International Journal of Pure and Applied Mathematics

Volume 59 No. 1 2010, 39-57

OPTIMAL CONTROL FOR HIV THERAPY STRATEGIES ENHANCEMENT

Jose Marie Orellana

Department of Applied Mathematics
Conservatoire National des Arts et Metiers
292, Saint Martin Str., Paris, 75003, FRANCE
e-mail: jose.orellana@cnam.fr

Abstract: Highly Active Anti Retroviral Therapies (HAART) have proven to be extremely effective in improving and prolonging the patient's life. Though, a concern arises since a long term drug intake induces many strong sides effects and reduces reactivity of the virus to any therapy. The purpose of the paper is to use numerical analysis and optimization tools to suggest improved therapies to handle HIV infection. The evolution of the infection is modelled by an ordinary differential equation system which includes both immune response and multi-drug effects. For a fixed time, one looks for a two drugs control strategy based on Pontryaguine's minimum principle with an objective function which takes into account three contributions: the viral load, the transient evolution of infection and the quantities of drug used. Simulations are carried out using an indirect optimization method along with Runge-Kutta five order scheme algorithm. Numerical solutions to the optimality system are obtained and related histories are shown. The possibility of scheduled treatment interruption is also examined.

AMS Subject Classification: 92D30, 49K15, 34B15
Key Words: Fixed-end-time optimization, HIV, mathematical model, multi-drug therapy, STI

Received: December 30, 2009

1. Introduction

During the two last decades, immunodeficiency virus treatments did improve. Despite the fact that preventative vaccine is still unavailable, more accurate assays and new regimen help improving and prolonging the patient's life. Highly Active Anti Retroviral Therapies (HAART) consisting in a combination of Reverse Transcriptase Inhibitors (RTIs) and Protease Inhibitors (PIs) drugs have proven to be extremely effective. Patients maintain low viral load and have their immunity system restored so that not to be vulnerable to any opportunistic potentially lethal infection. Though, it is still impossible to eradicate the virus because an undetectable virus load in blood does not mean infection is no longer present. Virus could hide out in one part of organism such as the lymph nodes, the brain, testes or the retina in quiescent state waiting any opportunity to bounce back and therefore is not targeted by immune defence neither treatments. Another concern is that a long term drug intake induces many sides effects. Among them, strong side effects like nervous breakdown, anaemia, pain, weakness, fat redistribution are common not to mention others serious illness like insulin resistance, cardiovascular pathologies, hepatitis or myopathies due to the toxicity of treatment. Other concerns also arise from viral rebound due to mutation of the virus. Indeed on the one hand, virus replicates at extremely high rates and have many opportunities to mutate. On the other hand, reverse transcritptase process leads to frequent DNA virus mistakes producing mutant which are likely to resist treatments. Regularly drugs changes are needed and in some cases inability to find any appropriate pharmaceutical drug combinations is noted since virus is no longer reactive to any therapy. Hence poor compliance with drug prescription is currently noticed in the patient's behaviour. Up to now, the solution proposed by the World Health Organisation is to administrate a constant antiviral drug doses which efficiency is assumed to be stable in time and which can be changed from time to time according patient's condition. Idealistic solution will be to lower and maintain the virus load at such a level that the immune system controls with low amount of drugs over short spells. Although mathematical studies were first ignored by the experimental community, the disease has become the subject of intense theoretical modelling efforts. Many important papers investigate dynamic models of host-drug-virus interactions see Ho et al [11], Murray [16], Nowak et al [17] and Perelson et al [18]. Mathematical models have become essential tools to make assumptions, suggest new experiments or help one explaining easily complex processes. Different aspects are encompassed in each model which are by the time more and more comprehensive and accurate refer to Callaway et al [5], Culshaw et al [6],

Karrakchouca et al [12], Kirschner et al [14], Kwon [15], Snedecor [22], Stengel [23], Velichenko et al [25] and Wodarz et al [28]. But complete analysis can hardly be achieved with involved models and simple conclusions are difficult to deduce. Also all new parameters introduced, which values must be known to carry out any simulation, may not be accurately fit by experimental data or they require new measurement method see Adams et al [1], Bortz et al [3] and Perelson et al [19]. Most of the models are deterministic prey-predator systems of non-linear differential equations. Sometimes stochastic terms are included to address the random behavior of features of disease process. Typically, dynamic changes are modelled considering cell numbers progression of CD4+T cells, infected cells and virus population under drugs effects see Joshi [10], Kirschner et al [13] and Nowak et al [17]. At the same time, optimal control have received much attention especially in mechanical and aerospace engineering for example to the re-entry shuttle problems. The main idea is to use optimization techniques and theories to propose an alternative treatment based on administrating continually adjustable antiviral drug doses once a proper model is obtained.

The remainder of this paper is organized as follows: in Section 2, the deterministic model chosen with its specific aspects is presented and explained. In Section 3 an optimal control is derived by using Pontryaguine's minimum principle and the adjoint method. Numerical results are illustrated and commented in the last section.

2. Mathematical Model

The present model accounts for multi-drug therapy combination and also include specific immune response to HIV. The infection mechanism is described by the system of non-linear ordinary differential equations with six compartments. Namely, the state variables are T the concentration of uninfected CD4+T cells, L, the concentration of latently infected T-cells, I, the concentration of actively infected cells, V, the concentration of infectious viruses, N, the concentration of non-infectious viruses by the action of protease inhibitor, E, the concentration of cytotoxic lymphocytes effector. These state variables are the key-compartments commonly observed in clinical data and obviously must be positive along our calculus. Drugs efficiency is represented by the controls u_1 and u_2 $(0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1)$, which accounts respectively for reverse transcriptase and protease inhibitors actions.

$$\dot{T} = rT(1 - \frac{T+L+I}{T\max}) - \mu_T T - (1-u_1)k_1 VT + s_1, \qquad (1)$$

$$\dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 I, \quad (2)$$
$$\dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 I - \mu_I I - k_3 IE, \quad (3)$$
$$\dot{V} = a(1-u_2)I - k_1VT - \mu_V V, \quad (4)$$
$$\dot{N} = au_2 I - \mu_V N, \quad (5)$$
$$\dot{E} = k_4 ITE - \mu_E E + s_2, \quad (6)$$

or in vector form

$$\dot{x} = F(x(t,u),u(t)), \quad (7)$$
$$x(0) = {}^t(T_0,0,0,V_0,0,0), \quad (8)$$

where $x(t) = {}^t(T,L,I,V,N,E)$; ^{t} denotes the transposition. The concentration N and the ode (5) can be omitted since they are decoupled and do not affect the remaining system. Source and death rates of cells population s and μ terms respectively, are not commented in order to focus on non-linear terms introduced by cells interactions. Nevertheless definitions and numerical values for the parameters are summarized in Table 1 and taken from Culshaw et al [6], [7] and Garira et al [8].

As we assume the system is well mixed, mass action law is used to account for them at a first approximation. For example, the viral particle is tightly linked to receptors on the lymphocyte membrane enabling fusion with the cell membrane. Therefore each time a cell is infected one virion is lost and we add the term $-k_1VT$ to (4). Once viral RNA and enzymes enter the host cell's cytoplasm, reverse transcriptase reads and transcribes the sequence of viral genome into a complementary DNA sequence. Reverse transcriptase inhibitor blocks the recoding process and viral RNA is eventually degraded. The cell is only temporarily infected. Then to model drug action we include $(1-u_1)k_1VT$ term to (1) to account for uninfected T cells loss. Viral DNA once integrated in cell nucleus, may remain dormant, in the latent stage. Thus we introduce ω to represent fraction of latently infected CD4+T cells in infected cells production and then we add $(1-\omega)(1-u_1)k_1VT$ to (2) and $\omega(1-u_1)k_1VT$ to (3). We assume that latently infected cells which have not yet produce viruses, switch to productively infected cell with rate k_2 in (2). The virus genome, provirus, is transcribed into new RNA and new enzymes. HIV protease inhibits cleavage of viral polyprotein and new virions will lack functional enzymes. The viruses produced are defective. We add $a(1-u_2)$ to (4) and au_2 to (5) to model protease inhibitor effect. Among immune responses, cytotoxic T lymphocytes action is known to be particularly effective. CTLs response had been investigated under different assumptions in various papers Adams et al [1], Bonhoeffer et al [2], Callaway et al [5], Perera [20] and Wodarz [27]. CTLs kill infected cells

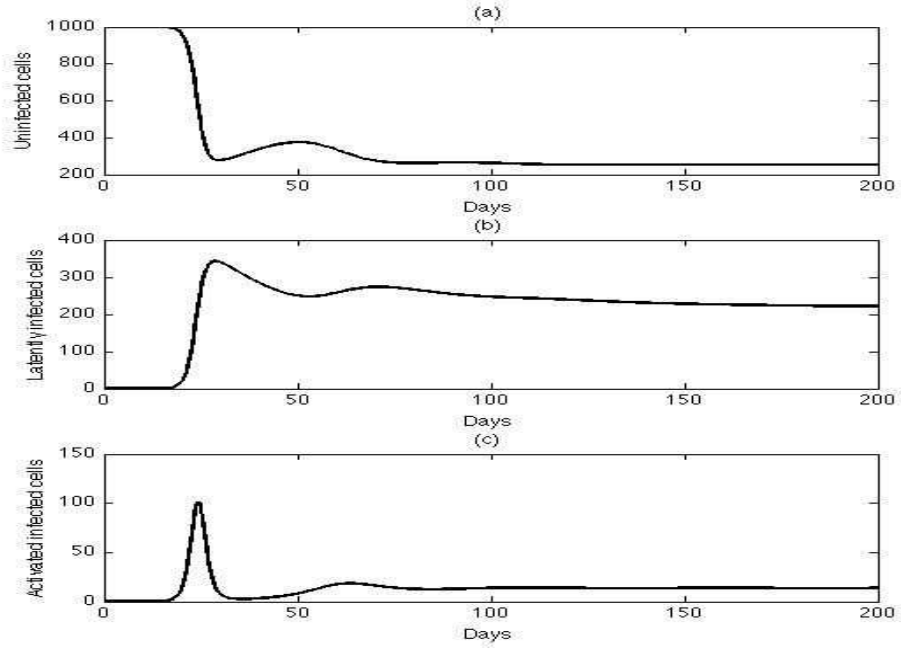

Figure 1: Numerical solutions to the ordinary differential system with no treatment. Controls are fixed to $u_1 = 0$ and $u_2 = 0$. $T_0 = 1000$ cells and $V_0 = 1e-3$ virus for $1mm^3$ of blood. The figures show history of: (a) – the uninfected CD4+T cell population; (b) – the latently infected CD4+T cells; (c) – the infected CD4+T cells.

without being targeted by HIV virus and prevent uninfected cells from being contaminated by the chemokines they release Garira et al [8]. The reduction of viral infectivity is not examined and only effector CTL population is considered in this paper. CTLs proliferate proportionately with the number of infectious CD4+T cells since it is an immune specific response to HIV. They are also dependent on CD4+ T cell helper and of CTLs, hence the trilinear term in (6) is introduced Culshaw et al [7], Garira et al [8], Wodarz et al [27], [28]. Elimination of infectious CD4+T cells by CTLs are added by $-k_3IE$ term in (4). Early infection is simulated by introducing one virus particles per ml of blood. We assumed that half of infected cells becomes latently before actively infected. Natural response of the system is shown in Figure 1 and Figure 2. Further

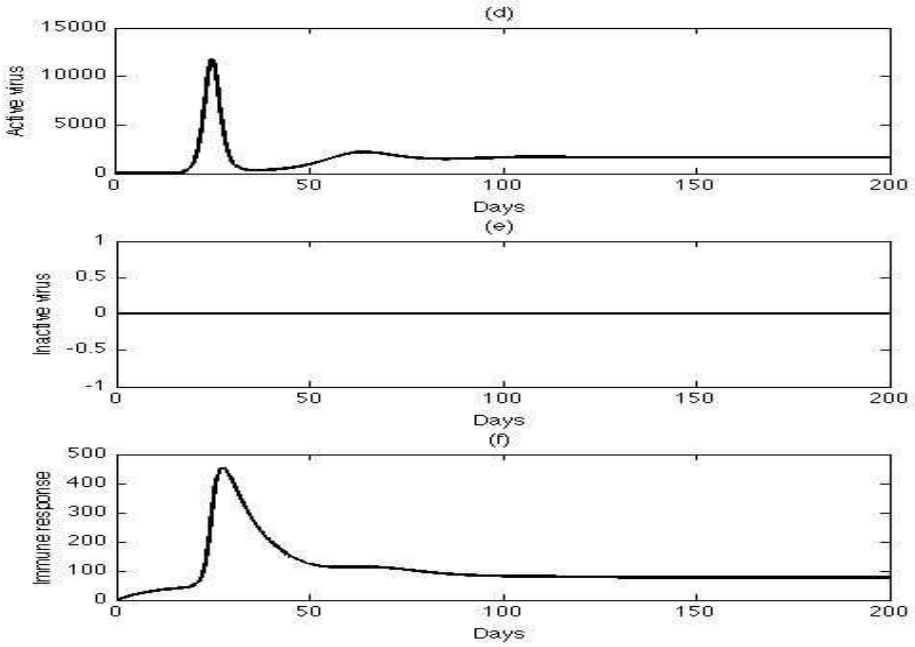

Figure 2: Numerical solutions to the ordinary differential system with no treatment. Controls are fixed to $u_1 = 0$ and $u_2 = 0$. $T_0 = 1000$ cells and $V_0 = 1e-3$ virus for $1mm^3$ of blood. The figures show history of: (d), active virus; (e), inactive virus; (f), cytotoxic T lymphocytes.

analysis shows that the system has two biologically significant steady states: an uninfected steady state $\bar{x}_1 = (1000, 0, 0, 0, 0, 50)$ which is unstable and an infected steady state $\bar{x}_2 = (254, 221, 13, 1644, 0, 77)$ which is locally stable. The first corresponds with healthy state and the last with HIV seropositive state. When full treatment is administered, the system drives toward the uninfected state which is an evidence of medication efficiency.

3. Optimal Control

The model described by (1)-(6) can simulate the course of the disease under a prescribed treatment along with immune response but the issue of finding a

Parameter and constants	Values.
r: rate growth of uninfected CD4+T	0.03 d^{-1}
μ_T: death rate of uninfected CD4+T	0.02 d^{-1}
μ_I: death rate of infected CD4+T	0.26 d^{-1}
μ_V: death rate of virus	2.4 d^{-1}
μ_E: death rate of CTL	0.1 d^{-1}
k_1: rate CD4+T becomes infected by virus	2.4e-5mm^3d^{-1}
k_2: rate latently infected convert to actively infected	3e-3 d^{-1}
T_m: maximum CD4+ T population	1500 mm^{-3}
a/μ_I: number of virus produced by cells lysis	1200.
s_1: source term for uninfected CD4+T	10 $mm^{-3}d^{-1}$
s_2: source term for CTL	5 $mm^{-3}d^{-1}$
k_3: rate actively infected cells deleted by CTL	2e-3 mm^3d^{-1}
k_4: rate growth of CTL	1e-5 mm^6d^{-1}
ω: fraction of latently / infected CD4+T	[0;1] .

Table 1: Parameters and constants used in the model.

control law such as a certain optimality criterion would be achieved has not been yet addressed. Many studies have already been carried out using a control theoretical approach to design an optimal drug therapy. But investigations were based on other type of mathematical models and mainly different objective functionals refer to Culshaw et al [7], Fister et al [9], Garira et al [8], Joshi [10], Kirschner et al [13] and [14] a Stengel [23]. As we do not intend to model any mutation leading to drug resistance or to avoid side effects, the control is applied in a finite short time interval $[t_0, t_f]$ with $t_f - t_0 < 100$ days. The end-time control problem is considered with the cost function given by

$$J^{\varepsilon,\alpha,\beta}(x,u) = \phi(x_{t_f}) + \int_{t_0}^{t_f} L(x,u,t)dt \tag{9}$$

with

$$L(x,u,t) = \frac{\alpha}{2}V^2 + \frac{\beta}{2}\dot{V}^2 + \frac{\varepsilon}{2}\left({u_1}^2 + {u_2}^2\right), \tag{10}$$

$$\phi(x_{t_f}) = \frac{\alpha}{2}V(t_f)^2, \tag{11}$$

where

$$u \in \vartheta : \left\{u = (u_i) \ / u_i \in L^2\left(]t_0, t_f[: \mathbb{R}\right), 0 \leq u_i \leq 1, \ i = 1,2\right\} \tag{12}$$

and $L(x, u, t)$, the Lagrangian of the problem. Unlike most papers, all parameters are squared in the objective functional. Existence of the result can be verified since all sufficient conditions are gathered but uniqueness can be debated see Pontryagin et al [21]. Scalar cost function includes a terminal cost associated to values of virus load at the end of the treatment as well as an integral cost of state and control along the period. Parameters α, β, ε are respectively weight constants for the virus, for the virus velocity and for the control inputs. They allow the balancing of size for each term and thus cost function can address various goals. First of all, one's target is to find a regimen which reduces high values of virus population both at the end time and during the period of the treatment. Also, we do not only want to minimize systemic cost of drugs in the aim to prevent from side effects and mutation of virus but also to slow down virus progression. An optimal control $u^*(t)$, $t_0 \leq t \leq t_f$ is sought such as $u^*(t)$ minimizes the cost function $J^{\varepsilon,\alpha,\beta}$,

$$u^* = \arg\min_{u\in\vartheta} J^{\varepsilon,\alpha,\beta}(V, u) \tag{13}$$

with the corresponding state $x^*(t)$ solution of state system subject to initial condition $x^*(t_0)$

$$\dot{x}^* = F(x^*, u^*), \qquad x^*(t_0) \text{ given.} \tag{14}$$

Methods for solving optimal control problem (OCPs) can be roughly classified in two different types – direct and indirect approaches see Stengel [24] and Von Stryk [26]. The direct methods optimise directly the cost functional using the parametrisation of control by approximating control and state vector with a sum of function expansion. The advantage is a good numerical robustness with respect to the initial guess but low accuracy of results is noticed. The indirect methods are based on Pontryaguine's minimum principle. The numerical convergence is fast and the solutions are accurate if one starts with a good initial guess see Bryson et al [4]. The optimality system obtained is a two-point boundary value problem, where initial conditions are specified for the state system (14) and terminal conditions are identified after calculations for the adjoint system (16), (18). Namely, the Hamiltonian of the problem is introduced

$$H^{\varepsilon,\alpha,\beta}(x, u, p) = J^{\varepsilon,\alpha,\beta}(x, u) + {}^t pF(x, u), \tag{15}$$

where p is the costate vector which components are called adjoint variables or more commonly Lagrange multipliers. According the Pontryaguine's minimum principle refer to Adams et al [1], Callaway et al [5], Culshaw et al [6], Fister et al [9], Garira et al [8], Joshi [10], Kirschner et al [14] and Stengel [23], the

optimality conditions are,

$$\dot{p} = -^t \left(\frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial x} \right) (x^*, u^*, p), \tag{16}$$

or rather

$$\dot{p} = -^t \left(\frac{\partial F}{\partial x} \right) (x^*, u^*) p - {}^t \left(\frac{\partial L}{\partial x} \right) (x^*, u^*) \tag{17}$$

with transversality condition

$$p(t_f) = \frac{\partial \phi(x_{t_f})}{\partial x_{t_f}} = {}^t(0, 0, 0, \alpha V(t_f), 0, 0) \tag{18}$$

and

$${}^t \left(\frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial u} \right) (x^*, u^*) = 0, \tag{19}$$

or another way

$${}^t \left(\frac{\partial F}{\partial u} \right) (x^*, u^*) p + {}^t \left(\frac{\partial L}{\partial u} \right) (x^*, u^*) = 0. \tag{20}$$

4. Numerical Results and Discussion

Analytical solution for optimal control is difficult to obtain since the systems are non-linear. One should proceed with an iterative gradient descent method. The dynamic systems response is exactly computed with adjusted control history from one iteration to the next in order to reduce cost function at each step. A starting guess for the control history u_1^0 and u_2^0 is made for the two controls on $[t_0, t_f]$. Commonly zero or a constant control is chosen to initiate calculus. The state system (14) is solved forward from t_0 to t_f using a variable step-size Runge-Kutta's algorithm taking into account initial state conditions. The cost function is then evaluated. Using the state values one solves the adjoint system backward integrating back from the end condition specified by (18). Unlike most papers the terminal state condition is not reduced to zero due to end time first quadratic term and derivative term $\dot{V}$ under the integral in the cost function. Cost function gradient is then computed and condition (19) is checked. Since the condition is generally not satisfied a steepest-descent method is used to update the control,

$$u^{k+1} = u^k - \rho_k \frac{\partial J^{\varepsilon,\alpha,\beta}}{\partial u}(u^k) \quad 0 \leq \rho_k \leq \rho_0, \tag{21}$$

or according to control constraints

$$u^{k+1} = P_\vartheta(u^k - \rho_k \frac{\partial J^{\varepsilon,\alpha,\beta}}{\partial u}(u^k)), \tag{22}$$

where P_ϑ denotes projection operator on ϑ, ρ_k is a small positive constant and k an iteration index. Proper selection of the step size ρ_k is critical to get rapid convergence. In this paper, ρ_k is set in order to minimize

$$\rho \in \mathbb{R} \to f(\rho) = J^{\varepsilon,\alpha,\beta}(P_\vartheta(u^k - \rho \frac{\partial J^{\varepsilon,\alpha,\beta}}{\partial u}(u^k))). \tag{23}$$

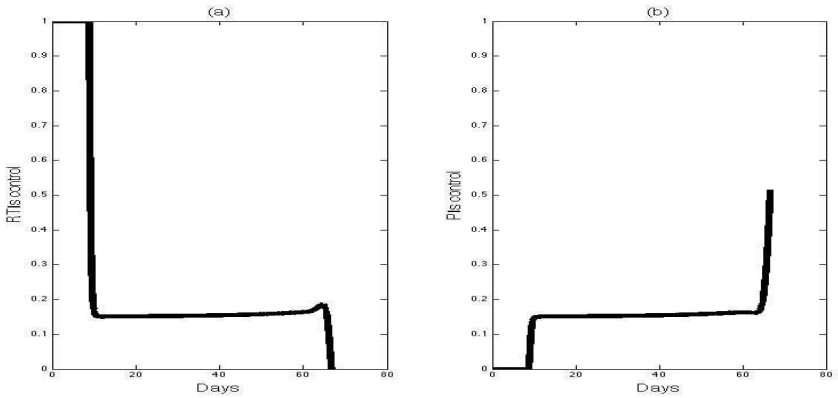

Figure 3: Numerical solutions to the optimality system showing reverse transcriptase inhibitor (a) and protease inhibitor (b) history when treatment is administered for 60 days

Minimizing f is not an easy task due to the non-linearity of the system. High instability of the optimality system in the adjoint variables can also be noticed. Variations of the adjoint variables even in controlled case can be very large. At each testing value ρ, a corresponding u_ρ must be calculated and introduced to system (7)-(8) to compute corresponding solution x_ρ. A Nelder-Mead simplex algorithm is applied. This method is convenient because analytical or numerical gradient are not to be supplied and it is robust enough to handle non-linear problems.

Noting that it depends mainly on the initial values of control u^0 whether the method succeed in finding the minimum point for the cost index. It may sometimes get to a saddle or even get lost. All calculus were carried out in

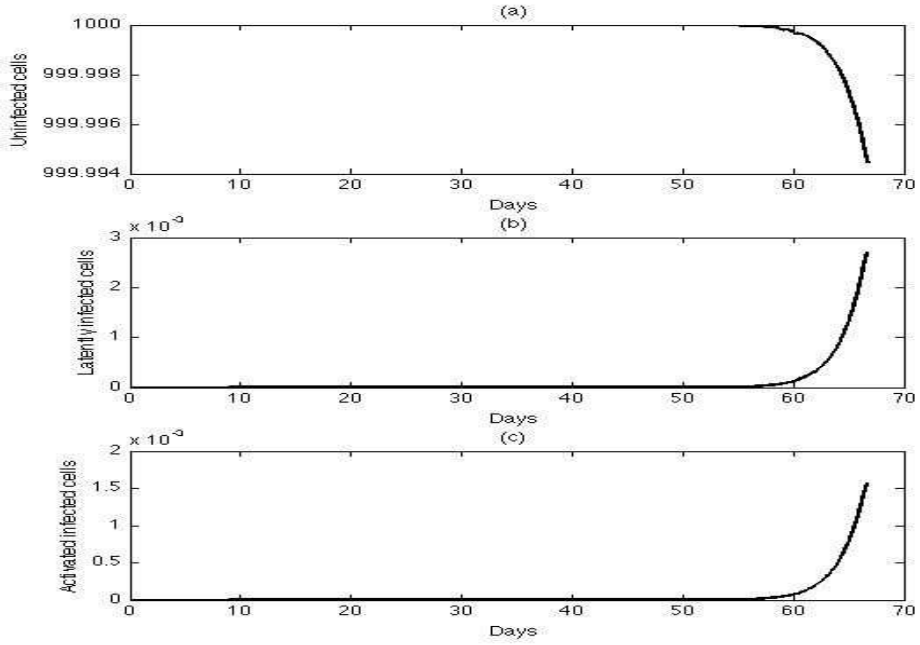

Figure 4: Numerical solutions to the optimality system when treatment is administered for 60 days

a *MATLAB* environment. Results were also verified by employing a commercial package to solve continuous time optimal control problem for nonlinear dynamics, *PROPT*.

Simulations are run with $t_f = 30$, $t_f = 60$ and $t_f = 100$ days. In Figure 3 to Figure 8, results of population progression are presented in the case of optimal therapy for $1mm^3$ of blood. Weighting constants must be chosen according to the relative significance between size of virus population and drug cost we want to establish in the objective function. As a drastic reduction of virus load is sought, we set $\alpha = 1e6$, $\epsilon = 1$ and $\beta = 1e5$. None of these short term treatments eliminates totally infected sources and thereafter infection can resume. From a mathematical point of view, we force the model to drive toward the unstable healthy state by applying controls. Though optimal treatment allows to maintain constant CD4+ T cells almost the entire length of therapy without giving whole drug quantities. An acceptable approximation of the optimal

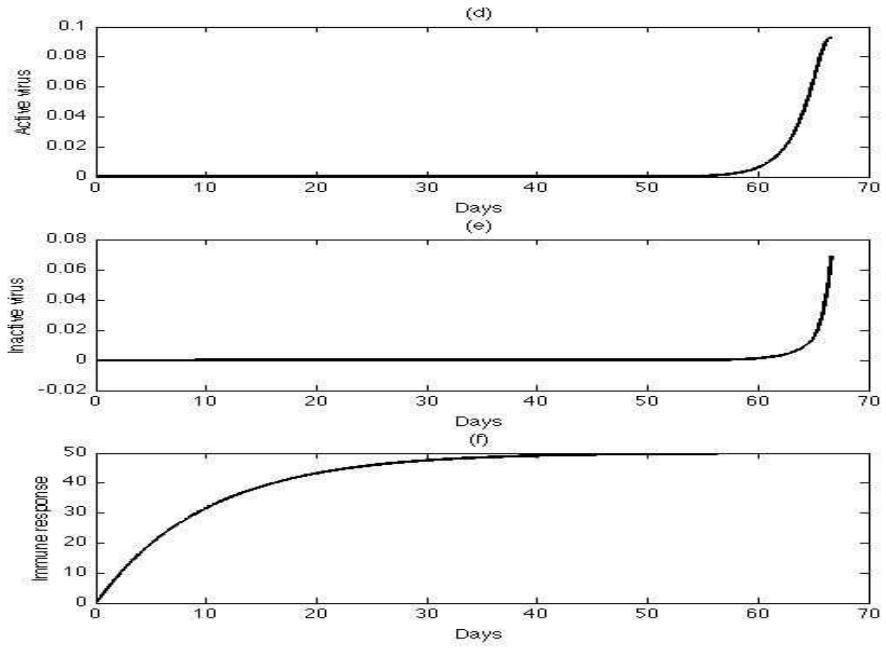

Figure 5: Numerical solutions to the optimality system when treatment is administered for 60 days

control is able to make virus load decrease to values smaller than 100 copies per ml of blood at the end of treatment and therefore maintains a high healthy white cell count more than 800 copies. Treatment windows correlate with the period where greater oscillation takes place. The phenomenon is delayed and is drastically reduced in magnitude. In all cases, infected cell peaks of small magnitude and corresponding healthy cell falls occur at the end of therapy. RTI and PI dosage graphs are very different. Especially at each starting and end period where RTI drug dosage and PI drug dosage behaves in an opposite way. Corresponding values of cost functional for optimal control are given in Table 2. For comparison, fully treated patient results are also provided. As expected, optimal cost is always smaller than fully treatment cost. As a matter of fact continuous variation of drug doses is difficult to apply in a real treatment of patient. For a practical implementation drug dosages are sought in quantized levels. According to optimal control curves, treatment is divided

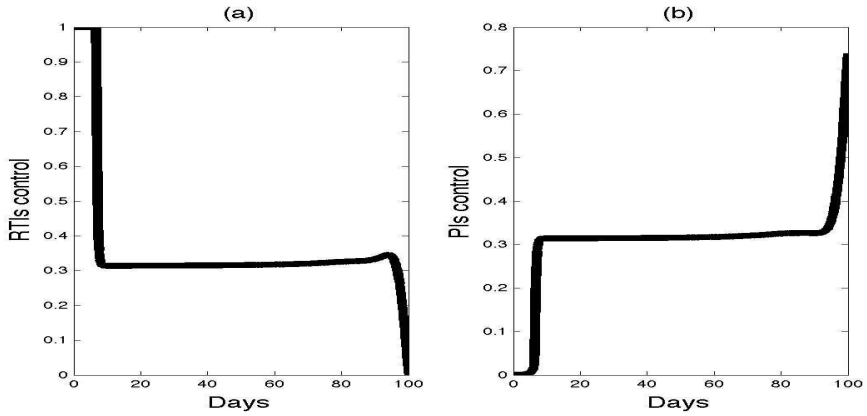

Figure 6: Numerical solutions to the optimality system showing reverse transcriptase inhibitor: (a) and protease inhibitor; (b) history when treatment is administered for 100 days

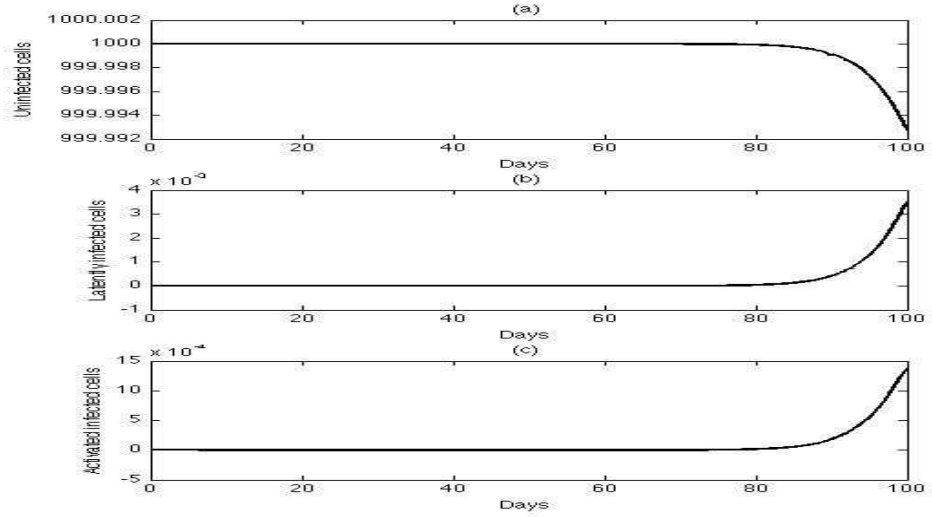

Figure 7: Numerical solutions to the optimality system when treatment is administered for 100 days

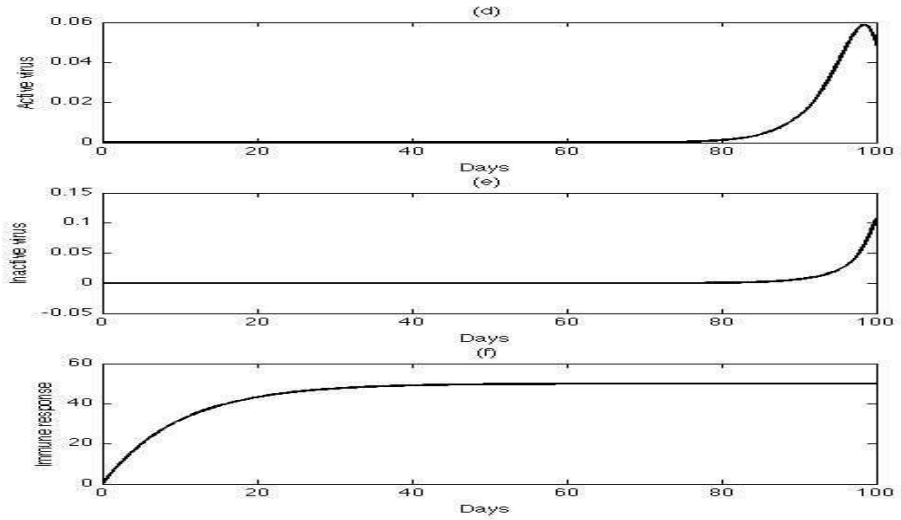

Figure 8: Numerical solutions to the optimality system when treatment is administered for 100 days

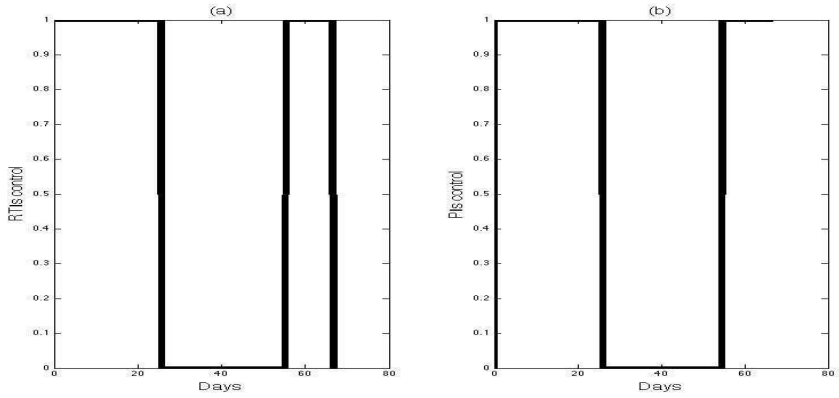

Figure 9: Numerical solutions to the optimality system showing reverse transcriptase inhibitor: (a) and protease inhibitor; (b) history when treatment is administered for 60 days.

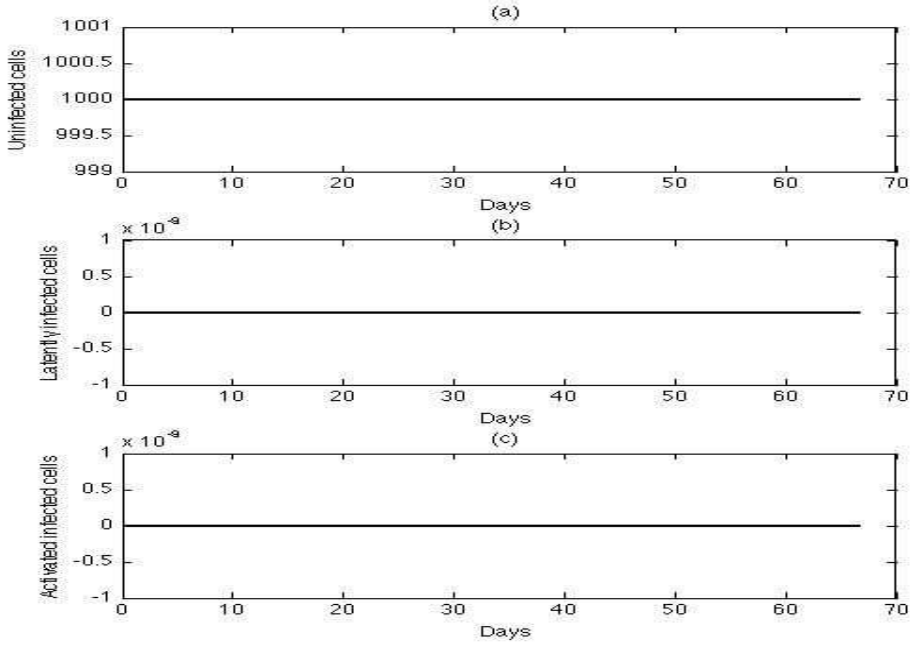

Figure 10: Numerical solutions to the optimality system when treatment is administered for 60 days

in three stages. For RTIs medication, we notice a full dose at the beginning during the first week, a constant level of 15% to 30% of dose during main part of treatment and finally a gradually reduction to no dose throughout the last days. For PIs medication, we observe that no dose is required at the beginning during the first week, a constant level of 15% to 30% of dose during main part of treatment and finally a half of full dose of drug throughout the last days. A bang-bang control can be applied as illustrated in Figure 9 to Figure 11 but is far from optimal in our problem since the cost index is $J^{\varepsilon,\alpha,\beta} = 1.191$ in sixty days treatment. It implies to put on and put off patient from treatment. It can be interpreted as scheduled interrupted treatments and has appeared to be a solution to bring relief from all those long term using drug complications.

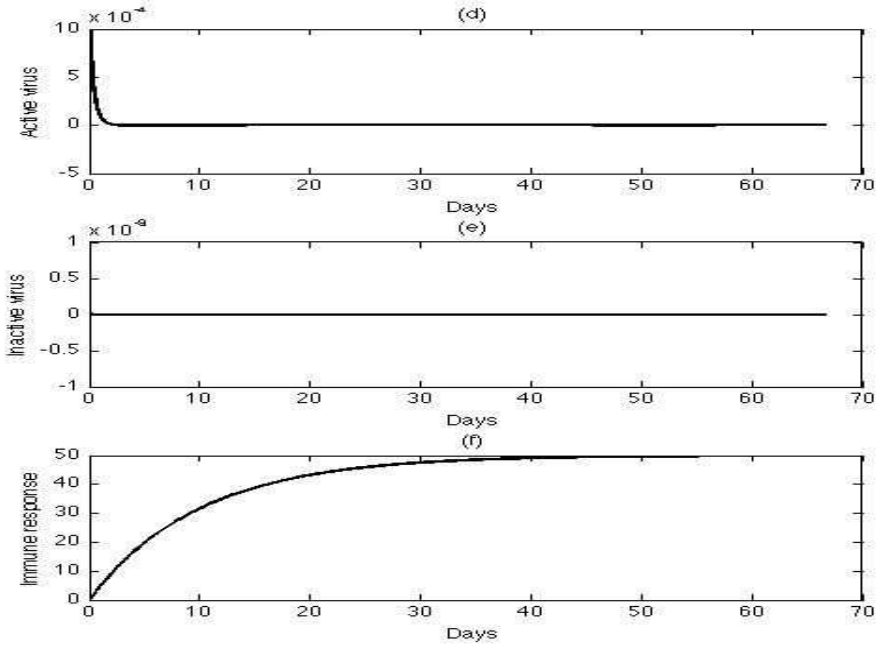

Figure 11: Numerical solutions to the optimality system when treatment is administered for 60 days

5. Conclusions

In this paper, a deterministic model including immune response and multi drug effects is introduced to model HIV infection evolution. We use optimization theories in order to derive optimal control solution and design improved treatments. We proved that a reduced dosage of drugs can achieved similar goals than a constant level therapy and then can replace it. The possibility of a scheduled interrupted treatment was also considered through a bang-bang control. It was not kept in our case since less optimal. The dynamic of infection is certainly far more complicated than the one captured by this simple mathematical model but this work illustrates the possibilities and difficulties of applying numerical methods of optimization to design future treatments. Above all, it must not be forgotten that non-linear programming problems are to be addressed in most of the cases. Optimal control problems have received much attention and

days	full control	optimal control	final state
30	1	0.08	(999.9,3e-3,2e-3,9e-2,7e-2,48)
60	2	0.18	(999.9,3e-3,1e-3,9e-2,7e-2,49.9)
100	3	0.67	(999.9,3e-3,1e-3,5e-2,0.11,50)

Table 2: Values of the cost function $J^{\epsilon,\alpha,\beta}$ with $\epsilon = 1$,$\alpha = 1e6$ and $\beta = 1e5$.

researches are still in progress to overcome solution convergence matters.

Acknowledgments

I would like to thank Professor Philippe Destuynder for critical and helpful comments on theoretical and numerical results.

References

[1] B. Adams, H. Banks, M. Davidian, H. Kwon, H. Tran, S. Wynne, E. Rosenberg, HIV dynamics: modeling, data analysis, and optimal treatment protocols, *Journal of Computational and Applied Mathematics*, **184**, No. 1 (2005), 10-49.

[2] S. Bonhoeffer, M. Rembiszewski, G. Ortiz, D. Nixon, Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection., *AIDS*, **14**, No. 15 (2000), 2313.

[3] D. Bortz, P. Nelson, Model selection and mixed-effects modeling of HIV infection dynamics, *Bulletin of Mathematical Biology*, **68**, No. 8 (2006), 2005-2025.

[4] A. Bryson, Y. Ho, *Applied Optimal Control*, Wiley New York (1975).

[5] D. Callaway, A. Perelson, HIV-1 infection and low steady state viral loads, *Bulletin of mathematical biology*, **64**, No. 1 (2002), 29-64.

[6] R. Culshaw, S. Ruan, A delay-differential equation model of HIV infection of CD4+ T-cells, *Mathematical Biosciences*, **165**, No. 1 (2000), 27-39.

[7] R. Culshaw, S. Ruan, R. Spiteri, Optimal HIV treatment by maximising immune response, *Journal of Mathematical Biology*, **48**, No. 5 (2004), 545-562.

[8] W. Garira, S. Musekwa, T. Shiri, Optimal control of combined therapy in a single strain HIV-1 model, *Electronic Journal of Differential Equations*, **52** (2005), 1-22.

[9] K. Fister, S. Lenhart, J. McNally, Optimizing chemotherapy in an HIV model, *Electronic Journal of Differential Equations*, **32** (1998), 1-12.

[10] H.R. Joshi, Optimal control of an hiv immunology model, *Optimal Control Appl. Methods*, **23** (2002), 199-213.

[11] D. Ho, A. Neumann, A. Perelson, W. Chen, J. Leonard, M. Markowitz, Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection, *Nature*, **373**, No. 6510 (1995), 123-126.

[12] J. Karrakchou, M. Rachik, S. Gourari, Optimal control and infectiology: Application to an HIV/AIDS model, *Applied Mathematics and Computation*, **177**, No. 2 (2006), 807-818.

[13] D. Kirschner, S. Lenhart, S. Serbin, optimal control of the chemotherapy of HIV, *J. Math. Biol.*, **35** (1997), 775-792.

[14] E. Kirschner, F. Webb, Immunotherapy of HIV-1 infection, *Journal of Biological Systems*, **6**, No. 1 (1998), 71-83.

[15] H. Kwon, Optimal treatment strategies derived from a HIV model with drug-resistant mutants, *Applied Mathematics and Computation*, **188**, No. 2 (2007), 1193-1204.

[16] J. Murray, *Mathematical Biology*, Springer (2003).

[17] M. Nowak, S. Bonhoeffer, G. Shaw, R. May, Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations, *Journal of Theoretical Biology*, **184**, No. 2 (1997), 203-217.

[18] A. Perelson, D. Kirschner, R. De Boer, Dynamics of HIV infection in CD4$\hat{+}$ T cells, *Mathematical Biosciences*, **114** (1993), 81-125.

[19] A. Perelson, P. Nelson, Mathematical analysis of HIV-I: dynamics in vivo, *Siam Review* (1999), 3-44.

[20] N. Perera, *Deterministic and Stochastic Models of Virus Dynamics*, Ph.D. Thesis, Texas Tech University (2003).

[21] L. Pontryagin, V. Boltyanskii, R. Gamkrelidze, E. Mishchenko, *The Mathematical Theory of Optimal Processes*, Wiley, New York (1962).

[22] S. Snedecor, Comparison of three kinetic models of HIV-1 infection: Implications for optimization of treatment, *Journal of Theoretical Biology*, **221**, No. 4 (2003), 519-541.

[23] R. Stengel, Mutation and control of the human immunodeficiency virus, *Mathematical Biosciences*.

[24] R. Stengel, *Optimal Control and Estimation*, Dover Pubns (1994).

[25] V. Velichenko, D. Pritykin, Numerical methods of optimal control of the HIV-infection dynamics, *Journal of Computer and Systems Sciences International*, **45**, No. 6 (2006), 894-905.

[26] O. Von Stryk, R. Bulirsch, Direct and indirect methods for trajectory optimization, *Annals of Operations Research*, **37**, No. 1 (1992), 357-373.

[27] D. Wodarz, P. Klenerman, M. Nowak, Dynamics of cytotoxic T-lymphocyte exhaustion., *Proceedings of the Royal Society B: Biological Sciences*, **265**, No. 1392 (1998), 191.

[28] D. Wodarz, M. Nowak, Mathematical models of HIV pathogenesis and treatment, *BioEssays*, **24**, No. 12.