Multiobjective control of clinical conditions for HIV seropositive patients

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Abstract

Optimisation theory has been used to determine drug doses to control the clinical evolution of the HIV seropositive patients. Generally, the assessment to clinical conditions for that kind of patients involves several factors, including some conflicting ones. Due to this fact, the present work proposes the use of multiobjective optimization techniques. More specifically, the drug doses used to treat patients with AIDS are found by aiming at to maximize, simultaneously, the count of CD4+T cells, to minimize the viral load and the side effects. The side effect is modelled by a dose dependent damage term. The treatment on the other hand, requires a combination of two classes of drugs: reverse transcriptase and protease inhibitors. These drugs' effects are then modelled by a set of nonlinear ordinary differential equations. In addition, the optimization process involves restrictions on the various variables in the form of inequalities. The results compares favourably with those obtained by using a single performance criterion.

1. INTRODUCTION

In 2005, there were 40.3 millions of human beings living with HIV in the world living with HIV in the world (UNAIDS, 2005). This shows how important it is the study and the development of news techniques to combat AIDS.

The use of optimal control theory in biomedical problems has received increasing attention in the last years. The main objective is to select a control law (i.e., "*a treatment scheme*") such that the controlled dynamic system (i.e., "*the infected organism*") reacts in such a way that minimizes a cost ("*an actual cost of the treatment plus the intensity of the side effects*") or maximizes the therapeutic efficiency (which is indicated by the reduction of the viral load for instance).

In the literature several mathematical models that describe the clinical evolution HIV seropositive patients can be found, such as, for example: (Perelson, 1989), (Nowak and Bangham, 1996) and (Tan and Wu, 1998). This work is based on a simplified version of the latter, which has four differential equations representing the uninfected CD4+T cells, latent infected CD4+T cells, active infected cells CD4+T and free HIV viruses, respectively.

One way to obstruct the viral replication is associated to the following drugs: reverse transcriptase inhibitors (AZT, DDI, 3TC) and protease inhibitors (Saquinavir, Indinavir, Ritonavir). The high amount doses of these drugs during the treatment can cause some side effects such as diarrhoea, vomiting, nauseas coetaneous rash, abdominal girth and abdominal fullness (Mittler et al, 1998).

This work optimises the doses of reverse transcriptase and protease inhibitors, keeping the patient in a satisfactory clinical region, that is, increasing the count of uninfected CD4+T cells and decreasing the count of viral particles. In order was used to attain this, multiobjective optimization techniques were used, where the goal is to minimize "*in the best possible way*" the various objective functions. In general, the problem does not have a unique optimal solution that could optimize all objectives simultaneously. Instead, there exists a set of equally efficient, or non-inferior, alternative solution, kwon as the Pareto-optimal set (Liu et al., 2003).

To find one and only one solution, here it was used the interactive method known as Fandel method, which the goal is to transform the problem so that it turns into a mono-objective optimization problem, associating a weight to every objective function and then take a weighted sum of all objective functions. Hence a new and unique objective function is obtained.

The results obtained through of the multiobjective optimal control are compared to a scheme of treatment where high drug dosages are used, with the knowledge that these results can be improved with the use of more realistic cost functions or the inclusion of alternative forms of HIV infection treatments.

2. MATHEMATICAL DYNAMIC MODEL OF AIDS

The use of mathematical models, especially in the field of immunology, has produced important results in the clinical care of AIDS patients (Asachenkov et al., 1994), (Cherrualt, 1986), (Levin et al., 1997).

Models for HIV infection dynamics can be found in (Nowak et al., 1991), (Perelson et al., 1993), (Murray et al, 1998), (Tan and Xiang, 1999) among others.

The mathematical model used in this work is a simplification of a more general one by (Tan and Wu, 1998) that includes stochastic terms. The model consists in a set of four differential equations, given by:

$$
\begin{aligned}
\frac{dx_1(t)}{dt} &= S(x_4(t)) + \lambda(x_1(t), x_2(t), x_3(t))\, x_1(t) + \\
&\quad - x_1(t)\{\mu_1 + k_1(m_1(t))\, x_4(t)\} \\
\frac{dx_2(t)}{dt} &= \omega k_1(m_1(t))\, x_4(t)\, x_1(t) + \\
&\quad - x_2(t)\{\mu_2 + k_2(m_2(t))\} \\
\frac{dx_3(t)}{dt} &= (1-\omega) k_1(m_1(t))\, x_4(t)\, x_1(t) + \\
&\quad + k_2(m_2(t))\, x_2(t) - \mu_3 x_3(t) \\
\frac{dx_4(t)}{dt} &= N(t)\mu_3 x_3(t) + \\
&\quad - x_4(t)\{k_1(m_1(t))\, x_1(t) + \mu_v\}
\end{aligned}
\tag{1}
$$

where the parameters S, λ, N are given by:

$$S(x_4(t)) = \frac{s\theta}{\theta + x_4(t)} \tag{2}$$

$$\lambda(x_1(t), x_2(t), x_3(t)) = r\left(1 - \frac{x_1(t) + x_2(t) + x_3(t)}{T_{\max}}\right) \tag{3}$$

$$N(t) = \beta_2 - (\beta_2 - N_0)e^{-\beta_1 t} \tag{4}$$

where

$\boldsymbol{x_1(t)}$ = uninfected cells $CD4^+T$;

$\boldsymbol{x_2(t)}$ = latently infected cells $CD4^+T$;

$\boldsymbol{x_3(t)}$ = active infected cells $CD4^+T$;

$\boldsymbol{x_4(t)}$ = free virus HIV;

$\boldsymbol{s}$: rate of generation of x_1 from precursors;

$\boldsymbol{r}$: rate of stimulated growth of x_1;

$\boldsymbol{T_{max}}$: maximum $CD4^+T$ cells population level;

$\boldsymbol{\mu_1}$: death rate of x_1;

$\boldsymbol{\mu_2}$: death rate of x_2;

$\boldsymbol{\mu_3}$: death rate of x_3;

$\boldsymbol{\mu_v}$: death rate of x_4;

$\boldsymbol{k_1}$: infection rate;

$\boldsymbol{k_2}$: conversion rate from x_2 to x_3;

$\boldsymbol{N(\beta_1, \beta_2, N_0)}$: number of infectious virus produced by an actively infected $CD4^+T$ cell and that depends on constants β_1, β_2 and N_0;

$\boldsymbol{\theta}$: viral concentration needed to decrease by s.

Figure 1 shows the scheme of the model described in the equations (1) – (4) and the relations of variables and parameters.

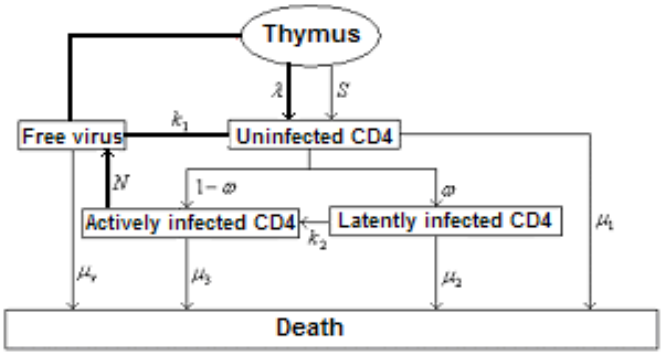

Fig. 1. Dynamic Model of Cycle HIV

The T cells are generated in the bone marrow and thymus. Accordingly to Tan (Tan and Wu, 1998) in presence of antigen and HIV, x_1 cells are stimulated to proliferate generating new x_1 cells with rate λ. Without the presence of HIV, the rate of generation is $S(x_4)$.

In the presence of HIV, uninfected cells x_1 can be infected to become either x_2 cells or x_3 cells, depending of probability of cells become either actively or latently infected with rate ω. The x_2 cells can be activated to become x_3 cells with rate k_2. The x_3 cells are short lived and will normally be killed upon activation with death rate μ_3. When x_3 cells dies, free viruses x_4 are released with rate N(t). The x_1, x_2 cells and x_4 free virus have finite life and the death rates are μ_1, μ_2 and μ_v, respectively.

There are two important enzymes in this process: the "*reserve transcriptase*" and the "*protease*". The two forms of controlling the generation of new free virus are precisely by stopping each of these enzymes.

"*Reserve transcriptase*" is an enzyme that the HIV virus uses to translate its RNA genetic material into DNA, and thus allowing its integration to the host cell. On the other hand, the "*protease*" is an enzyme responsible for the maturation of the HIV virus producing copies of it itself, capable to infect new cells.

So, the first method to control the generation of new free is to block the "*reverse transcriptase*" enzyme whereas the second one is to block the "*protease*" enzyme.

Both coefficients k_1 and k_2 are functions of the administered drugs that will obstruct the actions of each of these enzymes:

$$
\begin{aligned}
k_1(m_1(t)) &= k_{10}e^{-\alpha_1 m_1(t)} \\
k_2(m_2(t)) &= k_{20}e^{-\alpha_2 m_2(t)}
\end{aligned}
\tag{5}
$$

where m_1 and m_2 are, the doses of *transcriptase* and *protease* inhibitors respectively; k_{10} and k_{20} are initial values for the infection without drugs; α_i efficiency of drugs.

3. OPTIMIZATION OF DRUG DOSES

In optimization problems one or more objective function, or cost function, are defined. This objective function is to be either minimized or maximized considering some constraints, which all the parameters of the proposed solution must satisfy in order to be feasible.

So, the aim of optimal control theory is to determine the control signals for which a process will satisfy its physical constraints, as well as, to minimize (or maximize) some performance criterion.

The formulation of an optimal control problem (Kirk, 1970) requires:

- A mathematical description (or model) of the process to be controlled.
- A statement of the physical constraints.
- Specification of the performance criteria.

3.1 Multiobjective Optimization

The main difficulty normally found in mono-objective comes from the fact that modelling a problem with just one equation can be a very difficult task. Modelling the problem using just one equation could also introduce a bias during the modelling phase.

Multiobjective optimization allows a certain degree of freedom that lacks in mono-objective optimization. In a multicriterion optimization problem, the search will give us not a unique solution only, but a set of solutions. These solutions are called Pareto solutions, and the set of solutions found at the end of the search is called the "trade-off" surface.

After having found some solutions for the multiobjective optimization problem, one must select a solution from this set. Here, this selection is made through of the Fandel method.

A multiobjective optimization problem has the following form:

$$\begin{cases} min \quad \vec{f}(\vec{x}) \\ with \quad \vec{g}(\vec{x}) \le 0 \\ and \quad \vec{h}(\vec{x}) = 0 \end{cases} \tag{6}$$

where $\vec{x} \in \Re^n$, $\vec{f}(\vec{x}) \in \Re^k$, $\vec{g}(\vec{x}) \in \Re^m$ and $\vec{h}(\vec{x}) \in \Re^p$. Also, the vectors $\vec{g}(\vec{x})$ and $\vec{h}(\vec{x})$ represent a set of *m* inequality constraints and *p* equality constraints, respectively. This set of constraints delimits a restricted subspace to be searched for the optimal solution. The vector $\vec{f}(\vec{x})$ represents *k* functions to be optimized.

The goal to be reached during the solution of the multiobjective optimization problem is to minimize "in the best way possible" the various objective functions. In multicriterion optimization problem, we often have contradictory objectives, that is, when a decrease in one objective function leads somehow to an increase in another objective function.

When the multiobjective optimization problem is solved, then a multiplicity of solutions is found, but hopefully one should end with one, and only one, solution.

In order to find this solution, one must first to restrict the search to a subset of interest solutions, for this we must establish a domination relation between the solution considered and the other solution.

We say that a vector $\vec{x}_1$ dominates a vector $\vec{x}_2$ if $\vec{x}_1$ is as good as $\vec{x}_2$ for all objectives, and $\vec{x}_1$ is strictly better than $\vec{x}_2$ in at least one objective (Miettinen, 1998; Ehrgott, 2000).

Solutions which dominate the others but do not dominate themselves are called optimal solutions in the Pareto sense (or non dominated solutions).

3.2 Fandel Method

The problem is modified in the following way:

$$\begin{cases} min \quad \sum_{i=1}^{k} w_i \, f_i(\vec{x}) \\ with \quad \vec{g}(\vec{x}) \le 0 \\ and \quad \vec{h}(\vec{x}) = 0 \end{cases} \tag{7}$$

Also: $w_i \ge 0$ and

$$\sum_{i=1}^{k} w_i = 1$$

.

In order to obtain these coefficients w_i, one should proceed (Collette and Siarry, 2003) as follows:

At the first step, the minimum value for each of the objective functions (which is denoted by $\vec{f}_j$) satisfying the constraints is calculated (and is denoted by $\vec{f}_j$). This equivalent to solve the following problem:

$$\begin{cases} min \quad f_j(\vec{x}) \\ with \quad \vec{g}(\vec{x}) \le 0 \\ and \quad \vec{h}(\vec{x}) = 0 \end{cases} \tag{8}$$

with j = {1, 2, …, k}. The solution of this problem is denoted by $\vec{x}_j^*$ and the value of the vector of objective functions corresponding to this solution is denoted by $\vec{f}^{*j} = \vec{f}(\vec{x}_j^*)$.

Next, the vector of the values of the ideal objective function is constructed:

$$\vec{\bar{f}} = (\bar{f}_1, ..., \bar{f}_k)^T \tag{9}$$

and matrix B:

$$B = \left(\vec{f}^{*1}, ..., \vec{f}^{*k}\right) \tag{10}$$

The ideal objective function is obtained by minimizing each objective function separately.

At step M, the user will reach a solution which will be close to the ideal solution. Here, a vector $\vec{f}^{\,M}$ which will serve to reduce the size of the search space was calculated in the following way:

$$\vec{f}^{\,M} = \frac{1}{k}\sum_{i=1}^{k} \vec{f}^{\,*i} \tag{11}$$

Now, the size of the search space is reduced by using the constraints boundaries. The new space of constraints is denoted by $\hat{Y}^M$:

$$\hat{Y}^M = \left\{\vec{f}(\vec{x}) \in \Re^k \mid \vec{g}(\vec{x}) \le 0, \vec{h}(\vec{x}) = 0 \text{ and } \vec{f}(\vec{x}) \le \vec{f}^{\,M}\right\} \tag{12}$$

In this new constraint space, the objective functions are minimized:

$$\begin{aligned} &min \quad f_j(\vec{x}) \\ &with \quad \vec{g}(\vec{x}) \le 0 \\ &\qquad \vec{h}(\vec{x}) = 0 \\ &and \quad \vec{f}(\vec{x}) \le \vec{f}^{\,M} \end{aligned} \tag{13}$$

And then one returns to the first step.

The loop stops when converge to the only solution is reached.

4. PROBLEM FORMULATION

This work uses multiobjective optimization techniques in therapy of AIDS with the aim of maximizing the count of uninfected CD4+T cells and minimize the count of free virus, while evaluates simultaneously the dosages of drugs, that are not indirectly related with the treatment side effects. The optimization problem is the following:

$$\min_{(m_1,m_2)\in\Re^2} \begin{cases} f_1(m_1,m_2) = -x_1(t_f,m_1,m_2) + \\ \qquad\qquad + \varphi x_4(t_f,m_1,m_2) \\ f_2(m_1,m_2) = \phi_1\left(1-e^{-m_1^2\varepsilon_1}\right) + \\ \qquad\qquad + \phi_2\left(1-e^{-m_2^2\varepsilon_2}\right) \end{cases} \tag{14}$$

with

$$\begin{cases} m_1 \le 900\ mg \\ m_2 \le 1200\ mg \\ x_1(t_f) > x_1(0) \\ x_4(t_f) < x_4(0) \end{cases}$$

where:

t_f is the final time of simulation;

φ is the weight of x_4 in relation x_1;

ϕ_i are weights to force the control be the local minimum in the administration of drugs (the larger these parameters are, the smaller is the administration of drugs in order to not increase the objective function's value);

ε_i are the importance of the drugs during the treatment reflected in the objective function (if these parameters are large, then the drug efficiency is high).

The constraints mean that the drug dosage must be less than or equal to the dosage adopted and recommended by the World Health Organization (WHO).

The count of uninfected CD4+T cells in final phase of the treatment must be greater than its count in the initial phase of treatment.

Also, the count of free virus in the final stage of the treatment must be less than its count in the initial stage of treatment.

With this an optimal strategy of treatment for HIV seropositive patients can be achieved, as it will be shown in the next section.

5. SIMULATION RESULTS

In order to present a realistic example, the data belonging to Patient A in (Pontesilli et al., 1999) was used. The numerical values for the model parameters of Patient A are shown in Table 1.

Table 1. Model parameters used in the numerical simulations (Patient A)

$s = 10$	$r = 0.52$	$T_{max} = 1700$
$\mu_1 = 0.4$	$\mu_2 = 0.5$	$\mu_3 = 0.03$
$\mu_v = 2.4$	$k_{10} = 2.4\times10^{-6}$	$k_{20} = 0.3$
$N_0 = 1400$	$\beta_1 = 0.1$	$\beta_2 = 65470$
$\alpha_1 = 5\times10^{-3}$	$\alpha_2 = 5\times10^{-3}$	$\theta = 10^6$
$\omega = 0.5$	$\phi_1 = 1$	$\phi_2 = 1$
$\varepsilon_1 = 10^{-6}$	$\varepsilon_2 = 10^{-6}$	$x_1(0) = 357$
$x_2(0) = 10$	$x_3(0) = 100$	$x_4(0) = 133352$

For the two optimization procedures shown below, the final time (t_f) was fixed in 224 days and the weight φ was considered to be 0.01.

Figure 2 shows the optimal control using $m_1 = 900$ mg and $m_2 = 1200$ mg, dosages which are adopted and recommended by the World Health Organization (WHO).

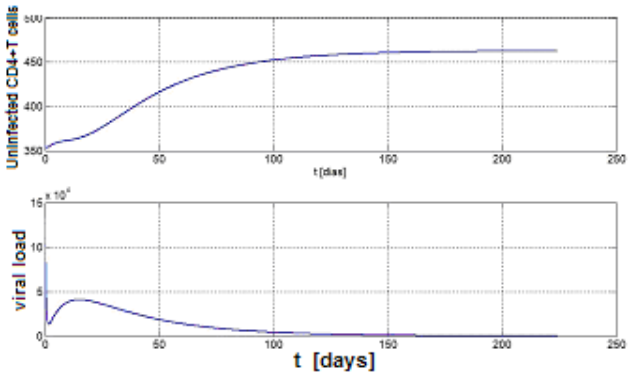

Fig. 2. Uninfected CD4+T cells count and free virus count for treatment with *$m_1 = 900$ mg and $m_2 = 1200$ mg.*

Here the following results were obtained:

$$x_1(t_f) \approx 463$$
$$x_4(t_f) \approx 104$$
$$f_1(m_1, m_2) = -461.96$$
$$f_2(m_1, m_2) = -4.4686$$

On the other hand, by applying, the multiobjective optimal control, the following trade-off surface shown in the figure 3 was found.

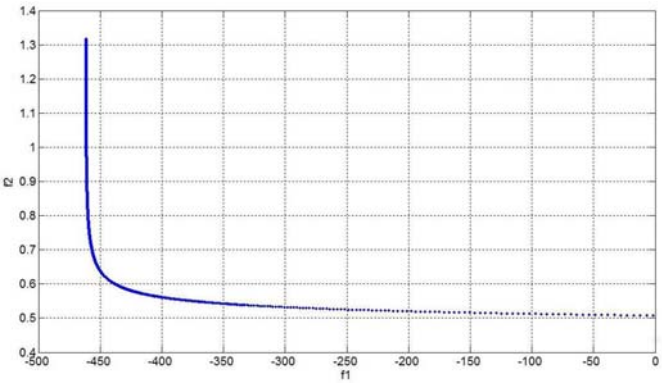

Fig. 3. Trade-off surface (non-dominated solutions)

Applying the Fandel Method, it is found that $m_1 = 824$ mg and $m_2 = 362$ mg. For these values of m_1 and m_2, the optimal control results are shown in figure 4.

Here one has that:

$$x_1(t_f) \approx 459$$
$$x_4(t_f) \approx 1455$$
$$f_1(m_1, m_2) = -444.45$$
$$f_2(m_1, m_2) = -1.1118$$

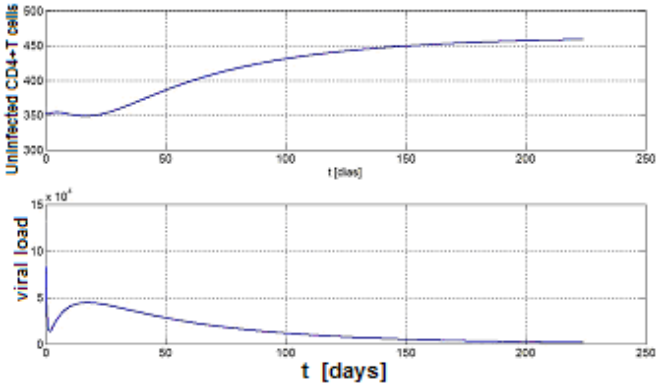

Fig. 4. Uninfected CD4+T cells count and free virus count for treatment with *$m_1 = 824$ mg and $m_2 = 362$ mg.*

Comparing figures 2 and 4, one can verify that these results are very similar.

They neither show a significant decline in the count of uninfected CD4+T cells nor they have any increase in the count of free virus.

So, the scheme proposed here is much better since one uses less medication and, as a consequence of that, a reduction of the side effects.

6. CONCLUSIONS

The aim of this work is to present a quantitative method to assist the medical staff in conducting clinical treatment schemes for patients with AIDS. The positive results such as the increase in the CD4+T count and reduction in the level of viral particles can be balanced with dose dependent side effect of the drugs.

This is done by using multiobjective optimization techniques, since multiple criterions must be satisfied.

One can observe, through of the optimal control procedures tested here, that with less drugs dosages it is possible to increase the count of uninfected CD4+T cells to the same level of that when high amount drugs dosages are used.

These results can still be improved by using more realistic cost functions, or more elaborate mathematical models, or also to include alternative forms of HIV virus infection treatments.

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