Congresso de Métodos Numéricos em Engenharia 2015
Lisboa, 29 de Junho a 2 de Julho 2015

A COMPARATIVE STUDY OF DIFFERENT OPTIMAL CONTROL STRATEGIES OF MEDICINE ADMINISTRATION FOR HIV VIRUS TREATMENT

Edilson F. Arruda[1*], Claudia M. Dias[2],Dayse H. Pastore[3], Roberto C. A. Thomé[3] and Hyan M. Yang[4]

1: Programa de Engenharia de Produção
Instituto Alberto Luiz Coimbra de Pós Graduação e Pesquisa de Engenharia
Universidade Federal do Rio de Janeiro
Centro de Tecnologia, Bloco F, sala 103, Ilha do Fundão. Caixa Postal 68507, 21941-972, Rio de Janeiro, RJ, Brasil
e-mail: efarruda@po.coppe.ufrj.br, web: http://www.po.coppe.ufrj.br/

2: Departamento de Tecnologias e Linguagens
Instituto Multidisciplinar
Universidade Federal Rural do Rio de Janeiro
Av. Governador Roberto Silveira, s/n, Moquetá , 26020-740, Nova Iguaçu, RJ, Brasil
e-mail:mazzaclaudia@gmail.com, web: http://r1.ufrrj.br/im/wp/

3: Departamento de Matemática
Centro Federal de Educação Tecnológica Celso Suckow da Fonseca
Av. Maracanã, 229, 20271-110, Rio de Janeiro, RJ, Brasil
e-mail: dpastore,rthome@cefet-rj.br, web: http://www.cefet-rj.br/

4: Departamento de Matemática Aplicada
Universidade Estadual de Campinas
Caixa Postal 6065, 13081-970, Campinas, SP, Brasil
e-mail: hyunyang@ime.unicamp.br, web: http://www.ime.unicamp.br/

Keywords: HIV, Mathematical Modelling, Optimal Control, Pontryagin's Maximum Principle, Finite Difference Method

Abstract. *Considering a simple model that describes the spread of HIV in the human body, this work proposes different strategies to minimize the side effects of medication by introducing control variables that represent the evolution of the medication levels with time. Each strategy corresponds to an optimization problem with respect to a prescribed performance function. For a given performance function, an optimal medication strategy is obtained by means of Pontryagin's maximum principle. To solve the set of nonlinear ordinary differential equations that describe the dynamics of susceptible, infected, active cells and HIV, we make use of grid refinement strategies to optimize the total computation time, and provide an insight into the computational economy resulting from the proposed refinement strategies.*

1 INTRODUCTION

Belonging to the family of retroviruses, the Human Immunodeficiency Virus (HIV) is responsible for AIDS. HIV infection results in a chronic, progressive disease that can lead to the destruction of the immune system. The disease is characterized by a high rate of viral replication, which results in the emergence of more virulent variants. HIV infection is currently characterized by the count of CD4+ T cells, by the amount of viral particles in the blood (viral load) and also by the clinical symptoms. Not all patients develop every stage of the disease, and the time elapsed between the infection and the manifestation of different clinical symptoms is highly variable, even though the causes of such a variation remain partly unknown.

To reproduce, HIV joins the membrane of the *T4* cell, which is vital to the immune response. The virus releases its *RNA* and an enzyme, which produces the *DNA* of the virus. Then, the *DNA* of the virus enters the nucleus and joins to the *DNA* of the cell, taking full control. The result of this union is the pro-viral *DNA*, that produces the messenger *RNA*, which contains the genetic code of the virus. The messenger *RNA* then reaches the cytoplasm and produces virions, which leave the host cell as newly formed *HIV's*. Thus, when joined to a T4 cell, a single virus produces many potential threats to other cells.

By making quantification possible, the analysis of viral load in HIV infection has facilitated the management of the disease. It turns out that an exponential decrease in viral levels in plasma can be attained by the reverse transcriptase inhibitors and protease that are included in Anti-retroviral Therapy (ART).

When HIV viruses invade the human body, they attack the CD4+ T cells in their way. When attacked, these *auxiliary* cells signal the presence of an invader to other immune cells (CD8+ T cells). The CD8+ T cells then respond to this signal and become Cytotoxic T Lymphocytes (CTL) by attempting to destroy the infected cells [5,18,21,23]. This process, which is not exploited in typical HIV models, plays an important role in the proposed approach. Indeed, a novel feature of the present work is the introduction of a variable to represent the CD8+ T cells. Such a variable is extremely important to the model, since it enables the decision maker to evaluate the interaction between the CD8+ T cells, CTL and the other variables in the model, such as the virus load [4].

This work proposes a simple mathematical model to describe the dynamics of the HIV in the human immune system. The proposed model introduces changes to several existing models in the literature [10, 19, 20, 22]. As mentioned above, one such change is the introduction of a new variable to provide a more detailed description of the defense of the immune system. This variable represents the number of unactivated CD8+ T defense cells, which can become activated (i.e. HIV-specific, or CTL) after being warned by some CD4+ T cell. In contrast to the formulation proposed by [18], which accounts for the activated cells but does not model the activation mechanism, the proposed model keeps track of both the unactivated CD8+ T cells and the activated cells, thus taking into

account the dynamics of the activation process.

Even though ART has produced undisputed advances in the treatment of HIV infection, it has been argued that the inhibitors that comprise ART may cause adverse effects, see for example [8, 24, 25]. Hence, one can argue that a compromise should be reached between the benefits obtained from ART and the adverse effects that it may cause. The ideal treatment should keep the benefits to a maximum degree while also minimizing the adverse effects. It is the development of such a treatment that we address in this paper, making use of the optimal control theory framework. We propose a dynamic model to represent the dynamics of the HIV infection, which takes into account the effects of the ART therapy and introduces control parameters that determine the intensity of the medication. An optimal control problem is then proposed to determine the optimal medication levels in such a way as to maximize the benefits of the therapy, while keeping the medication to a minimum efficient level. This side effects assessment is another novelty of the paper, which also strives to provide insights into the evaluation of side effects by proposing and analyzing different possibilities of cost functionals and their effect into the optimal prescribed treatment for infected patients.

In order to achieve our goal and minimize the side effects, optimal control theory is applied to the HIV infection model encompassing drug treatments. That, on the other hand, produces a problem whose solution is numerically obtained by standard algorithms, such as the gradient descent method; for more details on these algorithms we refer to [12]. These algorithms, however, are typically time consuming. Hence, we also analyze techniques to optimize the convergence time of the proposed algorithms while maintaining its performance with respect to the quality of the solution. Numerical experiments are provided which shed light both on the performance of the proposed cost functionals and also on the effectiveness of the techniques proposed for computational cost reduction.

2 MODELLING

Based on the above discussions, a simplified model regarding to the HIV infection was presented in [4]. The model is the following set of ordinary differential equations:

$$\begin{cases} \dot{x} &= \lambda_x - \mu_x x - \beta_v x v - u_1 x \\ \dot{x_p} &= u_1 x - \mu_x x_p \\ \dot{y} &= \beta_v x v - \mu_y y - p_y y z_a - u_2 y \\ \dot{y_b} &= u_2 y - \mu_y y_b \\ \dot{v} &= k_v \mu_y y - \mu_v v - p_v v z_a \\ \dot{z} &= \lambda_z - \mu_z z - \beta_z z v \\ \dot{z_a} &= \beta_z z v - \mu_z z_a. \end{cases} \tag{1}$$

System (1) is described briefly here. For more details, we refer to [4]. In virus replication, free viruses (v) and uninfected CD4 + T cells (x) produce infected cells (y) at rate β_v. Uninfected and defense CD8 + T cells (z) are assumed to be generated at constant

rates λ_x and λ_z, respectively. Uninfected, infected and defenses cells and the free virus decline at rates μ_x, μ_y, μ_z and μ_v, respectively.

Infected cells produce new virus particles at rate $k_v\,\mu_y$. One can observe the introduction of two variables z and z_a to represent respectively the defense cells (CD8 + T) and the HIV activated defense cells (CTL). Defense cells z are activated for HIV at rate β_z and the activated cells z_a eliminate infected cells y and free viruses v at rates p_y and p_v, respectively.

The model also includes the effects of cocktail drugs typically used in infected patients by means of the control variables u_1 e u_2. The variable u_1 represents the effects of the inhibitors, which protect the uninfected cells x, preventing their change into infected cells y. To account for that, we introduced the state variable x_p to represent the cells that are protected by the action of the inhibitors. The variable u_2 represents the effects of the inhibitors that block the infected cells, preventing the spread of the virus in the body. To account for this effect, we introduced the state variable y_b to represent the cells that were blocked by the inhibitors. We assume that $x_p(0) = y_b(0) = 0$.

For this model the basic reproduction number of the virus before the treatment is given by:

$$R_0 = \frac{\lambda_x \beta_v k_v}{\mu_x \mu_v}. \tag{2}$$

If constant medication dosages are applied, such a number is changed to:

$$R_c = \frac{\mu_x}{\mu_x + u_1} \cdot \frac{\mu_y}{\mu_y + u_2} \cdot R_0; \tag{3}$$

it is worth reinforcing that, for the expression above to hold, the control parameters u_1 and u_2 have to be kept constant with respect to time.

Note that if $R_0 < 1$, there will be no infection (virus extinction). In contrast, if $R_0 > 1$, infection is verified (HIV propagation). Observe that if $u_1 = u_2 = 0$ (no treatment), then $R_0 = R_c$.

3 THE ADAPTIVE FINITE DIFFERENCE APPROACH

To solve the system of equations described in the previous section we will make use of numerical methods. These methods provide an approximate solution for problems that, in general, have no analytical solution, or whose analytical solution is very difficult to obtain. Approximations of the derivatives by the Finite Difference Method are employed; the approximation of a derivative y', for example, is made by the forward difference method [6],

$$y'(x) = \frac{y(x+h) - y(x)}{h} - \frac{h y''(\xi)}{2}, \quad x \leq \xi \leq x + h, \tag{4}$$

where h as the mesh step. The error in the approximation of the derivative is of order $O(h)$.

In order to obtain a desired accuracy, optimizing at the same time the computational cost (computation time), this paper proposes the use of an adaptive mesh refinement strategy. This strategy iteratively refines the mesh step, in order to make better use of the computational resources.

Consider an iterative algorithm of the type

$$V_{k+1}(x) = TV_k(x),\ x \in S, \tag{5}$$

with $|S|$ defined as the cardinality of the set states and V_0 as the starting point. In order to simplify the calculation of the above system, it is possible to reset the algorithm in the form:

$$V_{k+1}(x) = \tilde{T}_k V_k(x),\ x \in S, \tag{6}$$

where the operator $\tilde{T}_k, k \geq 0$ is an approximation of the operator T, such that

$$\|TV_k(x) - \tilde{T}_k V_k(x)\| < e_k. \tag{7}$$

Note that $\tilde{T}_k$ is an approximate operator whose application generates computational savings with respect to the operator T. The price of this economy is the inclusion of an error, bounded above by the sequence $e_k,\ k \geq 0$. To generate computational savings, the operator $\tilde{T}_k$ can use, for example, a more spaced mesh in the case of a system of differential equations.

Note that the accuracy of Eq. (4) is a function of the mesh step value h. Consequently, Eq. (4) can be simplified when using a mesh with fewer points (bigger h), which ensures computational economy. Moreover, a grid with fewer points creates a greater error, whose magnitude is limited and depends on the mesh step used. Thus, the concepts underlying Eq. (6) can be used in the numerical evaluation of the equations of the model discussed in this work. The objective is to find the best form of mesh refinement, so that the computational cost to obtain the desired accuracy is minimized.

With respect to the application of operators in the form of (6), it was demonstrated by Almudevar and Arruda [3] that the best way to decrease the sequence e_k of inserted errors with respect to the computational cost, for linearly convergent algorithms, is by making:

$$e_{k+1} \propto re_k, \tag{8}$$

where r is the rate of convergence of the linear algorithm. With this decrease, the approximate algorithm converges to the exact solution of the problem optimally with respect to the computational cost.

This work employs the results of Almudevar & Arruda [3] to the problem of solving the equations of the model by means of the finite difference method. The objective is to minimize the computational cost of solving the system up to a prescribed accuracy.

The rate of convergence in (8) is estimated, for our problem, as the residue between two successive mesh solutions in the optimal control problem of Section sec:optimalcontrol.Thus, for the k-th iteration of the of progressive differences method, a step mesh h_k will be applied, so that:

$$h_{k+1} = r_k h_k,$$

with $h_0 = h_{\max}$ and $r_0 \triangleq \frac{1}{2}$. Note that $h_{\max}$ is a parameter of the algorithm and $r_k,\ k > 0$, is the residue of the corresponding solutions at the mesh steps h_k and h_{k-1}. This strategy was tested in the article by Dias & Arruda [3] with success for an H1N1 flu model.

4 OBTAINING THE COST FUNCTION

In order to minimize the side effects of drug treatments, we propose a cost functional, presented in Eq. (9). Such a functional is devised in such a way that the decision maker is provided with an optimal strategy for the medication levels $u_1(t),\ t \geq 0$ and $u_2,\ t \geq 0$, which are the control parameters and, for that reason, are allowed to vary over time. The optimal strategy obtained from Problem (9) is designed to minimize the side effects, by lowering the medication dosages as much as possible, while also maximizing the number of protected and blocked cells and minimizing the virus load in the system dynamics described by Eq. (1).

$$\begin{aligned} &\text{Maximize} \quad \mathrm{J} = \tfrac{1}{2}\int_0^{\mathrm{T}} \left(\mathrm{c_1 x_p^2} - \mathrm{c_2 u_1^2} - \mathrm{c_3 u_2^2} + \mathrm{c_4 y_b^2} - \mathrm{c_5 v^2}\right) \mathrm{dt}, \\ &\quad \text{subject to (1).} \end{aligned} \tag{9}$$

To solve Eq. (9), one can apply Pontryagin's Maximum Principle [12], which results in the following co-state equations:

$$\begin{cases} \frac{dw_1}{dt} &= -\frac{\partial H}{\partial x} = & \mu_x w_1 + \beta_v v w_1 + u_1 w_1 - u_1 w_2 - \beta_v v w_3 \\ \frac{dw_2}{dt} &= -\frac{\partial H}{\partial x_p} = & -c_1 x_p + \mu_x w_2 \\ \frac{dw_3}{dt} &= -\frac{\partial H}{\partial y} = & c_6 y + \mu_y w_3 + p_y z_a w_3 + u_2 w_3 - u_2 w_4 - k_v \mu_y w_5 \\ \frac{dw_4}{dt} &= -\frac{\partial H}{\partial y_b} = & -c_4 y_b + \mu_y w_4 \\ \frac{dw_5}{dt} &= -\frac{\partial H}{\partial v} = & c_5 v + \beta_v x w_1 - \beta_v x w_3 + \mu_v w_5 + p_v z_a w_5 + \beta_z z w_6 - \beta_z z w_7 \\ \frac{dw_6}{dt} &= -\frac{\partial H}{\partial z} = & \mu_z w_6 + \beta_z v w_6 - \beta_z v w_7 \\ \frac{dw_7}{dt} &= -\frac{\partial H}{\partial z_a} = & p_y y w_3 + p_v v w_5 + \mu_z w_7, \end{cases} \tag{10}$$

where $w_i(T) = 0, \quad i = 1, \ldots, 7$ and H is the Hamiltonian, which can be obtained by defining an appropriate expanded problem based on Problem (9); for more details on this

procedure we refer to [12]. Applying optimal control theory, we obtain:

$$\begin{aligned} u_1^* &= max\left\{0\ ,\ \tfrac{(w_2-w_1)x}{c_2}\right\} \\ u_2^* &= max\left\{0\ ,\ \tfrac{(w_4-w_3)y}{c_3}\right\}. \end{aligned} \tag{11}$$

Hence the optimal control for the problem is characterized by Eq. (11). It is worth mentioned that, even though (11) provides an analytic solution to the problem, it cannot be directly obtained, for it holds only for the optimal trajectory, which results from the application of the optimal control, not known a priori. It can, however, be obtained by a standard gradient descent algorithm, which generates a sequence of increasingly accurate approximations to the optimal control strategy. This sequence converges to the solution of the system, described by Eq. (11).

To evaluate the effect of different parameters in the optimal control functional, we will focus on four different cases, derived from the general form of the proposed functional in Eq. (9).

4.1 Case 1

This case is concerned with minimizing the side effects of the treatment and maximize the number of protected cells. That is attained by fixing $c_4 = c_5 = 0$, which results in:

$$\begin{aligned} &\text{Maximize} \quad \mathrm{J} = \tfrac{1}{2} \cdot \int_0^{\mathrm{T}} \left(\mathrm{c_1 x_p^2 - c_2 u_1^2 - c_3 u_2^2}\right) \mathrm{dt}, \\ &\quad \text{subject to} \quad (1). \end{aligned} \tag{12}$$

In the numerical experiments, we replicate an example from [4] by defining $c_1 = 10^{-3}, c_2 = c_3 = 1$:

4.2 Case 2

The functional defined below, for which we fix $c_5 = 0$, is devised to take account of the side effects and the number of protected and blocked cells. In the numerical simulations that follow, we fix $c_1 = 10^{-3}, c_2 = c_3 = c_4 = 1$ for Case 2.

$$\begin{aligned} &\text{Maximize} \quad \mathrm{J} = \tfrac{1}{2} \cdot \int_0^{\mathrm{T}} \left(\mathrm{c_1 x_p^2 - c_2 u_1^2 - c_3 u_2^2 + c_4 y_b^2}\right) \mathrm{dt}, \\ &\quad \text{subject to} \quad (1). \end{aligned} \tag{13}$$

4.3 Case 3

In Case 3, we make use of all the parameters defined in Problem (9). For the numerical experiments below, we set Case 3 with $c_1 = 10^{-3}, c_2 = c_3 = c_4 = c_5 = 1$:

$$\begin{aligned} &\text{Maximize} \quad \mathrm{J} = \tfrac{1}{2} \cdot \int_0^{\mathrm{T}} \left(\mathrm{c_1 x_p^2 - c_2 u_1^2 - c_3 u_2^2 + c_4 y_b^2 - c_5 v^2} \right) \mathrm{dt}, \\ &\quad \text{subject to} \quad (1). \end{aligned} \tag{14}$$

4.4 Case 4

In case 4, we disregard the protected and blocked cells and focus on the other parameters by making $c_1 = c_4 = 0$. For the numerical experiments below, we set for Case 4 $c_2 = c_3 = c_5 = 1$:

$$\begin{aligned} &\text{Maximize} \quad \mathrm{J} = \tfrac{1}{2} \cdot \int_0^{\mathrm{T}} \left(\mathrm{-c_2 u_1^2 - c_3 u_2^2 - c_5 v^2} \right) \mathrm{dt}, \\ &\quad \text{subject to} \quad (1). \end{aligned} \tag{15}$$

The optimal solution was found iteratively by means of a gradient algorithm [12]. At each iteration, a different mesh is used, and the optimal mesh refinement rate in (8) is applied.

5 NUMERICAL EXPERIMENTS

For the numerical experiments we have used the dataset described in Tables 1 and 2. We let the system evolve without control for one year to simulate the infection period prior to diagnosis and we define a one-year treatment period.

Table 1: Initial Conditions

State Variables	Variable	Value
CD4+ T cells in body (susceptible)	x	$10^3\ mm^{-3}$
CD4 + T cells infected by HIV	y	$0\ mm^{-3}$
Free HIV in the body	v	$10^{-3}\ mm^{-3}$
Defense cells CD8+ T HIV specific	z	$500\ mm^{-3}$
Activated defense cells	z_a	$0\ mm^{-3}$

The results for Cases 1 to 4 can be observed in Figures 1, 2, 3 and 4, respectively.

The model adequately describes the behavior of the HIV virus in the human body. Early in the treatment, there is a reduction of the target cells (susceptible), given that

Table 2: Parameters

Parameters and Constants	Variable	Value
Mortality of susceptible cells	μ_x	$0.02\,day^{-1}$
Mortality of infected cells	μ_y	$0.24\,day^{-1}$
Mortality of the virus	μ_v	$2.4\,day^{-1}$
Mortality of defense cells	μ_z	$0.04\,day^{-1}$
Average number of free virus from infected cells	k_v	360
Activation of immunologic response rate	β_z	$5 \cdot 10^{-6}\,mm^3 day^{-1}$
Virus infection rate	β_v	$2.4 \cdot 10^{-5}\,mm^3 day^{-1}$
Infected cells destruction rate	p_y	$0.02\,mm^3 day^{-1}$
Virus destruction rate	p_v	$0.02\,mm^3 day^{-1}$
Susceptible cells supply rate	λ_x	$20\,day^{-1} mm^{-3}$
Defense cells supply rate	λ_z	$20\,day^{-1} mm^{-3}$

these cells become protected with treatment. The same can be observed with the infected cells, that decrease while the blocked cells increase over the same period. It is also observed that the number of free viruses decays rather quickly while keeping very close to zero (trivial equilibrium).

Observe that the medication levels differ from experiment to experiment, but their level is considerably decreased in Cases 1 and 4. It is specially reduced in Case 4, where the side effects are confronted with the viral load. In all cases, the optimal control prescribes high dosages in the early stages, to control the spread of the disease and comparably low dosages in the following stages, in order to keep the disease under control. Note that in experiment 4 the level of x_p is comparatively lower with respect to the other experiments. That happens because it is not explictly taken into account in the functional, which strives to keep the medication levels low, while also keeping the viral load under control. That can be accomplished by a rather considerable dosage of medication in the early stages, followed by very low dosages that manage to prevent the disease from spreading.

5.1 Computational Performance

To better evaluate the strategy that we propose in this work we need an alternative adaptive mesh refinement method to be used as a benchmark for comparison. Although adaptive strategies are currently found in greater numbers in publications aimed at the treatment of partial differential equations (see [2,14,26]), they are also found in the context of ordinary differential equations as in [11,16]. However, unlike the method proposed here, these methods are purely empirical and do not directly address the problem of minimizing the computational cost.

One optimal method in terms of of worst-case computational complexity was proposed by Chow & Tsitsiklis [7] for a stochastic optimization problem. While the residue (difference between the current and previous solution), r is bigger than a tolerance, this method

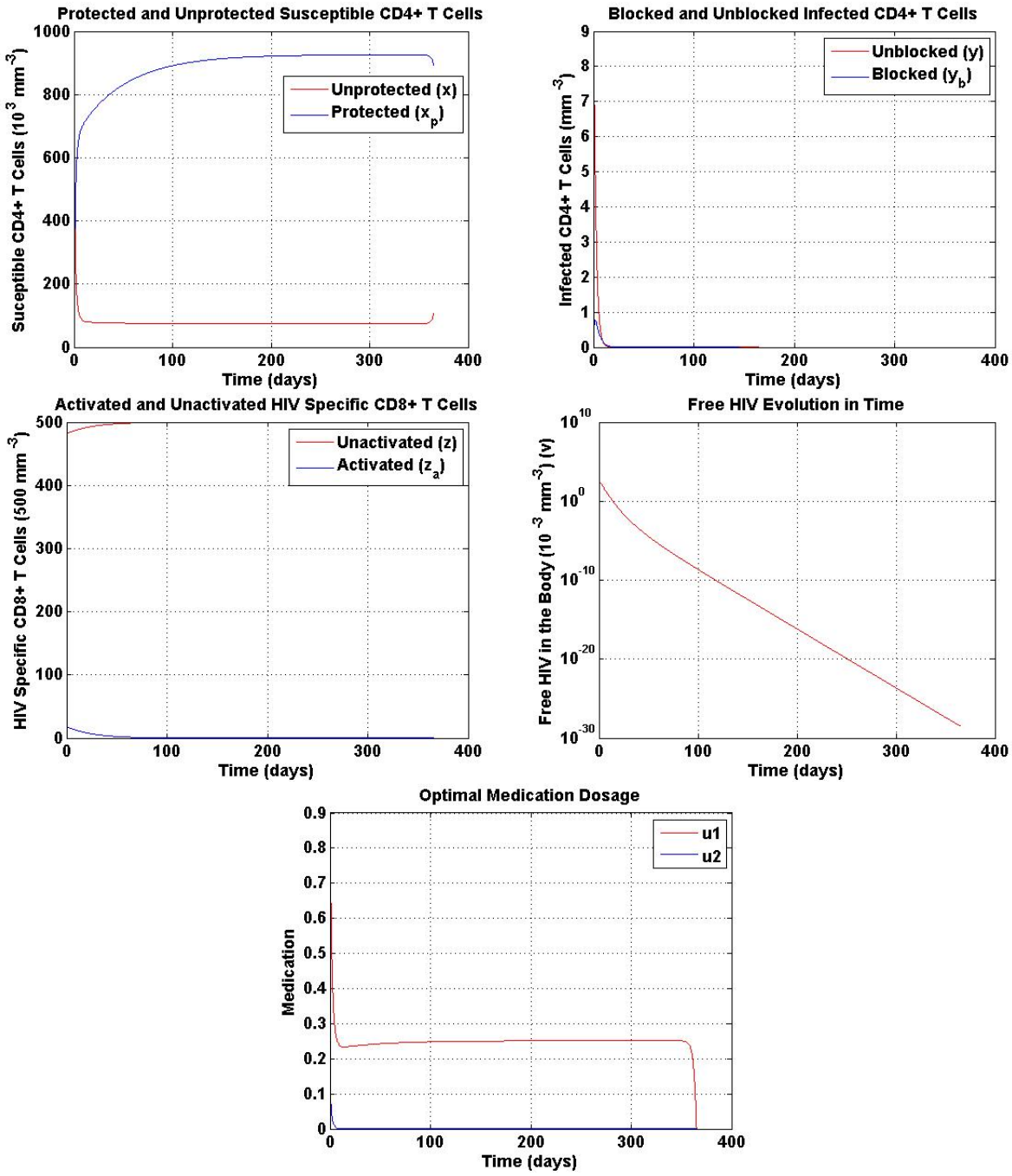

Figure 1: Numerical Simulation - Case 1.

makes $h_{k+1} = 0.5\, h_k$, where k is the current iteration number. To apply this method, we assume that $h_{\max} = h_0$. Furthermore, $h > h_{\min}$, for some prescribed values h_0 and $h_{\min}$. This method is implemented in practice in many adaptive algorithms for the solution

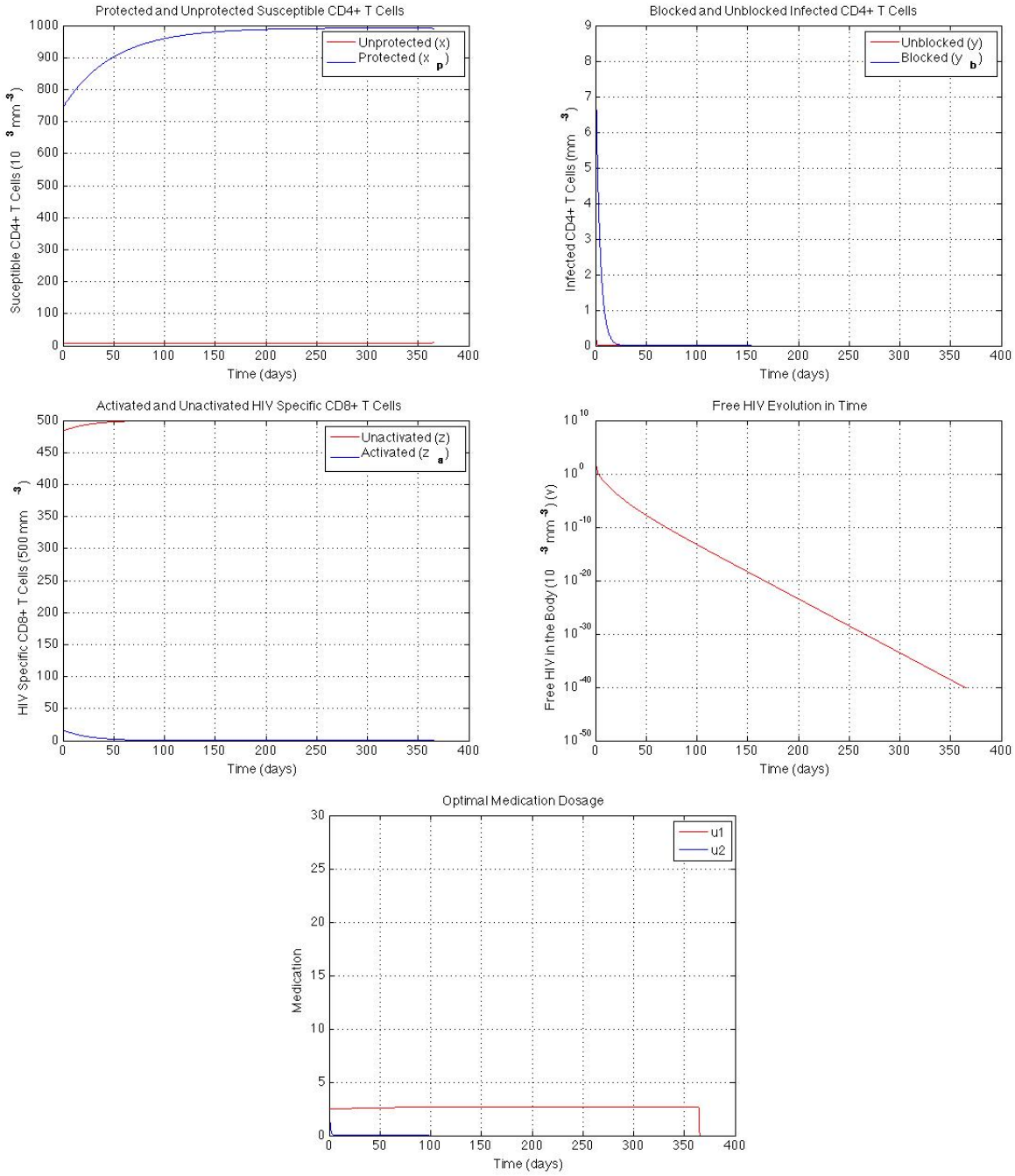

Figure 2: Numerical Simulation - Case 2.

of partial differential equations models, and will be compared to the proposed adaptive mesh refinement strategy. Both algorithms are employed to solve Problem (9) and their performances is compared below.

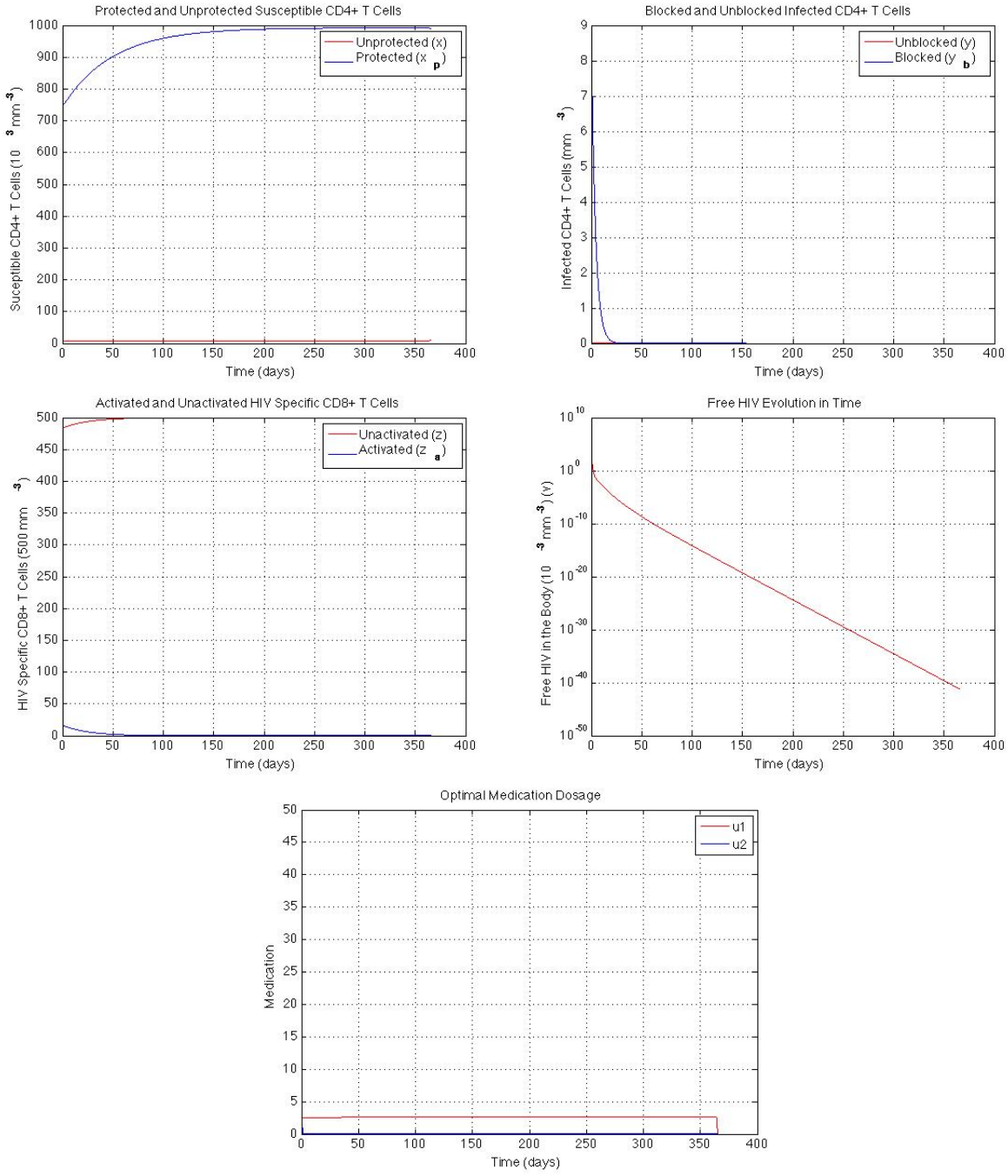

Figure 3: Numerical Simulation - Case 3.

Comparative results can be observed at Table 3 for Case 1, that indicate a economy about 83.4% in computational time with the use of the proposed adaptive method with respect to the non optimized code. At Table 3, the Computational Cost is expressed by

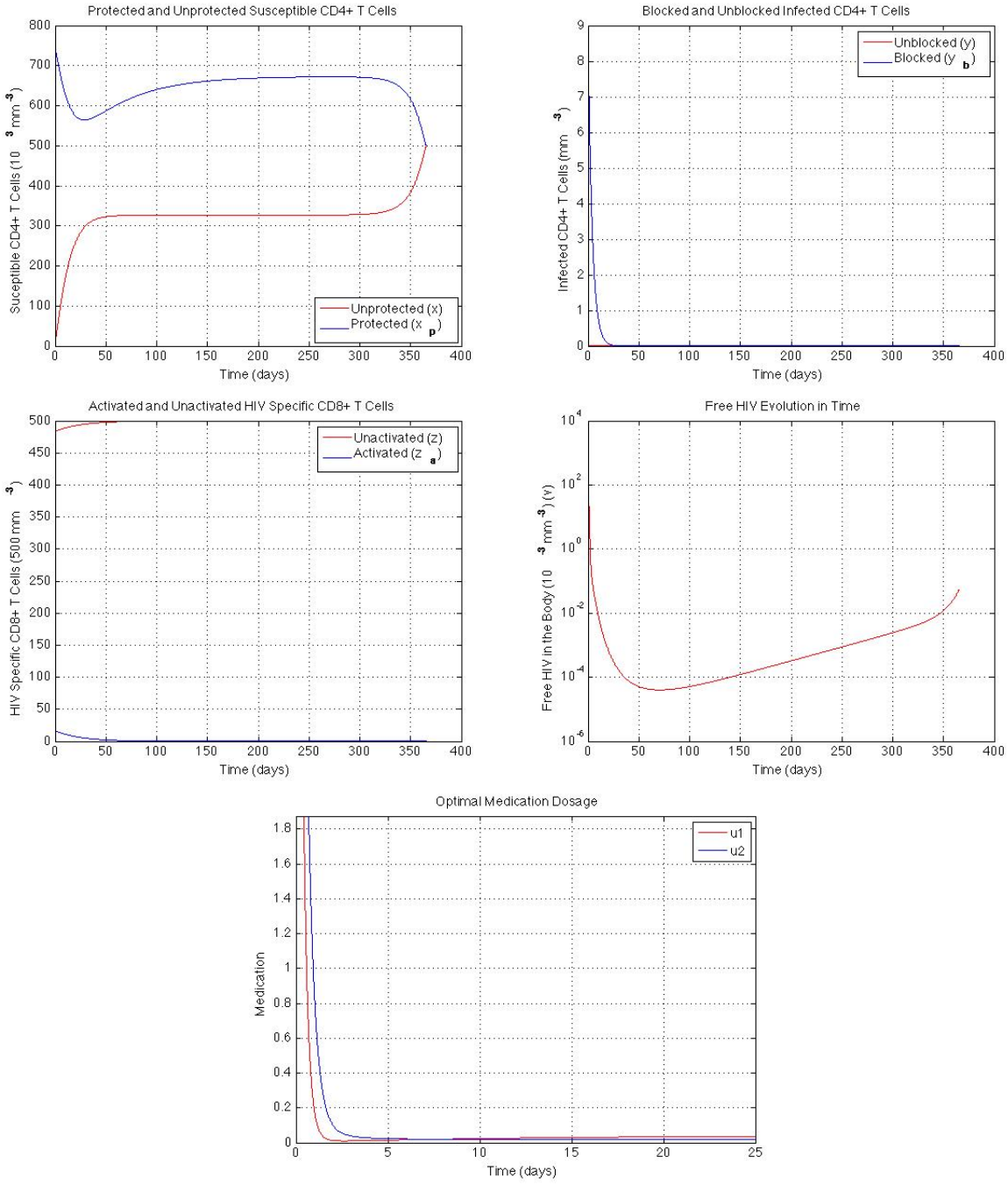

Figure 4: Numerical Simulation - Case 4.

the cumulative number of points at each mesh plus the number of evaluations of the cost function. Note that the proposed adaptive strategy is also superior to the strategy in [7] which, being optimal with respect to worst case complexity, is used as a benchmark. The

other experiments yield similar results.

Table 3: Results.

Strategy	Computational Effort
Traditional Algorithm (Non adaptive mesh + Traditional optimization)	18.085.750
Adaptive mesh $h_{k+1} = 0.5\, h_k$ + Efficient optimization methodology	3.375.540
Adaptive mesh $h_{k+1} = r\, h_k$ + Efficient optimization methodology	2.993.269

6 CONCLUSIONS

This papers presented a simple model do HIV immunology. The model includes an optimal control strategy to minimize side effects of treatment. We proposed a general optimization functional to include the side effects as well as the level of protection and viral load resulting from a treatment. In particular, four different functionals were analyzed.

This paper also presented an optimal adaptive strategy to perform the numerical calculation of the optimal solution to the proposed problem. The presented methodology proved efficient, preserving the quality of the solutions and presenting significant savings in computational cost (more than 83%).

The computational cost optimization proposed enables one to solve more complex problems in reduced time, making the prescription of HIV treatments by means of optimal control theory possible. It also opens the possibility of developing and solving more complex models, possibly taking into account other effects of the treatment.

ACKNOWLEDGEMENTS

The authors would like to thank The Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro, FAPERJ, for supporting the research by means of grants E-26/110.379/2014 and E-26/110.087/2014. This work was partially supported by the Coordination for the Improvement of Higher Education Personnel of Brazil - CAPES, under grant No. BEX2025/14-0, and by the National Council for Scientific and Technological Development - CNPq, under grant No.302716/2011-4.

REFERENCES

[1] M. Amendoeira. Conceitos e métodos para a formação de profissionais em laboratórios de saúde. EPSJV, Rio de Janeiro (2009).

[2] B. S. Ahmed and S. J. Monaquel. Multigrid Method for Solving 2D-Poisson Equation with Sixth Order Finite Difference Method, *International Mathematical Forum*, Vol. 6(55), pp.2729 - 2736 (2011).

[3] A. Almudevar and E. F. Arruda. Optimal Approximation Schedules for a Class of Iterative Algorithms, With an Application to Multigrid Value Iteration. *IEEE Transactions on Automatic Control*, 57(12), pp. 3132-3146 (2012).

[4] E. F. Arruda, C. M. Dias, D. H. Pastore, R. C. A. Thomé, H. M. Yang. An Optimal Control Approach to HIV Immunology. Submitted (2015).

[5] M. Balamurali, J. Petravic, L. Loh, S. Alcantara, S. J. Kent, S. and M. P. Davenport. Does cytolysis by cd8+ t cells drive immune escape in hiv infection? *The Journal of Immunology* ,185 (9), 5093-5101 (2010).

[6] R. L. Burden and J. D. Faires. Análise Numérica. Cengage Learning, 2a Ed.(2008).

[7] C. Chow and J. N. Tsitsiklis. An optimal one-way multigrid algorithm for discrete-time stochastic control, *IEEE Transactions on Automatic Control*, 36(8), pp.898 -914 (1991).

[8] E. Daugas and J. Rougier. HAART-related nephropathies in HIV-infected patients. *Kidney International*, 67, 393, 403 (2005).

[9] C. M. Dias and E. F. Arruda. Computational Cost Optimization for Influenza A (H1N1) Epidemic Model. Proceedings of the 7th International Congress on Environmental Modelling and Software, June 15-19, San Diego, California, USA. ISBN: 978-88-9035-744-2 (2014).

[10] J. M. Grégio, M. A. Caetano and T. Yoneyama. State estimation and optimal long period clinical treatment of HIV seropositive patients. Anais da Academia Brasileira de Ciências, n. 81, pp. 3-12 (2009).

[11] A. Jameson. Solution of the Euler equation for two Dimensional Transonic Flow by a Multigrid Method, *Applied Mathematics and Computation*, 13, pp. 327-355 (1983).

[12] D. Kirk. Optimal control theory: An introduction. Prentice-Hall (1970).

[13] N. Komarova and M. A. Nowak. The evolutionary dynamics of the lexical matrix. *Bulletin of Mathematical Biology*, n. 63, pp. 451-484 (2001).

[14] D. Y. Kwak, J. S. Lee. Multigrid analysis for higher order finite difference scheme, *Journal of Numerical Mathematics*, 12, (4), pp. 285-296 (2004).

[15] C. V. Magalhães, R. C. A. Thomé, D. H. Pastore and H. M. Yang. An Optimal Control Approach to HIV Immunology, Proceedings of the XXXIV Iberian Latin-American Congress on Computational Methods in Engineering, Z.J.G.N Del Prado (Editor), ABMEC, Pirinópolis, GO, Brazil, November 10-13 (2013).

[16] D. J. Mavriplis. Accurate multigrid solution of the Euler equations on unstructured and adaptive meshes, *AIAA Journal*, 28(2), pp. 213-221 (1990).

[17] J. D. Murray. Mathematical Biology. Biomathematics Texts, vol. 19, Springer, 2nd ed.(1993).

[18] M. A. Nowak and C. Bangham. Population dynamics of immune responses to persistent viruses. *Science*, 272 (5258), 74-79 (1996).

[19] M. A. Nowak and R. M. May. Virus dynamics mathematical principles of immunology and virology. Oxford (2000).

[20] A. S. Perelson and P. W. Nelson. Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Rev.*, vol. 41, n. 1, pp. 3-44 1999).

[21] A. Perelson. Modelling viral and immune system dynamics. *Nat. Rev. Immunol.* 2, 28-36 (2002).

[22] A. Perelson and R. Ribeiro. Modeling the within-host dynamics of HIV infection. *BMC Biology*, 11 (1), 96(2013).

[23] B. Siewe, J. Wallace, S. Rygielski, J. T. Stapleton, J. Martin, S. G. Deeks and A. Landay. Regulatory B Cells Inhibit Cytotoxic T Lymphocyte (CTL) Activity and Elimination of Infected CD4 T Cells after In Vitro Reactivation of HIV Latent Reservoirs. *PLoS ONE* 9 (4), e92934 (2014).

[24] S. Sreenivasan and V. Dasegowda. Adverse effects after HAART initiation in resource-limited settings: a prospective study from mysore, india. *J. Infect. Dev. Countries*, 4 (11), 750 -753 (2010).

[25] R. Torres and W. Lewis. Aging and HIV/AIDS: pathogenetic role of therapeutic side effects. *Laboratory Investigation*, 94, 120-128 (2014).

[26] S. M. Wise. Unconditionally Stable Finite Difference, Nonlinear Multigrid Simulation of the Cahn-Hilliard-Hele-Shaw System of Equations, *Journal of Scientific Computing*, 44 (1), pp. 38 - 68 (2010).