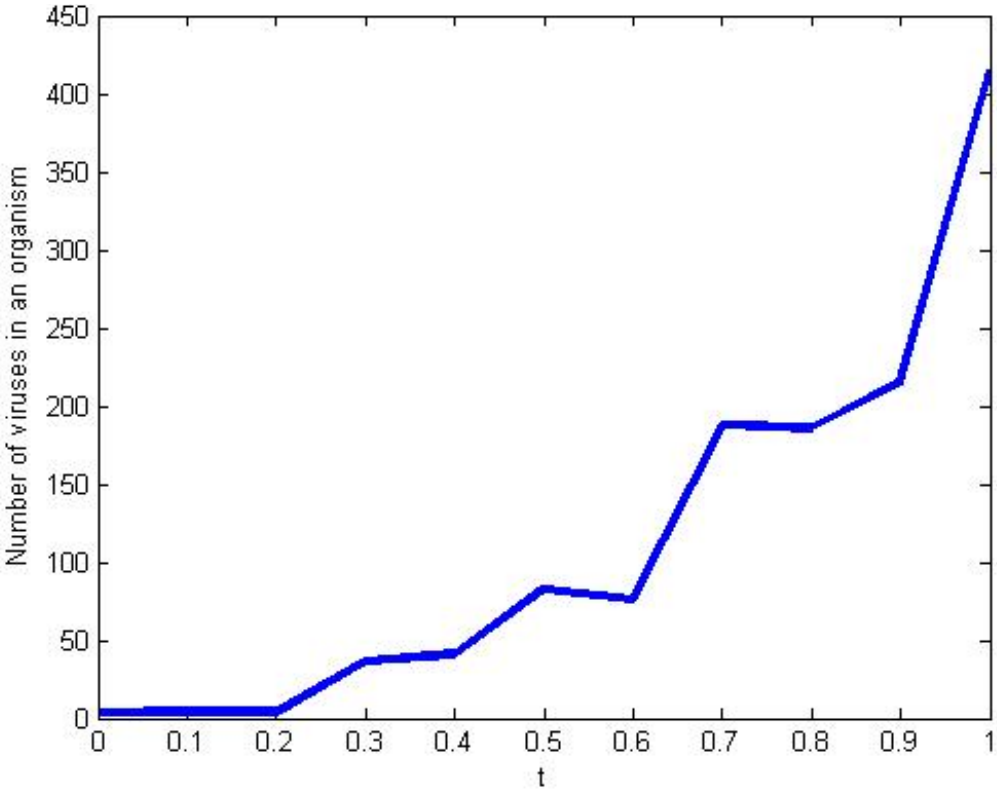

Figure 2. Viral load behavior.

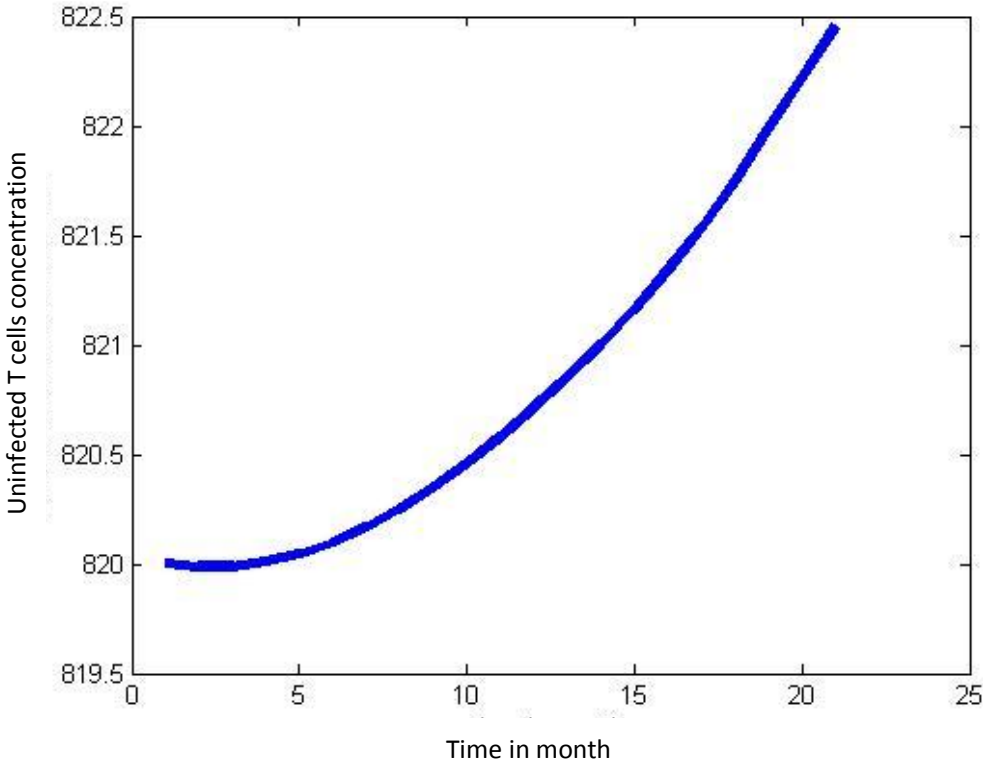

Figure 3. *T* cells behavior in the optimal control for every month (B=60).

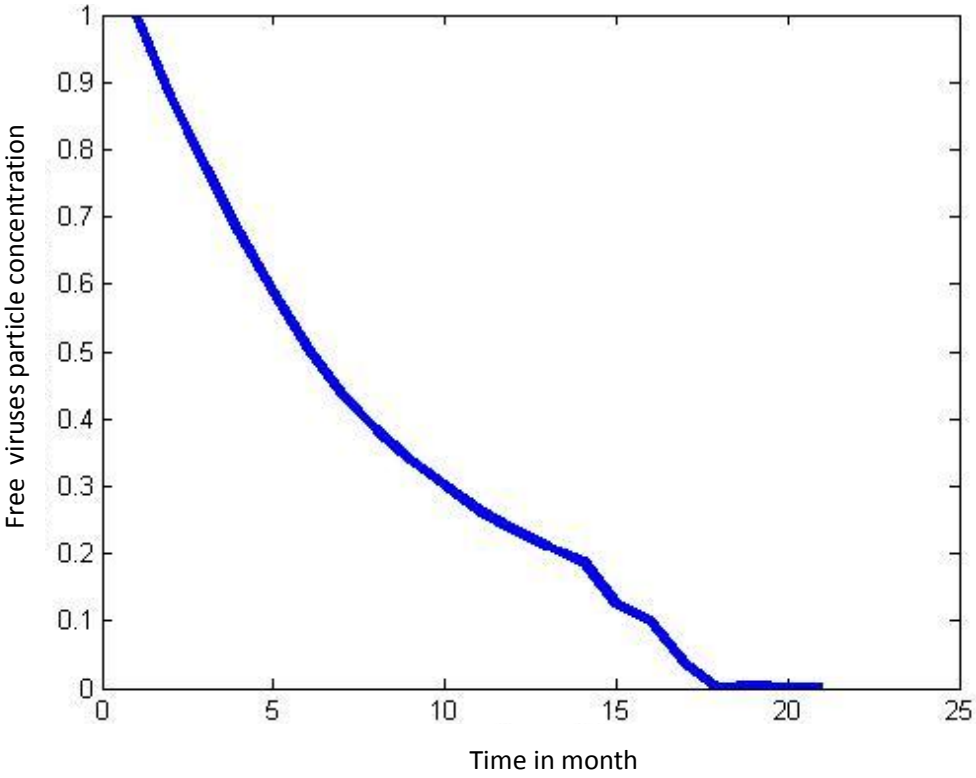

Figure 4. Viral load behavior in the optimal control for every month (B=60).

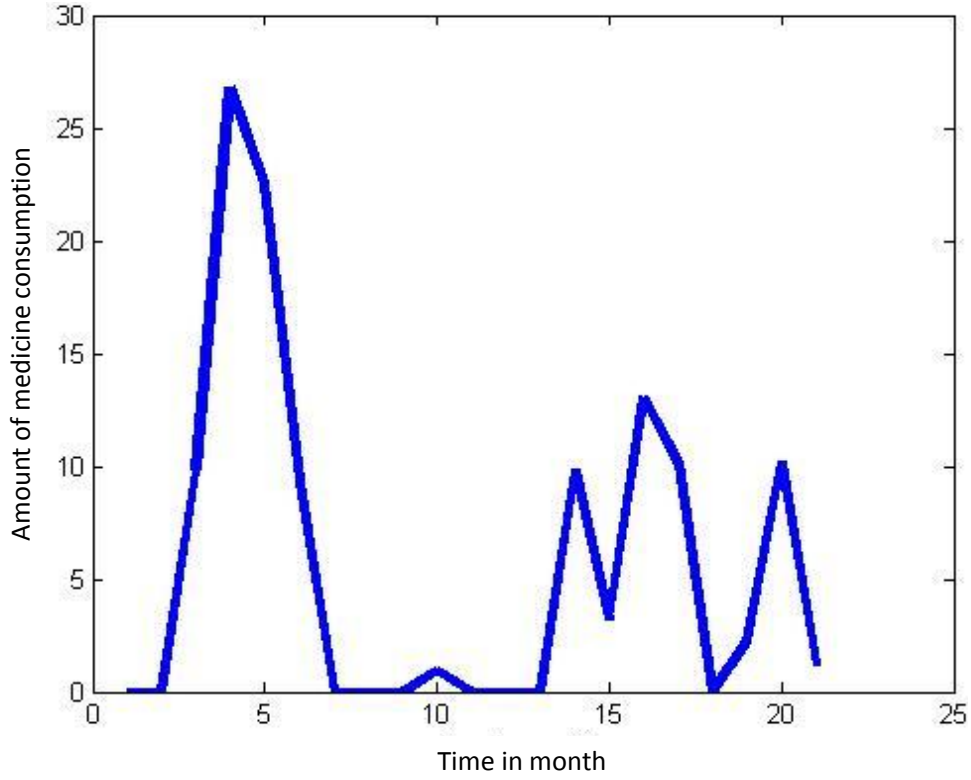

Figure 5. Amount of medicine consumption in the optimal control for every month (B=60).

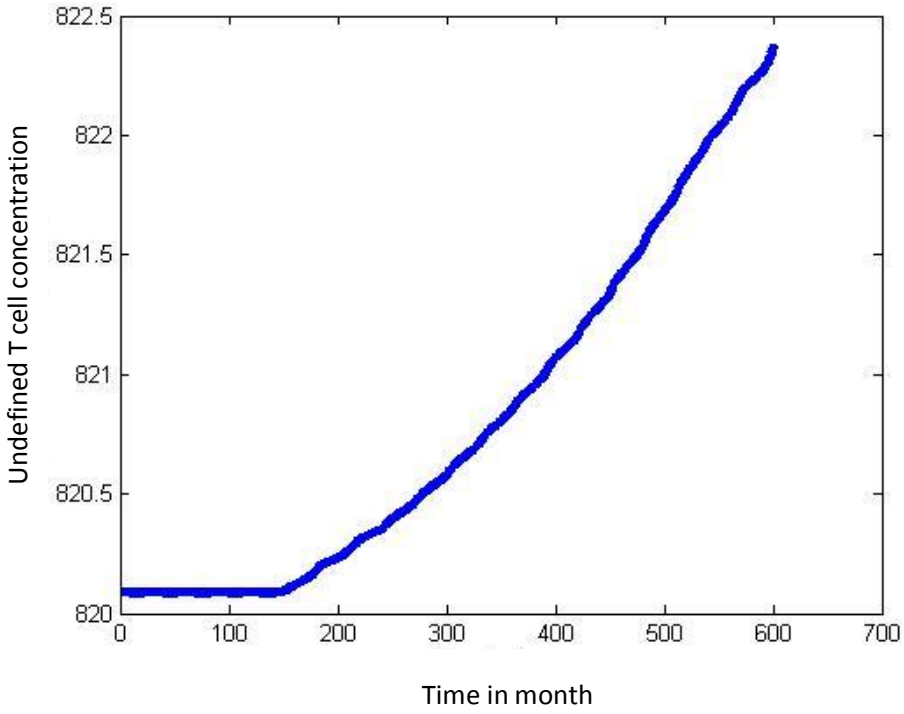

Figure 6. *T* cells behavior in the optimal control for everyday (B=60).

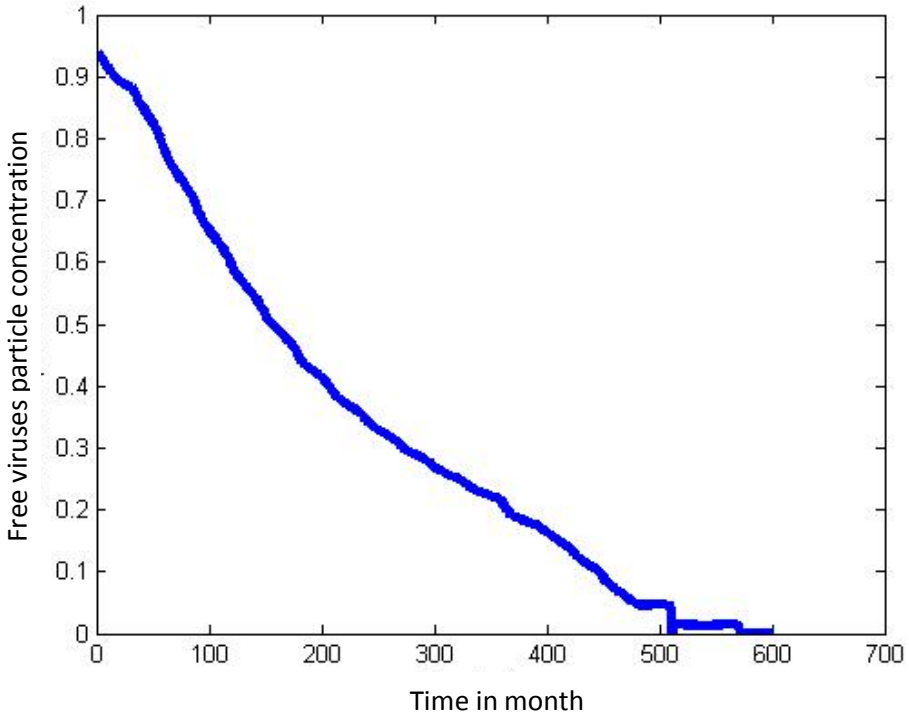

Figure 7. Viral load behavior in the optimal control for everyday (B=60).

infected CD4+T cells.

2. μ_z = 0.24/d: Death rate of actively infected cells.

3. μ_v = 2.4/d: Death rate of free virus.

4. K_x = 0.000024 mm^3/d: Rate at which CD4+T cells

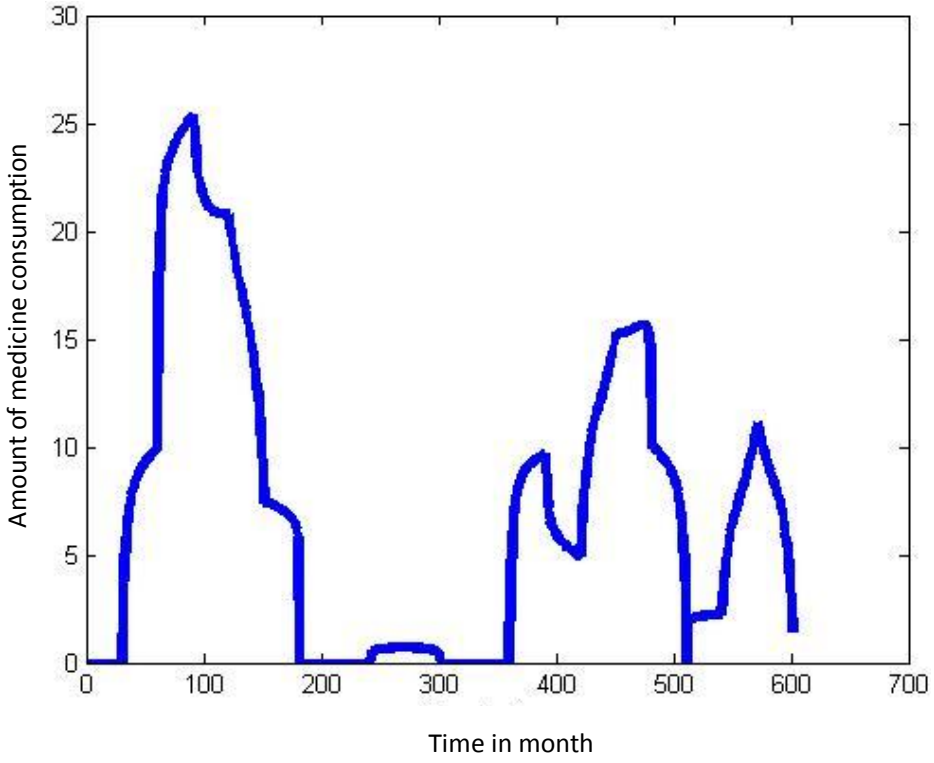

Figure 8. Amount of medicine consumption in the optimal control for everyday (B=60).

become infected by free virus.

5. K_Y = 0.003/d: Rate at which Y cells convert to actively infected.
6. r = 0.03/d: Rate of growth for the CD4+T cells.
7. N = 1200: Number of free virus produced by *Z* cells.
8. N_{max} = 1500/mm^3: Maximum CD4+T cell level.
9. s = 10/mm^3: Source term for uninfected CD4+T.

Now with using a fuzzy inference engine can find the efficient daily amount of drug and the level of CD4+T cells and viruses in everyday and get answers of the unknowns of the problem according to Figures 6 to 8.

Conclusion

We have applied a fast and Parsimonious solution for a simple HIV/AIDs finite dimensional mathematical model on interactions of the blood cells and a optimal control model of HIV and used AVK discretization method for its approximate solution and extended its result with fuzzy inference engine for other days without solving any equation or calculating the complex solution again. The results of model solution indicate that in spite of medicine consumption and optimal control on model, the rate of CD4+T increased and viruses' population decreased. It is shown that proposed method is fast, it's effective and reliable in nonlinear and non smooth equations.

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