Turkish Journal of Electrical Engineering & Computer Sciences

http://journals.tubitak.gov.tr/elektrik/

Research Article

Turk J Elec Eng & Comp Sci
(2020) 28: 3111 – 3125

doi:10.3906/elk-1906-65

Effects of sliding mode control antiretroviral drug on HIV-1 viral load

Musharif AHMED[1,*], **Saad ZAFAR**[1], **Muhammad Aamer SALEEM**[2], **Muhammad ZUBAIR**[1], **Ijaz Mansoor QURESHI**[3]

[1]Department of Software Engineering & Computer Science, Faculty of Computing, Riphah International University, Islamabad, Pakistan

[2]Department of Electrical Engineering, Faculty of Engineering Science and Technology, Hamdard University, Islamabad, Pakistan

[3]Department of Electrical Engineering & Computer Engineering, Faculty of Engineering, Air University, Islamabad, Pakistan

Received: 12.06.2019 • **Accepted/Published Online:** 28.05.2020 • **Final Version:** 30.11.2020

Abstract: Human immunodeficiency virus (HIV) has devastating effects on human society. Researchers have proposed many models for the decay of $CD4^+$ T cells, the growth of infected cells, and viral load. In this paper, four first-order nonlinear coupled differential equations have been considered. Four variables are $CD4^+$ T cells, which are healthy, less infected cells, more infected cells capable of producing virus, and finally the viral load. Apart from the two drug therapies, protease inhibitor (PI) and reverse transcriptase inhibitor (RTI), which have already been considered in the literature, we have proposed antiretroviral drug (ARD) that works as sliding mode controller. We have used numerical methods to study the effect of RTI, PI, and ARD on healthy cells, infected cells, and the viral load. We have expressed our solutions in terms of log sigmoid functions and used memetic computing for the solution which is a hybridization of GA, a global optimizer, and sequential quadratic programming, a local optimizer. ARD, as a sliding mode controller, does help to improve the situation of the HIV patient, especially, in further reducing the viral load and also decreasing the infected cells which have the potential to produce virus. This helps in giving relief to the patient and an increase in life expectancy.

Key words: Sliding mode control, antiretroviral drug, drug therapy, HIV/AIDS, memetic computing

1. Introduction

Due to the catastrophic effect of HIV on human society, it has motivated the researchers to formulate accurate and representative models for this disease. Usually, the models for HIV in the literature are represented by three or four first-order nonlinear coupled differential equations. They investigate the internal dynamics of the infected cells, the target cells, viral production, viral clearance, and the impact of antiretroviral drugs in the treatment [1–4].

Being a retrovirus, HIV primarily targets the $CD4^+$ T cells, which are an integral part of the human immune system. It diminishes the $CD4^+$ T cells and thus lowers the resistance of the immune system. [1, 5, 6]. During the infection process, HIV inserts its genetic material RNA into the host cell by binding itself to the $CD4^+$ T cell. As a consequence, viral RNA is reversely transcribed into DNA and is integrated into the genome of the host cell through integrase. On the activation of the cell, the production of viral RNA starts. The viral

*Correspondence: musharif.ahmed@riphah.edu.pk

particles come out of the infected cells and start infecting other $CD4^+$ T cells [7]. This process of life cycle for the virus continues and finally breaks down the human immune system.

It is known that even after three decades of the first emergence of HIV, there is no absolute cure; therefore, different methods for its treatment are suggested. The recommended methods include both preventive and treatment measures. The preventive methods are used to reduce the number of new HIV infections, whereas treatment measures are used with the objective of increasing life expectancy of the patients and reducing the rate of HIV transmission in the already infected persons. Various clinical trials have been carried out to develop different treatment measures and investigate their risks and gains in order to determine the optimal treatment. As different host–pathogen interaction mechanisms are not known, the questions like the best treatment combination, optimal dosage cannot be answered yet [8].

Drugs like protease inhibitors (PIs) and reverse transcriptase (RTIs) are used to inhibit enzymes that are used in the replication cycle. The role of the entry inhibitors is to prevent a virus from entering into a cell. The main responsibility of enzyme integrase is to integrate the HIV DNA to human DNA, while the integrase inhibitors are used to suspend the activity of enzyme integrase. The virus multiplication and the enzyme action are directly blocked by reverse transcriptase inhibitors (RTIs). Production of infectious virus particles from infected cells is prevented through protease inhibitors (PIs). Since the virus replication rate is extremely high, effective therapies for HIV integrate concurrent administration of two or more antiretroviral drugs. [9–12].

Most of the mathematical models use optimal control theory to assist in treatment strategies for infected patients. Optimal control theory finds optimal ways of controlling a dynamical system [13]. Specifically, it helps to decide the optimal dosage for different types of available drugs. Optimal control problems are studied to determine the effects of these drugs. For instance, Srivastava et al. [14] considered an initial infection model with reverse transcriptase inhibitors (RTIs). The study claimed that an infected cell reverts to susceptibility by using RTIs. Hattaf et al. [15] analyzed two optimal treatments of HIV infection model. The study aimed at measuring the efficiency of RTIs and PIs. Kamboj et al. [16] proposed a model and also analyzed the effect of joint drug therapy, i.e. RTI and PI, on different parameters involved in the dynamics of T cells.

In this paper, we have proposed an antiretroviral drug in the form of a sliding mode controller. We have used a novel sliding surface and proved that it takes a finite time to reach this surface. This directly affects and reduces the viral load of the HIV patient. The decrease in viral load does help to increase the expectancy of life for HIV patients. For numerical solution, we have used log sigmoid functions which are entire domain basis functions. We have used a genetic algorithm to find the coefficients as a global optimizer, while sequential quadratic programming has been used as a local optimizer. The use of hybrid algorithms, known as memetic computing, is a recent phenomenon that has become popular in the last decade [17–22].

The rest of the paper is organized as follows. Section 2 gives an HIV model without drug therapy. Section 3 gives HIV model with drug therapy. Section 4 gives the proposed antiretroviral drug as a sliding mode controller, Section 5 gives the heuristic method for solving the equations. Section 6 gives the results and discussion while Section 7 concludes and gives future directions.

2. HIV model without drug therapy

HIV model without RTI and PI drug therapy is given below by four coupled nonlinear differential equations.

$$\frac{dT}{dt} = p - \mu T + rT(1 - \frac{T + I_1 + I_2}{T_{max}}) - kVT + cI_1 \tag{1}$$

$$\frac{dI_1}{dt} = kVT - \mu_1 I_1 - \delta_1 I_1 - cI_1 \tag{2}$$

$$\frac{dI_2}{dt} = \delta_1 I_1 - \delta_2 I_2 \tag{3}$$

$$\frac{dV}{dt} = N\delta_2 I_2 - \mu_v V \tag{4}$$

T represents the number of $CD4^+$ T cells present in a blood unit. I_1 represents the infected T cells prior to reverse transcription (pre-RT class) and are not yet capable of producing virus. I_2 denotes the number of infected T cells for which the reverse transcript has been accomplished and has the potential to produce a virus. It is called the post-RT class. V represents the count of virus particles.

Here in Eq. (1), p represents the rate of supply of healthy $CD4^+$ T cells from precursors in thymus while μ is the natural death rate. The T cells can also be created by the reproduction of existing T cells; therefore, the term $rT(1 - \frac{T+I_1+I_2}{T_{max}})$ is more realistic to represent the proliferation of T cells. The proliferation is density-dependent and decreases as T cell count increases and stops when it is equal to T_{max}. A portion of the infected class for which the transcription process is not completed may revert to uninfected class and is represented with c. kVT represents the infection of healthy T cells. μ_1 in Eq. (2) is the rate of death of infected cells, while δ_1 represents the rate of transition from pre-RT infected class to productively infected class (post-RT). δ_2 in Eq. (3), represents the death rate of actively infected cells and takes into account the bursting of infected T cells, while N is the average amount of viral particles produced by an infected cell. μ_v in Eq. (4) represents the viral clearance rate. The variables and parameters of the model are summarized in Table.

Table . Parameters used in the model.

Term	Description
T	Number of $CD4^+$ T cells measured in a unit of blood
p	Rate of supply of healthy T cells from precursors in thymus
μ	Average per capita death rate of T cells
r	Average growth rate in the absence of population limitation
I_1	Density of infected T cells before reverse transcription takes place (pre-RT class) not yet capable of producing virus
I_2	Post-RT class represents the density of infected T cells in which reverse transcript is completed and are capable of producing virus
c	Reverting rate of infected T cells
μ_1	Death rate of infected T class
k	Interaction infection rate of T cells
δ_1	Rate at which pre-RT class cells (I_1) leave and join the productively infected class (post-RT class)
δ_2	Death rate of actively infected cells which includes the bursting of infected cells
$\delta_2 I_2$	Production of viral particles at an average rate of N per infected cell of I_2 class
μ	Clearance rate of virus

3. HIV model with drug therapy

Earlier models, proposed by Perelson [23, 24], were used and extended by various researchers to understand the various aspects of HIV in order to devise and analyze the effects of drug therapy interventions [3–5, 25, 26].

Most of the existing RTI-based drug therapy models [12, 27, 28] consider the effect of a drug only on the interaction-infection rate. The role of RTI is to inhibit the reverse transcription only after the virus has entered the host cell but it does not directly affect the interaction-infection rate. It is important to note that the effect of reverse transcription takes place before an infected T-cell starts producing virus particles [16]. Using these facts, infected cells are divided into two different classes, namely, pre-RT class and post-RT class [29]. The infected cells for which the reverse transcription has not been finished are represented by pre-RT class whereas the infected cells that have completed the reverse transcription process and are capable of producing new virus are represented by the post-RT class. It is also studied in [14] that a fraction of the infected cells may revert to uninfected cells. Also, some of the infected cells in the pre-RT class will revert to uninfected class because RTI may stop the reverse transcription. Since no drug is effective in total, despite drug therapy, only a fraction of infected cells in the pre-RT class will revert to uninfected cells and the remaining cells in this class will progress to complete the reverse transcription and will be producing virus by becoming productively infected. Various models based on pre-RT class and post-RT class are proposed and the effect of RTI [14] and drug inhibitor called PI [30] is analyzed on the dynamics of HIV. Kamboj et al. [16] proposed a model and analyzed the effect of combined drug therapy, RTI plus PI on the growth of T cells, and decrease of viral load of different parameters involved in the dynamics of T cells.

Let there be an RTI drug with efficiency η_R. Without RTI drug $\delta_1 I_1$ cells were leaving the pre-RT class and going to post-RT class. With RTI drug having efficacy $\eta_R, \delta_1 I_1$ cells is divided into two classes. $\eta_R \delta_1 I_1$ cells from pre-RT class join back to healthy T cells, while $(1-\eta_R)\delta_1 I_1$ join the post-RT class. kVT represents the loss of healthy cells in Eq. (5) and it is also a source term for infected cells in Eq. (6). PI, with efficacy $\eta_P \in (0,1)$, causes post-RT cells to produce noninfectious virions with rate $\eta_P N$. Thus, $(1-\eta_P)N$ is the rate of production of infectious virions which PI has not been able to inhibit. The noninfectious virions $\eta_P N$ do not play any role in the dynamics of T, I_1, I_2 and V.

Thus, HIV model with RTI + PI drug therapy is modified as follows:

$$\frac{dT}{dt} = p - \mu T + rT(1 - \frac{T + I_1 + I_2}{T_{max}}) - kVT + cI_1 + \eta_R \delta_1 I_1 \tag{5}$$

$$\frac{dI_1}{dt} = kVT - \mu_1 I_1 - \delta_1 I_1 - cI_1 \tag{6}$$

$$\frac{dI_2}{dt} = (1-\eta_R)\delta_1 I_1 - \delta_2 I_2 \tag{7}$$

$$\frac{dV}{dt} = (1-\eta_P) N \delta_2 I_2 - \mu_v V \tag{8}$$

Remodified HIV model with RTI + PI drug therapy, along with the antiretroviral drug (ARD) that directly affects the viral load, has the same first three equations (5-7). However, the last equation is modified

as follows:

$$\frac{dV}{dt} = (1-\eta_P)N\delta_2 I_2 - \mu_v V + u(t) \tag{9}$$

where u(t) represents the antiretroviral drug.

4. Proposed antiretroviral drug as sliding mode controller

We consider the two critical equations for I_2 and V in Eq. (7) and Eq. (9) and use sliding surface $\sigma = mI_2 + V$

where $m > 0$ is a design parameter. Using Eq. (7) and Eq. (9) we get

$$\dot{\sigma} = m\dot{I}_2 + \dot{V} = (1-\eta_R)m\delta_1 I_1 + ((1-\eta_P)N - m)\delta_2 I_2 - \mu_V V + u(t) \tag{10}$$

The controller $u(t)$ is designed below in Eq. (11):

$$u(t) = -\varrho sgn(\sigma) - ((1-\eta_P)N - m)\delta_2 I_2 + \mu_v V \tag{11}$$

Substitute Eq. (11) in Eq. (10) we get:

$$\dot{\sigma} = (1-\eta_R)m\delta_1 I_1 - \varrho sgn(\sigma) \tag{12}$$

Multiply Eq. (12) by σ and use the fact $\sigma sgn(\sigma) = |\sigma|$ we get:

$$\sigma\dot{\sigma} = -\varrho|\sigma| + \sigma(1-\eta_R)m\delta_1 I_1 \leq -\varrho|\sigma| + |\sigma|(1-\eta_R)m\delta_1 I_1$$

$$\sigma\dot{\sigma} \leq -|\sigma|(\varrho - (1-\eta_R)m\delta_1 I_1)$$

Let

$$\varrho = (1-\eta_R)m\delta_1 T_{max} + \eta \qquad where \quad \eta > 0 \tag{13}$$

$$\sigma\dot{\sigma} \leq -|\sigma|\big[(1-\eta_R)m\delta_1(T_{max} - I_1) + \eta\big] \leq -\eta|\sigma| \qquad \text{since } T_{max} > I_1$$

Hence, we have achieved the reachability condition. The time to reach the sliding surface $\sigma = 0$ is given as

$$t_r \leq \frac{|\sigma(0)|}{\eta}$$

Substituting Eqs. (11) and (13) in Eq. (9) we get:

$$\begin{aligned} \dot{V} &= (1-\eta_P)N\delta_2 I_2 - \mu_V V - ((1-\eta_P)N - m)\delta_2 I_2 + \mu_V V - \big[(1-\eta_R)m\delta_1 T_{max} + \eta\big]sgn(\sigma) \\ &= m\delta_2 I_2 - ((1-\eta_R)m\delta_1 T_{max} + \eta)sgn(\sigma) \end{aligned} \tag{14}$$

Since $m \geq 0, I_2 \geq 0, V \geq 0$; hence, $\sigma \geq 0$

If $\sigma > 0$, $sgn(\sigma) = 1$ and Eq. (14) becomes:

$$\dot{V} = m\delta_2 I_2 - ((1-\eta_R)m\delta_1 T_{max} + \eta) \tag{15}$$

where m and η are to be adjusted to minimize the error.

This sudden dosage, which is like a step function, can be changed to the following case:

$$sgn(\sigma) = \frac{\sigma}{|\sigma|} \cong \frac{\sigma}{\sqrt{\sigma^2 + \epsilon}}$$

This continuous approximation of the sliding mode controller is more practical for the dosage. Just as in a system it avoids high-frequency chattering phenomenon, this will equivalently avoid or minimize any reaction in the human body. Moreover, with practical dosage, this ideal sliding is not there. The continuous control action drives the state to a neighborhood of the switching surface. In the literature, it is called pseudosliding.

Hence, if ϵ is very small, we shall hit the ideal surface $\sigma = 0$ at the cost of a sudden dosage to the patient. If ϵ is slightly large, we shall be giving dosage slowly to the patient but at the cost of staying away from ideal surface $\sigma = 0$ for a long time. Hence, an optimal ϵ needs to be chosen.

We shall look at the effect of this new $u(t)$ on virus rate V and uninfected cells T by solving these equations numerically.

5. Heuristic method for solving the equations

In order to solve this set of coupled nonlinear differential equations, we express T, I_1, I_2, and V as a linear combination of log sigmoid functions given as

$$\Phi(w_i, \theta_i, t) = \frac{1}{1 + \exp^{-(w_i t + \theta_i)}} \tag{16}$$

$$T = \sum_{i=1}^{n} a_i \Phi(w_i^a, \theta_i^a, t) \tag{17}$$

Similarly

$$I_1 = \sum_{i=1}^{n} b_i \Phi(w_i^b, \theta_i^b, t) \tag{18}$$

$$I_2 = \sum_{i=1}^{n} d_i \Phi(w_i^d, \theta_i^d, t) \tag{19}$$

$$V = \sum_{i=1}^{n} e_i \Phi(w_i^e, \theta_i^e, t) \tag{20}$$

$T(0) = 300,\ I_1(0) = 10,\ I_2(0) = 10,\ V(0) = 10$

The error term for Eq. (5) is given as follows:

$$\mathscr{E}_T = \frac{1}{11} \sum_{j=0}^{10} \Big[\frac{dT}{dt}(t_j) - p + \mu T(t_j) - rT(t_j)(1 - \frac{T(t_j) + I_1(t_j) + I_2(t_j)}{T_{max}}) + kV(t_j)T(t)j) - cI_1(t_j) - \eta_R \delta_1 I_1(t_j) \Big]^2$$

$$= \frac{1}{11}\sum_{j=0}^{10}\Big[\sum_{i=1}^{n} a_i\dot{\Phi}(w_i^a,\theta_i^a,t_j) - p + \mu\sum_{i=1}^{n} a_i\Phi(w_i^a,\theta_i^a,t_j) - r\sum_{i=1}^{n} a_i\Phi(w_i^a,\theta_i^a,t_j)$$
$$(1 - \frac{\sum_{i=1}^{n} a_i\Phi(w_i^a,\theta_i^a,t_j) + \sum_{i=1}^{n} b_i\Phi(w_i^b,\theta_i^b,t_j) + \sum_{i=1}^{n} d_i\Phi(w_i^d,\theta_i^d,t_j)}{T_{max}}) \tag{21}$$
$$+k\sum_{i=1}^{n} e_i\Phi(w_i^e,\theta_i^e,t_j)(\sum_{i=1}^{n} a_i\Phi(w_i^a,\theta_i^a,t_j)) - c\sum_{i=1}^{n} b_i\Phi(w_i^b,\theta_i^b,t_j) - \eta_R\delta_1\sum_{i=1}^{n} b_i\Phi(w_i^b,\theta_i^b,t_j)\Big]^2$$

Similarly, the error term for Eq. (6), (7) and (8) is given as follows:

$$\mathscr{E}_{I_1} = \frac{1}{11}\sum_{j=0}^{10}\Big[\sum_{i=1}^{n} b_i\dot{\Phi}(w_i^b,\theta_i^b,t_j) - k\sum_{i=1}^{n} e_i\Phi(w_i^e,\theta_i^e,t_j)\sum_{i=1}^{n} a_i\Phi(w_i^a,\theta_i^a,t_j) + (\mu_1+\delta_1+c)\sum_{i=1}^{n} b_i\Phi(w_i^b,\theta_i^b,t_j)\Big]^2 \tag{22}$$

$$\mathscr{E}_{I_2} = \frac{1}{11}\sum_{j=0}^{10}\Big[\sum_{i=1}^{n} d_i\dot{\Phi}(w_i^d,\theta_i^d,t_j) - (1-\eta_R)\delta_1\sum_{i=1}^{n} b_i\Phi(w_i^b,\theta_i^b,t_j) + \delta_2\sum_{i=1}^{n} d_i\Phi(w_i^d,\theta_i^d,t_j)\Big]^2 \tag{23}$$

$$\mathscr{E}_V = \frac{1}{11}\sum_{j=0}^{10}\Big[\sum_{i=1}^{n} e_i\dot{\Phi}(w_i^e,\theta_i^e,t_j) - (1-\eta_P)N\delta_2\sum_{i=1}^{n} d_i\Phi(w_i^d,\theta_i^d,t_j) + \mu_V\sum_{i=1}^{n} e_i\Phi(w_i^e,\theta_i^e,t_j)\Big]^2 \tag{24}$$

Four initial conditions given below need to be satisfied as well. Their error terms are given as follows;

$$T(0) = 300 \Rightarrow \mathscr{E}_{IC}^T = (\sum_{i=1}^{n} a_i\Phi(w_i^a,\theta_i^a,t=0) - 300)^2 \tag{25}$$

$$I_1(0) = 10 \Rightarrow \mathscr{E}_{IC}^{I_1} = (\sum_{i=1}^{n} b_i\Phi(w_i^b,\theta_i^b,t=0) - 10)^2 \tag{26}$$

$$I_2(0) = 10 \Rightarrow \mathscr{E}_{IC}^{I_2} = (\sum_{i=1}^{n} d_i\Phi(w_i^d,\theta_i^d,t=0) - 10)^2 \tag{27}$$

$$V(0) = 10 \Rightarrow \mathscr{E}_{IC}^{V} = (\sum_{i=1}^{n} e_i\Phi(w_i^e,\theta_i^e,t=0) - 10)^2 \tag{28}$$

Net error to be minimized is $\mathscr{E}$, given as follows:

$$\mathscr{E} = \mathscr{E}_T + \mathscr{E}_{I_1} + \mathscr{E}_{I_2} + \mathscr{E}_V + \mathscr{E}_{IC}^T + \mathscr{E}_{IC}^{I_1} + \mathscr{E}_{IC}^{I_2} + \mathscr{E}_{IC}^{V} \tag{29}$$

For sliding mode controller case, where the antiretroviral drug is given to directly finish the infectious virus, only the last equation has changed. The new equation is given as Eq. (14) and its error given by Eq.

(24) is modified as Eq. (30):

$$\mathscr{E}_{VSMC} = \frac{1}{11}\sum_{j=0}^{10}\Big[\sum_{i=1}^{n} e_i\dot{\Phi}(w_i^e,\theta_i^e,t_j) - m\delta_2\sum_{i=1}^{n} d_i\Phi(w_i^d,\theta_i^d,t_j) + m(1-\eta_R)\delta_1 T_{max} + \eta\Big]^2 \tag{30}$$

In order to minimize the error, we have to adjust the coefficients $\{a_i, b_i, d_i, e_i\}_{i=1}^{n}$. We use the genetic algorithm (GA) as a powerful heuristic technique along with local optimizer, sequential quadratic programming (SQP). Pseudosteps of GA and SQP are given below and the flowchart of the proposed solution is given in Figure 1.

Step 1: Initialization of GAs: The chromosomes in the initial population or generation are initialized by randomly generating real numbers between 2 and -2. Each chromosome consists of 120 genes, owing to 120 parameters to be optimized. The population consists of 100 chromosomes.

Step 2: Fitness evaluation: The fitness of each chromosome is evaluated using Eq. (29) above.

Step 3: Crossover and mutation: The chromosomes with higher fitness values are selected for crossover to generate a new chromosome for the next generation.

Step 4: Selection method for new population: Find the fitness of new children. For the new population, take fifty percent of the old population by choosing the best among them. Choose the next fifty percent of the new children by choosing the best among them in fitness.

Step 5: Termination criterion: The algorithm is stopped either depending on certain error value or the number of iterations.

Step 6: Initialization of SQP: After the termination of GA, the best-fit chromosome is handed over to SQP which is one of the most successful methods for the numerical solution of nonlinear optimization problems. Although it is a local search technique, its convergence is considerably fast.

Step 7: Fitness evaluation: Fitness evaluation is performed by using Eq. (29) as done in GA.

Step 8: Termination: If the proposed fitness is achieved, iteration stops else when the specified number of iterations is achieved, the algorithm stops.

6. Numerical simulation and discussion

Our main interest is to check the effects of drug therapies. Firstly, we would like to see the effect of the reverse transcriptase inhibitors (RTIs) that directly stops the enzyme action and multiplication of the virus and secondly, the effect of the protease inhibitors (PIs) that stop infected cells from producing infectious virus. Thirdly, we would like to see the effect of the antiretroviral drug (ARD) acting directly on HIV-1 viral load. This is our main contribution as we have fed in $u(t)$ in Eq. (9) for virus V and used sliding mode control and sliding surface as a linear combination of I and V. The constants that are adjusted, determined the dosage concentration.

The values of parameters have been taken from [14, 16, 23]. Initial conditions are $T(0) = 300mm^{-3}$, $I_1(0) = 10mm^{-3}$, $I_2(0) = 10mm^{-3}$, $V(0) = 10mm^{-3}$ $p = 10mm^{-3}/day$, $\mu = 0.01/day$, $k = 0.000024mm^{-3}/day$, $c = 0.05/day$, $\delta_1 = 0.4/day$, $\delta_2 = 0.26/day$, $\mu_1 = 0.015/day$, $\mu_V = 2.4/day$, $r = 0.03/day$, $T_{max} = 1500mm^{-3}$, $N = 1000$.

There are two main cases. The first case is when $u(t)$, as an antiretroviral drug, has not been used. Hence, $ARD = 0$. The second case is when $u(t)$ as sliding mode controller has been applied, i.e. $ARD \neq 0$. Each case has further subcases.

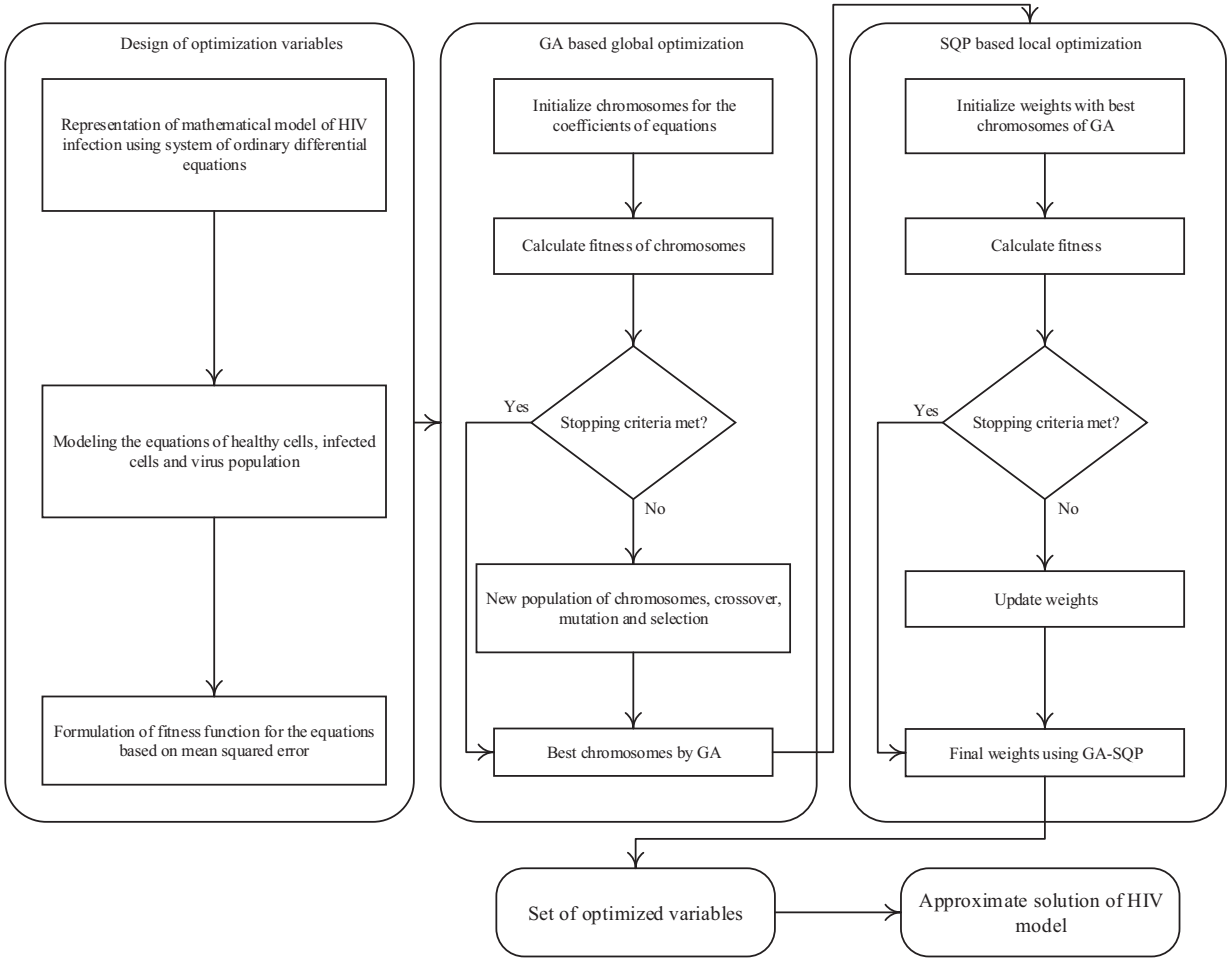

Figure 1. Flowchart of the proposed optimization algorithm using GA as global while SQP as local optimizer.

Case 1: ARD = 0

Subcase A: $RTI = 0,\ PI = 0$

In this case $\eta_R = \eta_P = 0$. $ARD = 0$ implies, $u(t)$ as a sliding mode controller, has not been used.

Subcase B: $RTI \neq 0,\ PI = ARD = 0$

Both the subcases A and B have been shown for T cells and viral load V in Figures 2a and 2b, respectively. One can observe that T cell population increases as η_R goes up from 0 to 0.9. Viral load as expected keeps decreasing in Figure 2b as η_R increases from 0 to 0.9.

In Figures 3a and 3b, we find the T cell population and viral load respectively when only PI drug therapy is applied, i.e. η_P efficacy is increased from 0.5 to 0.9. The T cell population improves with η_P. Similarly, the viral load decreases as η_P increases from 0.5 to 0.9. One should observe carefully that RTI prevents the pre-RT class to become a post-RT class and brings it back to healthy T cells. On the contrary, PI tries to prevent post-RT cells from producing viral load. Hence, RTI is more effective in increasing T cells while PI is more effective in decreasing viral load.

Subcase D: $RTI \neq 0,\ PI \neq 0$

In this, we vary drug efficacies, η_R and η_P, from 0.5 to 0.9.

As can be observed in Figure 4, $\eta_R = 0.5$, the T cells are increasing in the same respective manner as PI efficacy, η_P, increases from 0.5 to 0.9. Similarly, the viral load decreases with an increase in η_P. Similarly in Figures 5 and 6, better behavior is observed as η_R is increased from 0.7 to 0.9 along with the PI therapy, η_P increase from 0.5 to 0.9.

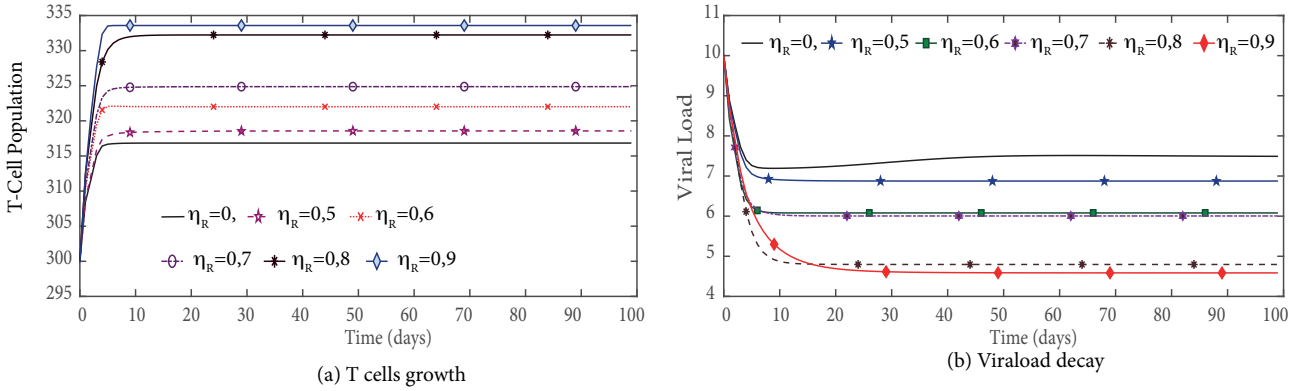

Figure 2. Growth of T cells and decay of viral load for subcases A and B where PI = 0 and RTI has different values

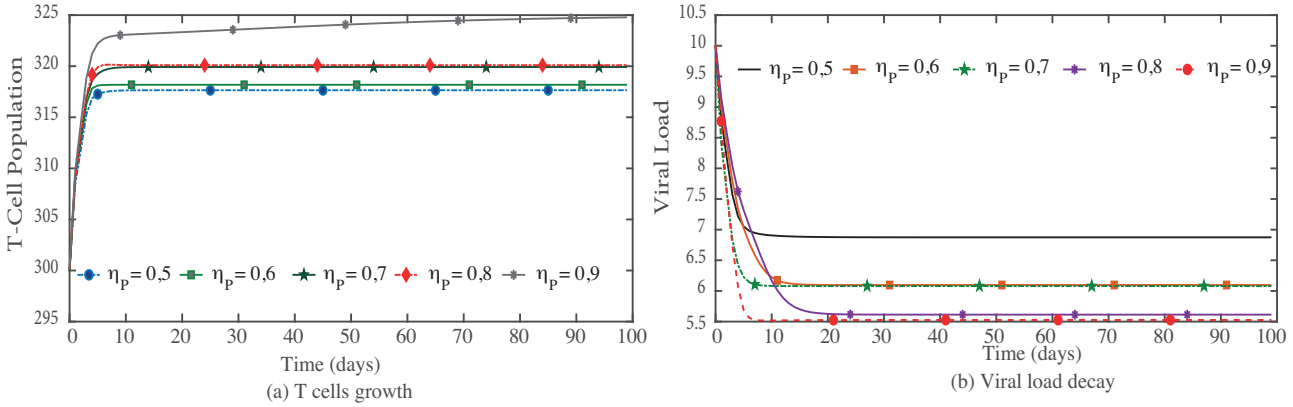

Figure 3. Growth of T cells and decay of viral load for subcase C where RTI = 0 and PI has different values

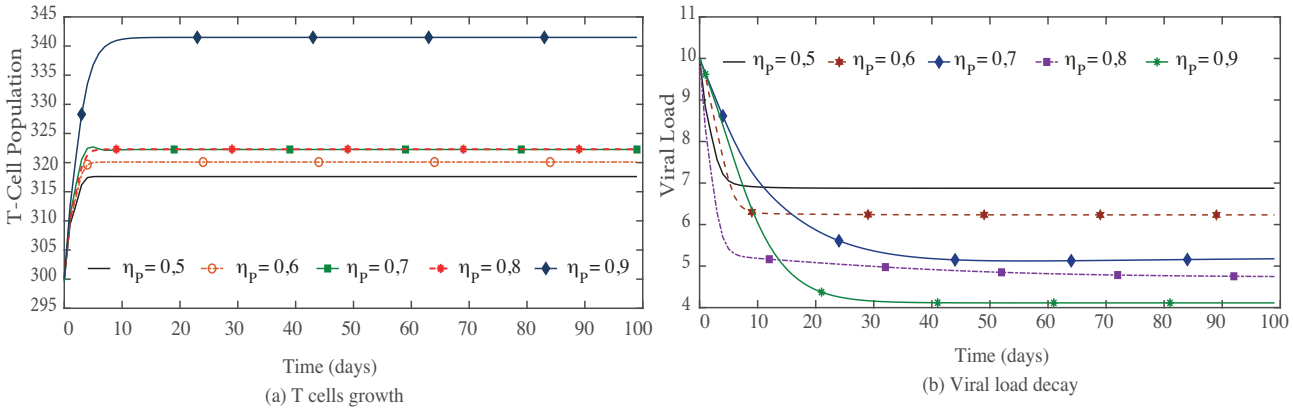

Figure 4. Growth of T cells and decay of viral load for the subcase D where RTI = 0.5 and PI has different values.

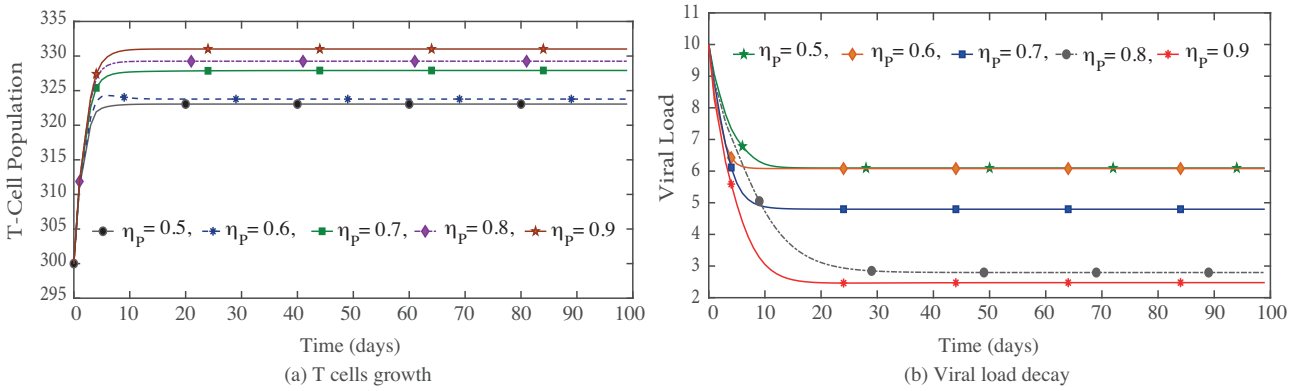

Figure 5. Growth of T cells and decay of viral load for the subcase D where RTI = 0.7 and PI has different values.

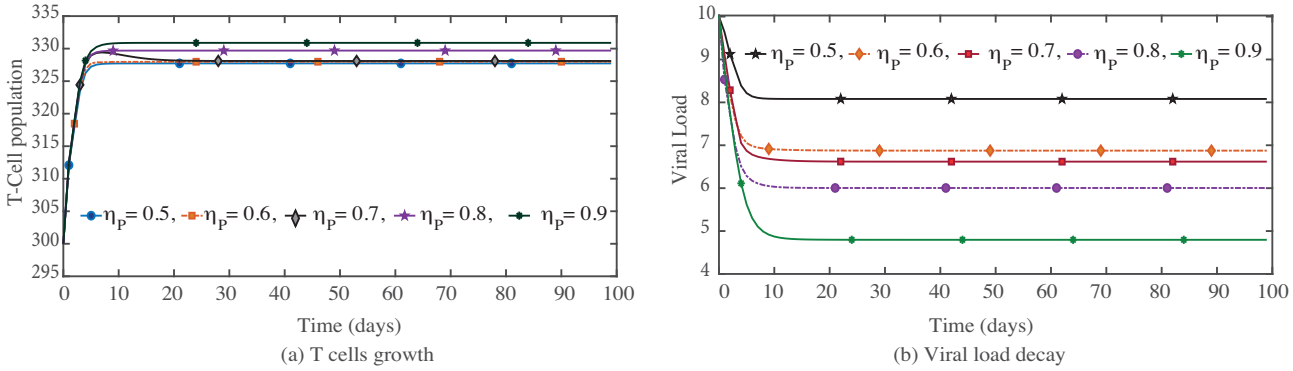

Figure 6. Growth of T cells and decay of viral load for the subcase D where RTI = 0.9 and PI has different values.

Case 2: $ARD \neq 0$

Subcase A: $RTI = PI = 0$

Subcase B: $RTI \neq 0,\ PI = 0$

Comparing Figure 2 ($\eta_R \neq 0,\ \eta_P = 0$ and $ARD \neq 0$) with Figure 7 ($\eta_R \neq 0,\ \eta_P = 0$ and $ARD = 0$), the viral load in Figure 7b is settling at lower levels compared with that of Figure 2b. We see its effect on viral load only, which in fact decreases. It does not increase T cell population.

Subcase C: $RTI = 0,\ PI \neq 0$

Figure 8 shows the case where η_P varies from 0.5 to 0.9 and $\eta_R = 0$. In this case, situation in T cells improves compared to the same case shown in Figure 3 ($\eta_R = 0,\ \eta_P = varying$ and $ARD = 0$). Similarly, viral load is decreased for the case $ARD \neq 0$ shown in Figure 8b compared to the equivalent case with $ARD = 0$ given in Figure 3b.

Subcase D: $RTI \neq 0,\ PI \neq 0$

In this case, where $\eta_R = 0.5$ while η_P varies from 0.5 to 0.9 shown in Figure 9, the ARD does not play a significant role, especially in T cells growth. However, the virus population does decrease compared to the same case when $ARD = 0$ which is given in Figure 4b.

Similarly in Figures 10 and 11, we do see improvement in T cells growth and comparative decrements in viral load if we compare these with Figures 5 and 6, respectively.

The performance of the sliding mode controller to increase healthy cells and to decrease viral load has proved to be better as compared to the cases where ARD, as sliding mode controller is not used. Beside better

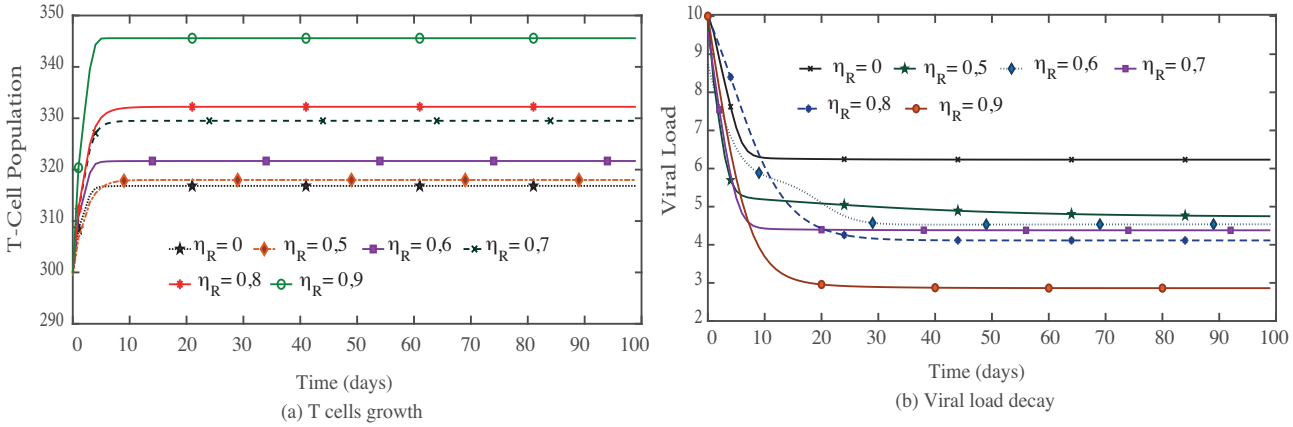

Figure 7. Growth of T cells and decay of viral load for the subcases A and B where PI = 0 and RTI has different values.

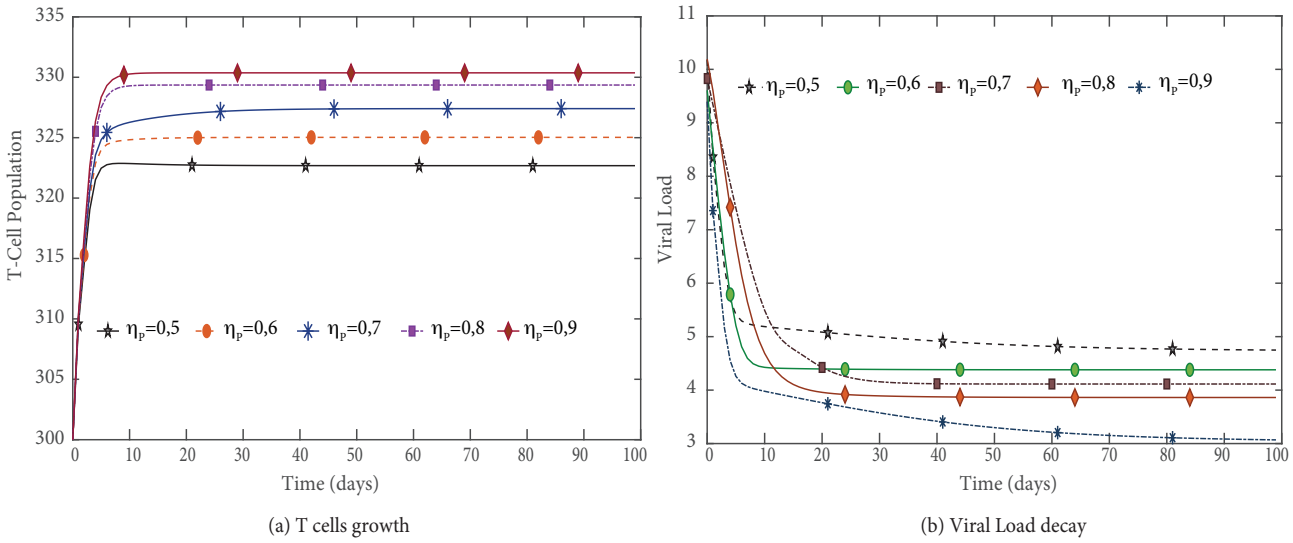

Figure 8. Growth of T cells and decay of viral load for the subcase C where RTI = 0 and PI has different values.

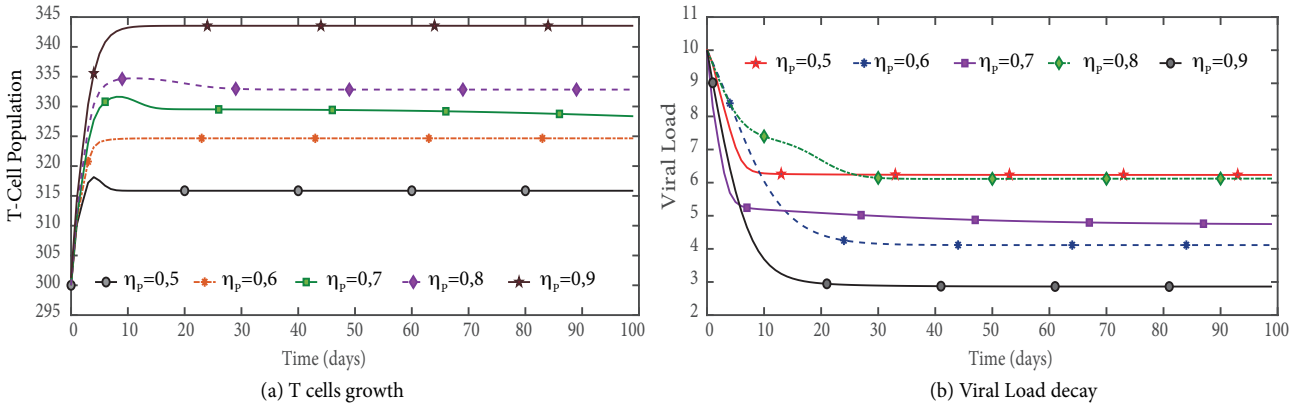

Figure 9. Growth of T cells and decay of viral load for the subcase D where RTI = 0.5 and PI has different values.

results, the mean squared error (MSE) is also very small. It dies down to 10^{-5} in 100 iterations as shown in Figure 12.

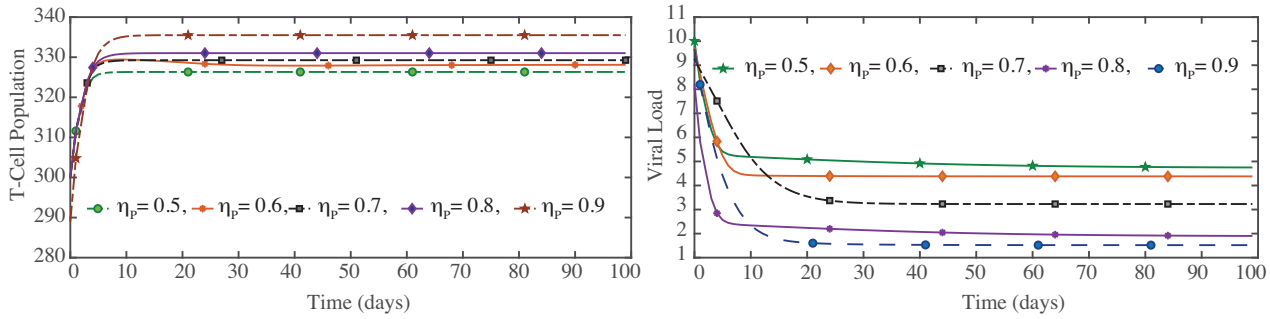

Figure 10. Growth of T cells and decay of viral load for the subcase D where RTI = 0.7 and PI has different values.

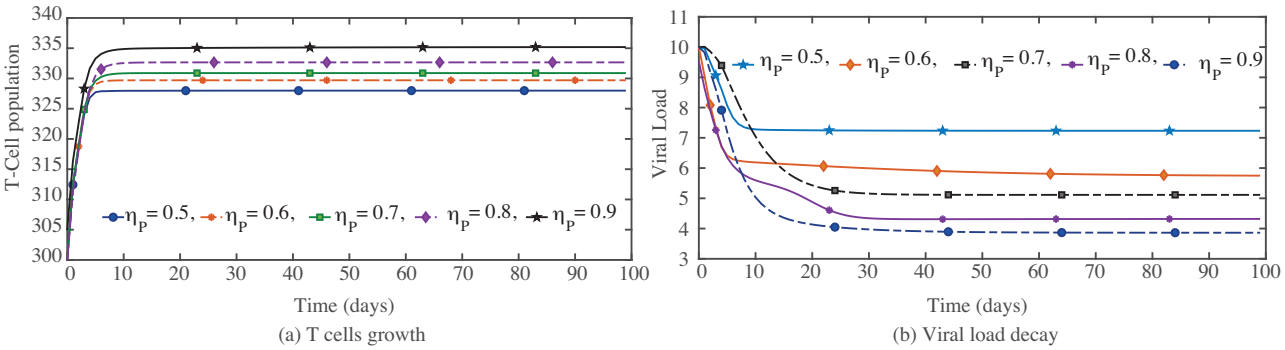

Figure 11. Growth of T cells and decay of viral load for the subcase D where RTI = 0.9 and PI has different values

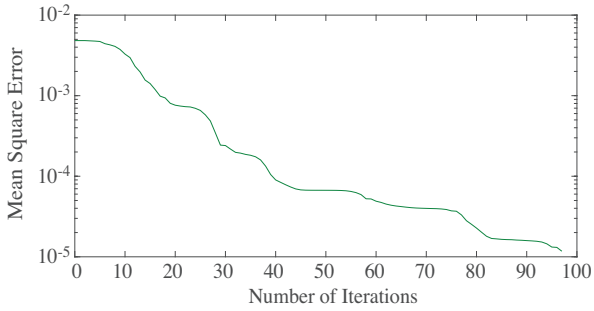

Figure 12. The convergence behavior of mean squared error.

7. Conclusion and future directions

The model used for HIV already exists in the literature. It is a classical epidemiological model considered in [16]. However, a modification has been made in the viral load equation. Apart from the protease inhibitor and reverse transcriptase inhibitor, we have introduced antiretroviral therapy as a sliding mode controller. It reduces the infected cells that have the potential to produce virus. Thus, viral load decreases on the HIV patient which results in increasing the life expectancy. In our further work, we shall make a study for finding the optimal dosage of the multitherapies in which time shall be taken as an important parameter. Moreover, we shall try to use a combination of a sliding mode controller and a synergetic controller to achieve better results.

References

[1] Perelson AS, Nelson PW. Mathematical analysis of HIV-1 dynamics in vivo. SIAM Review 1999; 41 (1): 3-44. doi: 10.1137/S0036144598335107

[2] Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM et al. Rapid turnover of plasma virions and cd4 lymphocytes in hiv-1 infection. Nature 1995; 373 (6510): 123. doi: 10.1038/373123a0

[3] Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. Hiv-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 1996; 271 (5255): 1582-1586. doi: 10.1126/science.271.5255.1582

[4] Bonhoeffer S, May RM, Shaw GM, Nowak MA. Virus dynamics and drug therapy. Proceedings of the National Academy of Sciences 1997; 94 (13): 6971-6976. doi: 10.1073/pnas.94.13.6971

[5] Wang L, Li MY. Mathematical analysis of the global dynamics of a model for hiv infection of cd4+ t cells. Mathematical Biosciences 2006; 200 (1): 44-57. doi: 10.1016/j.mbs.2005.12.026

[6] Nowak MA, May RM. Mathematical biology of hiv infections: antigenic variation and diversity threshold. Mathematical Biosciences 1991; 106 (1): 1-21. doi: 10.1016/0025-5564(91)90037-J

[7] Sierra S, Kupfer B, Kaiser R. Basics of the virology of hiv-1 and its replication. Journal of Clinical Virology 2005; 34 (4): 233-244. doi: 10.1016/j.jcv.2005.09.004

[8] Ngina P, Mbogo RW, Luboobi LS. Modelling optimal control of in-host hiv dynamics using different control strategies. Computational and Mathematical Methods in Medicine 2018; 2018: 9385080. doi: 10.1155/2018/9385080

[9] Dixit NM, Perelson AS. Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay. Journal of Theoretical Biology 2004: 226 (1): 95-109. doi: 10.1016/j.jtbi.2003.09.002

[10] Nowak MA, Bonhoeffer S, Shaw GM, May RM. Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations. Journal of Theoretical Biology 1997; 184 (2): 203-217. doi: 10.1006/jtbi.1996.0307

[11] Nelson PW, Mittler JE, Perelson AS. Effect of drug efficacy and the eclipse phase of the viral life cycle on estimates of hiv viral dynamic parameters. Journal of Acquired Immune Deficiency Syndromes 1999; 26 (5): 405-412.

[12] Nelson PW, Perelson AS. Mathematical analysis of delay differential equation models of hiv-1 infection. Mathematical Biosciences 2002; 179 (1): 73-94. doi: 10.1016/S0025-5564(02)00099-8

[13] Pontryagin LS. Mathematical Theory of Optimal Processes. 1st ed. London, UK: Routledge, 2018. doi: 10.1201/9780203749319

[14] Srivastava PK, Banerjee M, Chandra P. Modeling the drug therapy for hiv infection. Journal of Biological Systems 2009; 17 (02): 213-223. doi: 10.1142/S0218339009002764

[15] Hattaf K, Yousfi N. Two optimal treatments of hiv infection model. World Journal of Modelling and Simulation 2012; 8 (1): 27-36.

[16] Kamboj D, Sharma MD. Effects of combined drug therapy on hiv-1 infection dynamics. International Journal of Biomathematics 2016; 9 (5): 1650065. doi: 10.1142/S1793524516500650

[17] Junaid A, Raja MA, Qureshi IM. Evolutionary computing approach for the solution of initial value problems in ordinary differential equations. World Academy of Science, Engineering and Technology 2009; 3 (7): 578-5581

[18] Malik SA, Qureshi IM, Amir M, Malik AN. Nature inspired computational approach to solve the model for HIV infection of CD4 T cells. Research Journal of Recent Sciences 2014; 3 (6): 67-76.

[19] Kurdi M. An improved island model memetic algorithm with a new cooperation phase for multi-objective job shop scheduling problem. Computers & Industrial Engineering 2017; 111: 183-201. doi: 10.1016/j.cie.2017.07.021

[20] Jaddi NS, Abdullah S. Hybrid of genetic algorithm and great deluge algorithm for rough set attribute reduction. Turkish Journal of Electrical Engineering & Computer Sciences 2013; 21 (6): 1737-1750. doi: 10.3906/elk-1202-113

[21] Zahoor RMA, Khan JA, Qureshi IM. Evolutionary computation technique for solving Riccati differential equation of arbitrary order. World Academy of Science, Engineering and Technology 2009; 3 (10): 303-309.

[22] Ahmed M, Qureshi IM, Saleem MA, Zubair M, Zafar S. Between-host HIV model: stability analysis and solution using memetic computing. Turkish Journal of Electrical Engineering & Computer Sciences 2019; 27 (4): 2769-2783. doi: 10.3906/elk-1812-57

[23] Perelson AS, Kirschner DE, De Boer R. Dynamics of hiv infection of cd4+ t cells. Mathematical Biosciences 1993; 114 (1): 81-125. doi: 10.1016/0025-5564(93)90043-A

[24] Perelson AS. Modeling the interaction of the immune system with hiv. In: Chavez C (editor). Mathematical and Statistical Approaches to AIDS Epidemiology 1989, Berlin, Heidelberg: Springer, pp. 350-370.

[25] Smith HL, De Leenheer P. Virus dynamics: A global analysis. SIAM Journal on Applied Mathematics 2003; 63 (4): 1313-1327. doi: 10.1137/S0036139902406905

[26] Wodarz D, Hamer DH. Infection dynamics in HIV-specific CD4 T cells: does a CD4 T cell boost benefit the host or the virus?. Mathematical Biosciences 2007; 209 (1): 14-29. doi: 10.1016/j.mbs.2007.01.007

[27] Hu Z, Liu X, Wang H, Ma W. Analysis of the dynamics of a delayed hiv pathogenesis model. Journal of Computational and Applied Mathematics 2010; 234 (2): 461-476. doi: 10.1016/j.cam.2009.12.038

[28] Wang Y, Zhou Y, Wu J, Heffernan J. Oscillatory viral dynamics in a delayed hiv pathogenesis model. Mathematical Biosciences 2009; 219 (2): 104-112. doi: 10.1016/j.mbs.2009.03.003

[29] Rong L, Feng Z, Perelson AS. Mathematical analysis of age-structured hiv-1 dynamics with combination antiretroviral therapy. SIAM Journal on Applied Mathematics 2007; 67 (3): 731-756. doi: 10.1137/060663945

[30] Srivastava PK, Banerjee M, Chandra P. Dynamical model of in-host hiv infection: With drug therapy and multi viral strains. Journal of Biological Systems 2012; 20 (03): 303-325. doi: 10.1142/S021833901250012X