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Optimal drug scheduling for HIV therapy efficiency improvement

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ABSTRACT

The purpose of the paper is to use numerical analysis and optimisation tools developed for applied mechanic research to suggest improved therapies to try and cure 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-drug treatment strategy based on Pontryagin's minimum principle. Basically, the method applied in this paper can be considered as an optimal control one, where drug dose effects are regarded as control inputs.

The quadratic objective function considered takes into account three contributions: the viral load, the transient evolution of infection and the percentage of efficiency of drug used. Simulations are carried out using an indirect optimisation method. At each step the differential system is solved using Runge–Kutta scheme. The effectiveness of drug is assumed to be fully controlled by drug dose level. Results based on an high drug dose strength ratio hypothesis highlight that a progressive reduction of reverse transcriptase inhibitor drug dose on the one hand along with, on the other hand, a progressive increase of protease inhibitor one is needed for optimality in common cases. The possibility of improving scheduled interrupted treatment which has lacked benefits and moreover has appeared to be harmful in clinical trials so far, is then examined.

Contents

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. The viruses 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 are 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 other serious illness like insulin resistance, cardiovascular pathologies, hepatitis or myopathies due to the toxicity of treatment. Other concerns also arise viral rebound due to a mutation of the virus. Indeed on the one hand, the 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 mutants which are likely to resist treatments. Regularly drug changes are needed and in some cases the inability to find any appropriate pharmaceutical drug combinations is noted since virus is no longer reactive to any therapy. Hence

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poor compliance with drug prescription is currently noticed in the patient's behaviour. Up to now, the solution suggested by the World Health Organisation is to administrate a constant antiviral drug dose which efficiency is assumed to be stable in time and which can be changed from time to time according to the patient's condition. Idealistic solution will be to lower and maintain the virus load at such a level that the immune system controls it with low amount of drugs over short spells. A first logical response is to apply a scheduled interrupted treatment where patients are alternatively cycled on and cycled off from HAART during short spans. But results are deceiving because during treatment breaks, patients get the same symptoms as in acute HIV infection case and after resuming treatment they experience worse side effects. Two major clinical studies come to the conclusion of the inefficiency of this approach furthermore a faster disease progression and higher rate of HIV-related health problems or death are noticed. Hence structured treatments interruptions, initially intended to alleviate patient quality of life, lead to greater harm than benefit in most of clinical trials. The idea developed in this paper is to alternate fully dose treatment which is able to make viremia decrease below limit of detection with an optimal treatment, less toxic, which brings relief to patient state and stimulates immune response.

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 [1–4]. Mathematical models have become essential tools to make assumptions, suggest new experiments or help explaining easily complex processes. Different aspects are encompassed in each model which are by the time more and more comprehensive and accurate [5–13]. But a complete analysis can hardly be achieved with complicated models and simple conclusions are difficult to deduce. In addition, all new parameters introduced, whose values must be known to carry out any simulation, may not be accurately fit by experimental data or they require a new measurement method [14–16]. Most of the models are deterministic prey–predator systems of non-linear differential equations. Sometimes stochastic terms are included to address the random behaviour 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 [17,18,3,16]. At the same time, optimal control has received much attention especially in mechanical and aerospace engineering for example for the re-entry shuttle problems. The main idea is to use optimisation 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 organised as follows: in the second section, the deterministic model chosen with its specific aspects is presented and explained. In the third section an optimal control is derived by using Pontryagin's minimum principle and the adjoint method. Numerical results are illustrated and commented in the last section.

2. Methods

2.1. Mathematical model

The model introduced results from modifications made to published models taking account of multi-drug therapy combination along with specific immune response to HIV [19,20,16]. 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 due to the action of protease inhibitor, E, the concentration of cytotoxic T lymphocytes (CTLs). These state variables are the key-compartments commonly observed in clinical data and obviously must be positive along our calculus. Drug efficiency is represented by the controls u_1 and u_2, $(0 \le u_1 \le 1, 0 \le u_2 \le 1)$ which account respectively for reverse transcriptase and protease inhibitor actions.

Table 1
Parameters and constants used in the model.

Parameter and constants	Values with unit
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-5 $mm^3\ d^{-1}$
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 $mm^3\ d^{-1}$
k_4: rate growth of CTL	1e-5 $mm^6\ d^{-1}$

$$\dot{T} = rT\left(1 - \frac{T+L+I}{T\max}\right) - \mu_T T - (1-u_1)k_1 VT + s_1. \quad (1)$$

$$\dot{L} = \omega(1-u_1)k_1 VT - \mu_T L - k_2 I. \quad (2)$$

$$\dot{I} = (1-\omega)(1-u_1)k_1 VT + k_2 I - \mu_I I - k_3 IE. \quad (3)$$

$$\dot{V} = a(1-u_2)I - k_1 VT - \mu_V V. \quad (4)$$

$$\dot{N} = au_2 I - \mu_V N. \quad (5)$$

$$\dot{E} = k_4 ITE - \mu_E E + s_2. \quad (6)$$

or in vector form:

$$\dot{x} = F(x(t,u), u(t)), \quad (7)$$

$$x(0) = (T_0, 0, 0, V_0, 0, 0)^T \quad (8)$$

where $x(t) = (T, L, I, V, N, E))^T$ and ^{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 cell interactions. Nevertheless definitions and numerical values for the parameters are summarised in Table 1 and taken from [6,19,21]. Parameter values may vary on the one hand from a patient to the other and, on the other hand, may not be constant in time during the course of the disease [22]. As we assume the system is well mixed, mass action law is used to account for cells interacting 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 a virus is lost and we add the term $-k_1 VT$ 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 $(1-u_1)k_1 VT$ 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 a fraction of latently infected CD4+T cells in infected cells production and then we add $(1-\omega)(1-u_1)k_1 VT$ to (2) and $\omega(1-u_1)k_1 VT$ to (3). We assume that latently infected cells which haven't yet produce virus, 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 [14,23,5,20,24]. CTLs kill infected cells without being targeted by HIV virus and prevent uninfected cells from being contaminated by the chemokines they release [21]. The reduction of viral infectivity is not examined and all CTL population is considered in this paper without making differences between precursor and effector cells. 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 helper cells and on CTLs, hence the trilinear term in (6) is introduced [19,21,24,13]. Elimination of infectious CD4+T cells by CTLs are added by $-k_3IE$ term in (4). Unlike other models considering an immune response, CTLs production is also supposed to be performed by thymus at a constant rate s_2. The uninfected cells CD4+T are expected to satisfy a logistic growth whose carrying capacity is set by Tmax and rate growth by r.

When CD4+T cell count and viral load are satisfactory, fully dose treatment is interrupted. Hence control u_1 and u_2 values are set to zero. Rebound of infection occurs in blood due to incoming viruses from latent reservoirs. Therefore resuming infection is commonly simulated by an early infection with initial values $T(t_0)=1000$, $L(t_0)=I(t_0)=E(t_0)=0$ and $V(t_0)=0.001$ for $1\,\mathrm{mm}^3$ of blood for example. Another initial condition must be mentioned due to peculiar behaviour of virus in latently infected CD4+T cells. Indeed some latently infected T-cells will not become activated and instead revert back to a resting state similar to a memory T-cell state carrying an integrated provirus and capable of resuming virus production in blood after reactivation. The effect of latently infected cell reservoir can be set with different initial conditions in the model by $T(t_0)=1000$, $I(t_0)=V(t_0)=E(t_0)=0$ and $L(t_0)=0.001$ for $1\,\mathrm{mm}^3$. We also assume that half of the infected cells becomes latent before actively infected during the process hence $w=0.5$. If medication is not started again, the natural response of the system is shown in Figs. 1 and 2. A further analysis shows that the system has two biologically significative 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 to a healthy state and the last to a HIV seropositive state.

2.2. Optimal control

The model described by (1)–(6) can simulate the course of the disease under a prescribed treatment along with an immune response but the issue of finding a control law such as a certain optimality criterion would be achieved has not yet been addressed. Many studies have already been carried out using an optimal control theoretical approach to design an optimal drug therapy. But investigations were based on other type of mathematical models and mainly different objective functionals [19,25,21,17,18,8,11]. 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:

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

with:

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

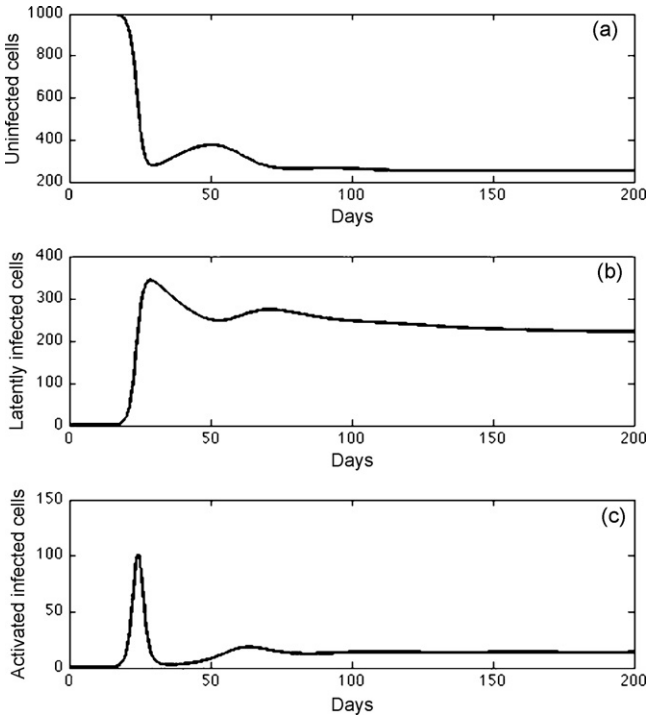

Fig. 1. Numerical solutions to the ordinary differential system with no treatment: (a), the uninfected CD4+T cell population; (b), the latently infected CD4+T cells; (c), the infected CD4+T cells. Initial conditions $T(t_0)=1000$, $L(t_0)=I(t_0)=N(t_0)=E(t_0)=0$ and $V(t_0)=0.001$ for $1\,\mathrm{mm}^3$.

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

where:

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

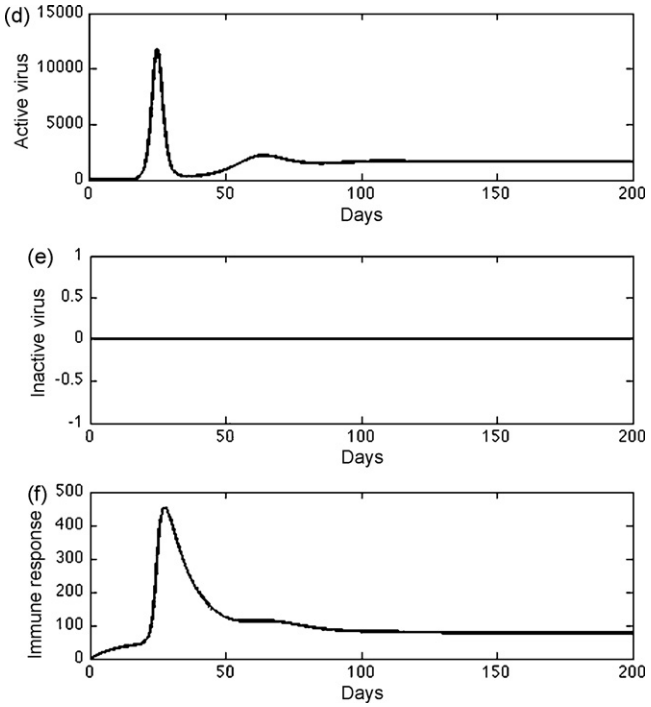

Fig. 2. Numerical solutions to the ordinary differential system with no treatment. (d), active virus; (e), inactive virus; (f), cytotoxic T lymphocytes; Initial conditions $T(t_0)=1000$, $L(t_0)=I(t_0)=N(t_0)=E(t_0)=0$ and $V(t_0)=0.001$ for $1\,\mathrm{mm}^3$.

and $L(x, u, t)$, the Lagrangian of the problem. Unlike in most papers, all parameters are squared in the objective functional. Existence of a solution can be verified since all sufficient conditions are gathered but uniqueness can be debated [26]. 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 treatment period. Also, we do not only want to minimise the systemic cost of drugs to reduce the treatment toxicity but we also want to slow down the virus progression. An optimal control $u^*(t)$, $t_0 \le t \le t_f$ is sought such as $u^*(t)$ minimises the cost function $J^{\varepsilon,\alpha,\beta}$:

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

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 [27,28]. 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 a low accuracy of results is noticed. Indirect methods are based on Pontryagin's minimum principle. Numerical convergence is fast and solutions are accurate if one starts with a good initial guess [29,27]. 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:

$$H^{\varepsilon,\alpha,\beta}(x, u, p) = L^{\varepsilon,\alpha,\beta}(x, u) + p^T F(x, u), \tag{15}$$

where p is the costate vector whose components are called adjoint variables or more commonly Lagrange multipliers. The optimality conditions are [29,30]:

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

or rather:

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

with transversality condition:

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

Since the controls are bounded, the Pontryagin's minimum principle [29,31,30] states:

$$H^{\varepsilon,\alpha,\beta}(x^*, u^*, p^*) \le H^{\varepsilon,\alpha,\beta}(x^*, u, p^*) \tag{19}$$

for all admissible $u \in \vartheta$ where * denotes optimal quantities. In many papers, additional Lagrange multipliers are introduced in (15) to account for the constraints on input controls and optimality inequality (19) is replaced by a stationarity condition which holds in unconstrained input control case [14,5,6,25,21,17,8,11]:

$$\left(\frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial u}\right)^T (x^*, u^*, p^*) = 0, \tag{20}$$

with:

$$\left(\frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial u}\right)^T = \left(\frac{\partial F}{\partial u}\right)^T p + \left(\frac{\partial L}{\partial u}\right)^T. \tag{21}$$

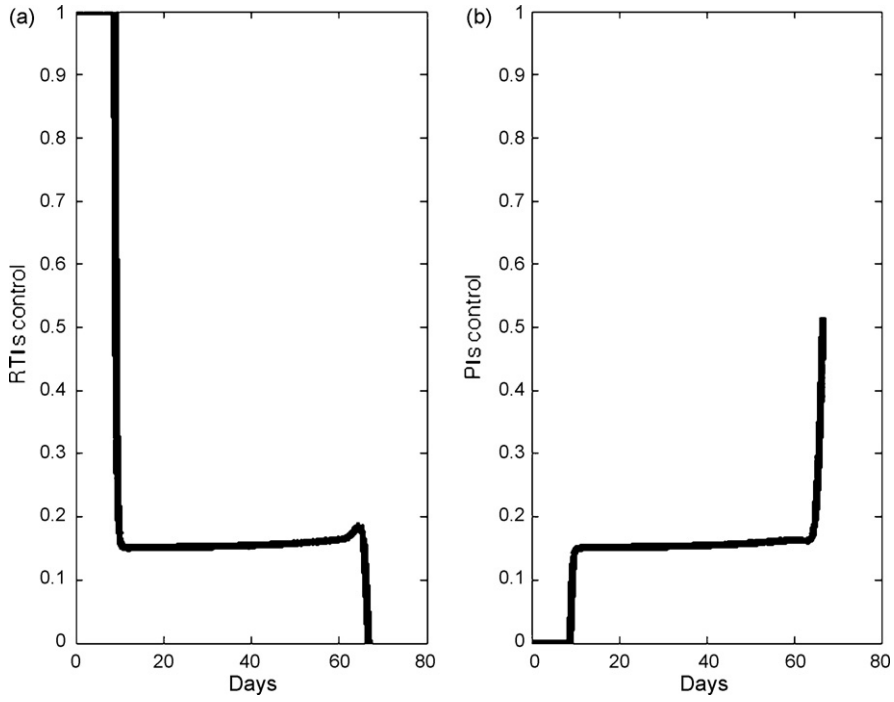

Fig. 3. Numerical solutions to the optimality system showing reverse transcriptase inhibitor (a) and protease inhibitor (b) histories when treatment is administered for 60 days. Initial conditions $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$ for 1 mm^3.

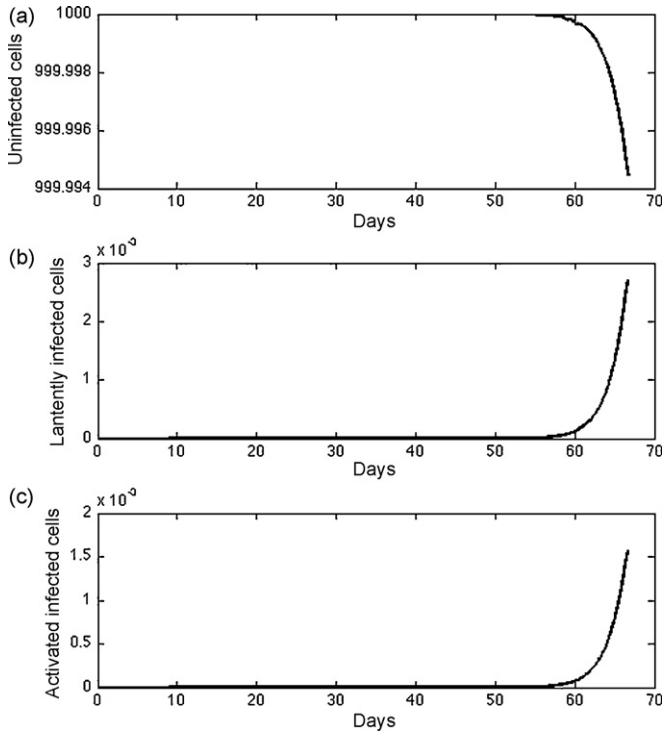

Fig. 4. Numerical solutions to the optimality system when treatment is administered for 60 days. $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$.

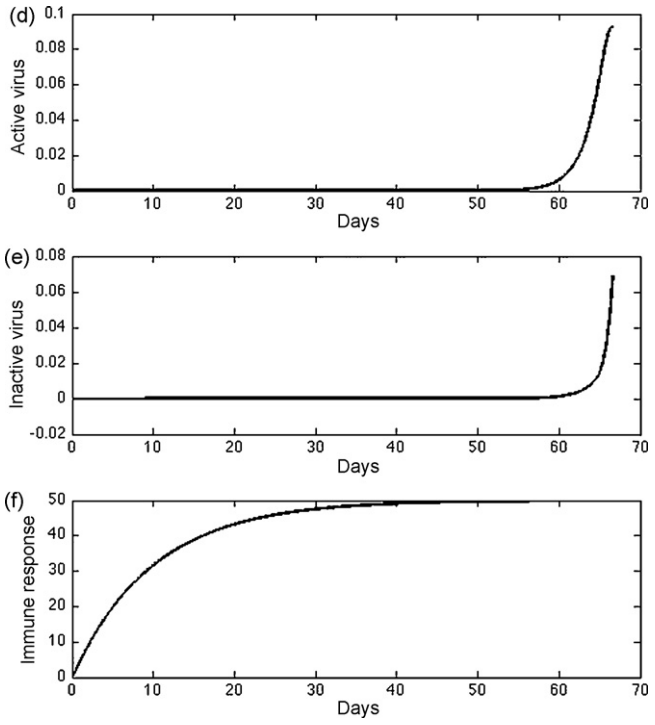

Fig. 5. Numerical solutions to the optimality system when treatment is administered for 60 days. $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$.

3. Numerical results and discussion

An analytical solution for optimal control is difficult to obtain since the systems are non-linear. One should proceed with a 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 $\left[t_0, t_f\right]$. 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. 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 in 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. Condition (19) implies that the Hamiltonian must be minimised with respect to the control input u. The partial derivative of the Hamiltonian along direction u (21) is then expected to get

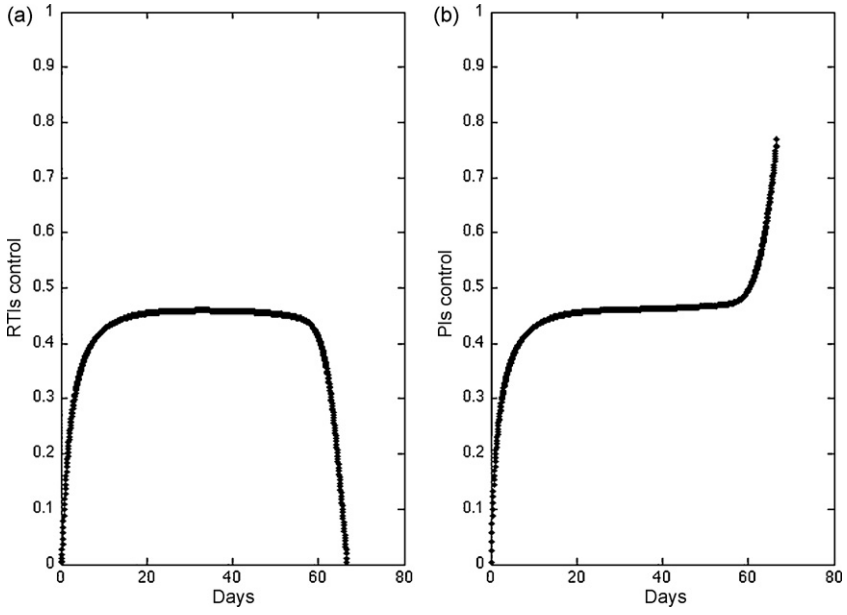

Fig. 6. Numerical solutions to the optimality system showing reverse transcriptase inhibitor (a) and protease inhibitor (b) histories for 60 days. Initial conditions $T(t_0) = 1000$, $I(t_0) = V(t_0) = N(t_0) = E(t_0) = 0$ and $L(t_0) = 0.001$ for 1 mm^3.

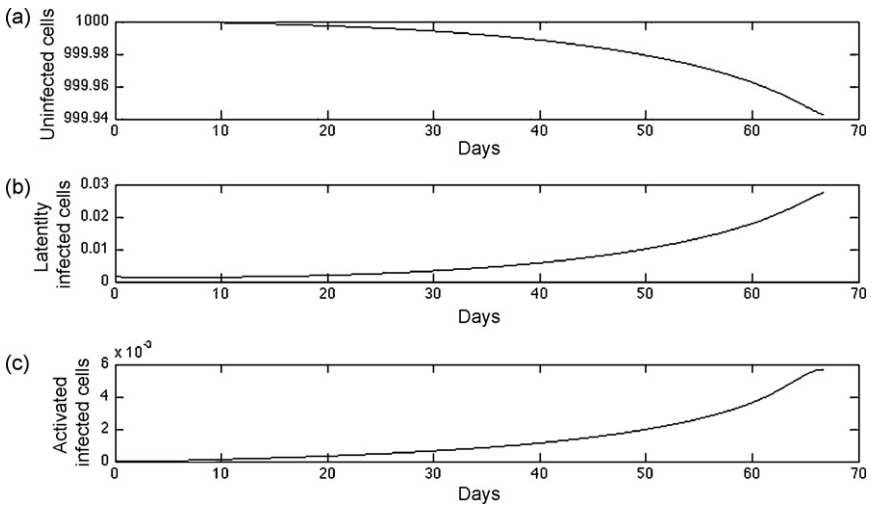

Fig. 7. Numerical solutions to the optimality system when treatment is administered for 60 days. $T(t_0) = 1000$, $I(t_0) = V(t_0) = N(t_0) = E(t_0) = 0$ and $L(t_0) = 0.001$.

close to zero as trajectory becomes optimal. Hence control history is updated as some function of this derivative. Namely:

$$u^{k+1} = u^k - \rho_k \frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial u}(u^k) \quad 0 \le \rho_k \le \rho_0 \tag{22}$$

or according to control constraints:

$$u^{k+1} = P_\vartheta \left(u^k - \rho_k \frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial u}(u^k) \right) \tag{23}$$

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 minimise

$$\rho \in \mathbb{R} \to f(\rho) = J^{\varepsilon,\alpha,\beta} \left(P_\vartheta \left(u^k - \rho \frac{\partial H^{\varepsilon,\alpha,\beta}}{\partial u}(u^k) \right) \right). \tag{24}$$

Minimising 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 important. 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 gradients are not to be supplied and it is robust enough to handle non-linear problems. Entire process is repeated as long as cost function value falls and stabilises around an acceptably small value. Noting that it depends mainly on the initial values of control u^0 whether the method succeeds in finding the minimum point for the cost index. It may sometimes get to a saddle or even get lost. All calculus are carried out in a MATLAB environment. Results are also verified by employing a commercial package to solve continuous time optimal control problem for non-linear dynamic system, PROPT-Matlab optimal control software distributed by Tomlab Optimization.

Simulations are run with 60-day period since a treatment is considered as effective provided it lowers strongly viral load (by at least 90 percent) within 2 months at the most according to American medical recommendations. From Figs. 3–8, results of population progression are presented in the case of optimal therapy for $1mm^3$ of blood. By substituting drug dose vacancy by optimal drug dose period, it is noticed that the large oscillations previously observed no longer take place and the phenomenon is delayed or drastically reduced in magnitude. Weighting constants must be chosen according to the relative significance between the size of the virus

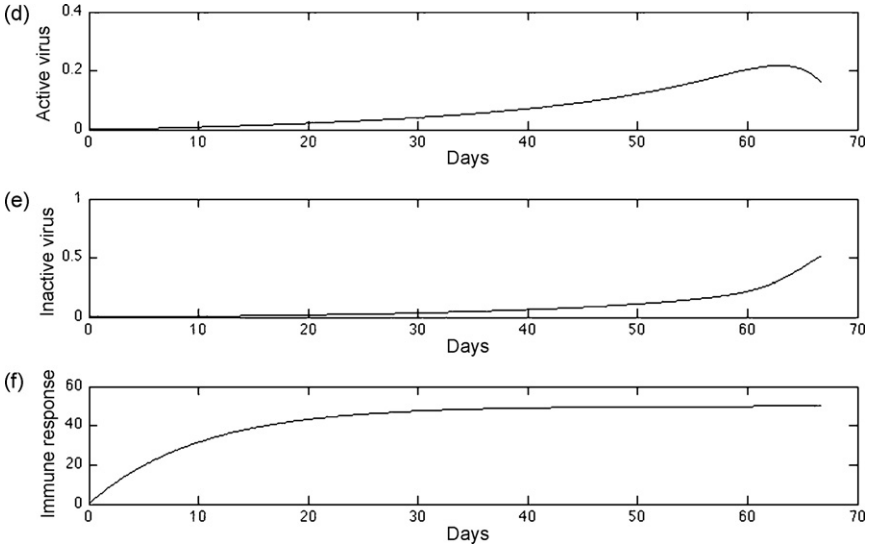

Fig. 8. Numerical solutions to the optimality system when treatment is administered for 60 days. $T(t_0) = 1000$, $I(t_0) = V(t_0) = N(t_0) = E(t_0) = 0$ and $L(t_0) = 0.001$.

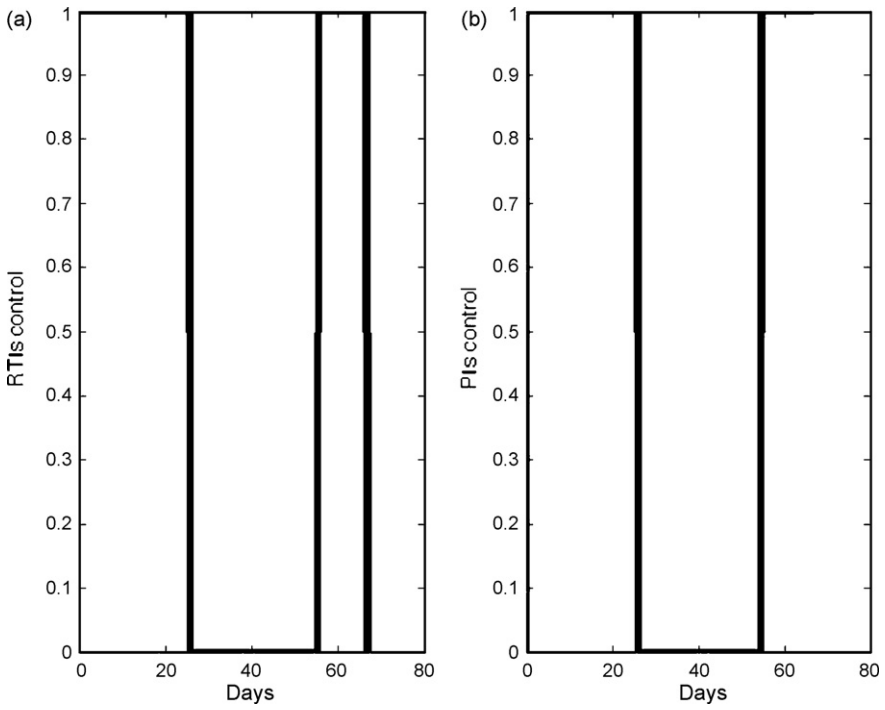

Fig. 9. Numerical solutions to the optimality system showing reverse transcriptase inhibitor (a) and protease inhibitor (b) histories when treatment is administered for 60 days. Bang bang control. Initial conditions $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$ for 1 mm^3.

population and the drug cost we want to establish in the objective function. As a strong reduction of virus load is sought, we set $\alpha = 1e6$, $\epsilon = 1$ and $\beta = 1e5$. As stated before, optimal short term treatment does not eliminate totally infected sources and thereafter it must be followed by fully dose medication until getting again satisfactory levels. Optimal treatment purpose is only to keep constant CD4+ T cell count and so to maintain patient in asymptomatic state during the time interval without giving whole drug quantities.

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 or ending period where RTI drug dosage and PI drug dosage behave in an opposite way in first optimal case. 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 or no treatment costs. As a matter of fact continuous variation of drug doses is difficult to apply in a real treatment of the patient. For a practical implementation drug dosages are sought in quantized levels. According to optimal control curves, treatment is divided in three steps. In the first case, for RTIs medication, we notice a full dose at the beginning during the first week, a 15% to 20% of dose during the main part of treatment and finally a gradual reduction to no dose throughout the last days. For PIs medication, we observe a gradually increasing dose at the beginning during the first week, a 15% to 20% of dose during main part of treatment and finally a full dose of drug throughout the last days. In the second case, curves have roughly the same plot features. Unlike first optimal case, RTI drug dose has to be increased gradually, certainly because of the lack of virus at initial state. A bang-bang control can be applied as illustrated from figures Figs. 9–11 but is far from optimal in our problem since the cost index is $J^{\varepsilon,\alpha,\beta} = 1.191$ in 60 days treatment. Nevertheless this therapy is advantageous since it is as successful as a full

Table 2
Values of the cost function $J^{\varepsilon,\alpha,\beta}$ with $\epsilon = 1, \alpha = 1e6$ and $\beta = 1e5$. (i) $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$. $T(t_0) = 1000$, $I(t_0) = V(t_0) = N(t_0) = E(t_0) = 0$ and $L(t_0) = 0.001$.

Control type	$J^{\varepsilon,\alpha,\beta}$	Final state
Free	4.57e7	(289.9, 271.2, 17.9, 2145.9, 0, 113.1)
Full	2	(1000, 0, 0, 0, 0, 50)
STI	1.191	(1000, 0, 0, 0, 0, 50)
Optimal (i)	0.18	(999.9, 3e-3, 1e-3, 9e-2, 7e-2, 49.9)
Optimal (ii)	0.40	(999.9, 2.5e-2, 5.5e-3, 0.16, 0.48, 49.9)

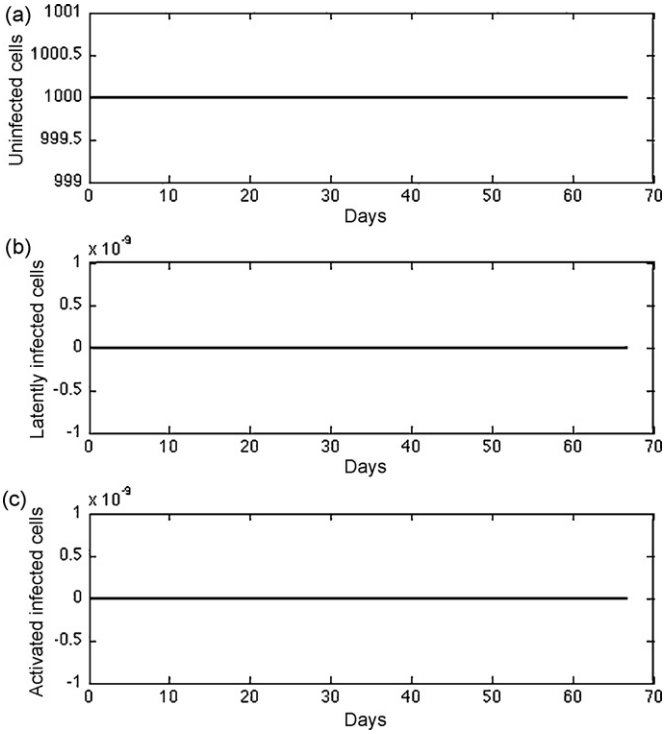

Fig. 10. Numerical solutions to the system with bang-bang control. Treatment is administered for 60 days. $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$.

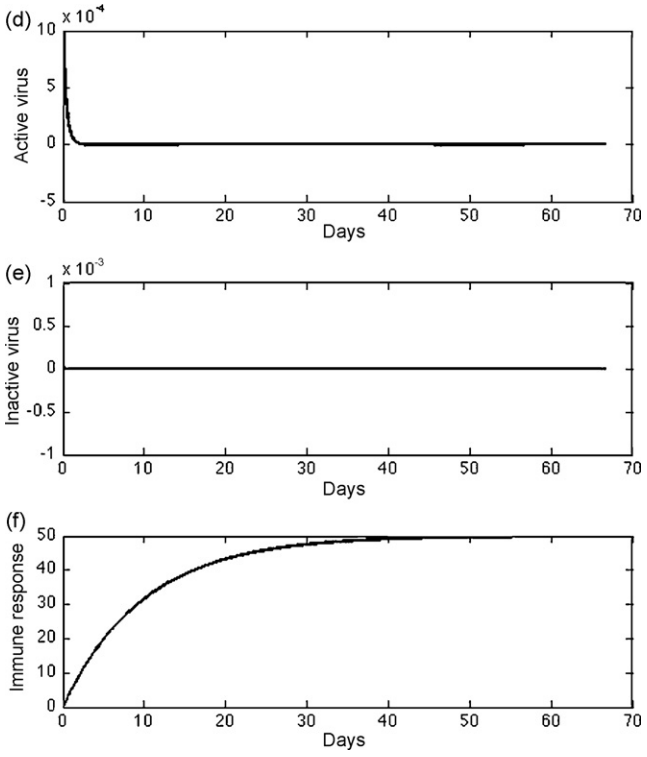

Fig. 11. Numerical solutions to the system with bang-bang control for 60 days. $T(t_0) = 1000$, $L(t_0) = I(t_0) = N(t_0) = E(t_0) = 0$ and $V(t_0) = 0.001$.

dose treatment for reducing or maintaining physiological parameters to acceptable levels with less toxicity. It can substitute for standard constant medication. It can be interpreted as scheduled interrupted treatment applied over shorter periods than usual ones. It is difficult to compare all optimal drug scheduling proposals published. Results are totally conditioned by parameters values along with initial conditions and command histories may differ drastically from one person to another. Many papers seem to come to the similar conclusion of fully dosing medication first at early stage to prevent virus load increase and after reducing it progressively [18,11,32]. These statements dispute the World Health Organization's prescription of constant drug doses and recommendations of waiting a low CD4+T cell count to start any therapy [33].

4. Conclusions

In this paper, a deterministic model including immune response and multi-drug effects is introduced to model HIV infection evolution. We use optimisation theories in order to derive optimal control solution and to improve already existing treatments. We proved that a reduced dosage of drugs can achieve similar goals to a constant level therapy and then can replace it. For a clinical practice, the possibility of an improved scheduled interrupted treatment where drug dose vacancies are replaced by optimal drug periods was considered. 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 optimisation 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 researches are still in progress to overcome solution convergence matters.

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