

# Control of drug dosage in the AIDS treatment

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The increase in the number of cases of AIDS have lead to the development of several new mathematical models which describe the dynamical behavior of the viral load on CD4<sup>+</sup>T cells counts as well as analyze the effects of treatment strategies [10].

On the other hand new treatment schemes has helped many sero-positives patients to have a normal life. In [8] one can see reports on success achieved by highly active antiretroviral therapy (HAART) that has prolonged the life of patients up to 3 years.

However, long-term use of HAART could have adverse effects, such as metabolic abnormalities and irreversible fat redistribution syndromes.

Also, the eventual intolerance against HAART by some patients may leads to treatment interruptions. In some instances [8] up to three stops were noted during the treatment.

The intense clinical research has made available now several quantitative descriptions of the dynamics of AIDS as well as more advanced mathematical modeling methods [5, 6, 9]. These models can be used to optimize the drug doses required in the treatment. Here we use a model that was originally proposed by Tan and Wu [6] and is similar to Perelson [9].

The authors have shown in [1] that it is possible to improve the treatment effectiveness by using closed loop drugs administration strategy and that these treatment schemes could have advantages when compared to the standard treatment because more information is used for the control of the drug doses.

Also, it is possible to use optimal control theory to reduce the side effects during a short-term treatment scheme while adequate therapeutic results are obtained [2] and comparative study and optimization methods were carried out in [3]. Responses corresponding to the actual observed data and simulation data were compared in terms of long-term period and short-term period drug administration strategies.

Here the main objective is to analyze the dynamics of the viral load and the CD4<sup>+</sup>T cells counts with a model that is fitted to match the actual data and considering the sub-optimization problem with dynamic constraints for multi-drug treatment case.

The data were provided by *Centro de Referência e Treinamento em DST-AIDS* in São Paulo, Brazil and to illustrate we mention the case one patient who went through the treatment during a period of around 340 days receiving AZT (600 mg) and 3TC (300 mg) before the start of HAART scheme. This patient had not received any specific drug for the treatment of AIDS previously.

The model adopted consists of four differential equations representing the CD4<sup>+</sup>T cells (uninfected, latent infected and actively infected) and also the free viruses.

We construct a performance index that tries to describe the side effects in a quantitative way following the model in Tan [6] that describes the HIV pathogenesis under treatment by antiviral drugs. It has four differential equations and stochastic terms in the variable that represent the number of latent infected T cells. It has also stochastic components on infection free HIV and non-infection free HIV variable.

$$\begin{cases} \dot{x}_1 = S(x_4) + \lambda(x_1, x_2, x_3)x_1 - x_1[\mu_1 + k_1(m_1)x_4] \\ \dot{x}_2 = \omega k_1(m_1)x_4x_1 - x_2[\mu_2 + k_2(m_2)] \\ \dot{x}_3 = (1 - \omega)k_1(m_1)x_4x_1 + k_2(m_2)x_2 - \mu_3x_3 \\ \dot{x}_4 = N(t)\mu_3x_3 - x_4[k_1(m_1)x_1 + \mu_4] \end{cases} \quad (1)$$

where

$x_1(t) \equiv$  uninfected CD4<sup>+</sup>T cells;

$x_2(t) \equiv$  latent infected CD4<sup>+</sup>T cells;

$x_3(t) \equiv$  actively infected CD4<sup>+</sup>T cells;

$x_4(t) \equiv$  free virus HIV

$s$  = the rate of generation of  $x_1$ ;

$r$  = rate of stimulated growth of  $x_1$ ;

$T_{\max}$  = maximum T cells population level;

$\mu_i$  = death rate of  $x_i$ ;  $i = 1, 2, 3, 4$ .

$k_1$  = infection rate from  $x_1$  to  $x_2$  by viruses;

$k_2$  = conversion rate from  $x_2$  to  $x_3$ ;

$N$  = the number of infectious virions produced by an actively infected T cell;

$\theta$  = viral concentration needed to decrease  $s$ .

and the coefficients  $k_1$  and  $k_2$  are functions of the drug doses  $m_1$  and  $m_2$ .

Basically,  $x_1$  cells are stimulated to proliferate with rate  $\lambda(x_1, x_2, x_3)$  in the presence antigen and HIV, that is,

$$\lambda(x_1, x_2, x_3) = r[1 - (x_1 + x_2 + x_3)/T_{\max}] \quad (2)$$

Without the presence of HIV the rate of generation is  $S(x_4)$ , that is,

$$S(x_4) = \frac{s\theta}{\theta + x_4} \quad (3)$$

Uninfected cells  $x_1$ , in the presence of free HIV  $x_4$ , can be infected to become  $x_2$  cells or  $x_3$  cells, depending on the probability of the cells to become actively or latently infected with rate  $\omega$ .

The  $x_2$  cells can be activated to become  $x_3$  cells. This activation rate is  $k_2$ .

The  $x_3$  cells are short living and will normally be killed upon activation with death rate  $\mu_3$ .

When  $x_3$  cells die free viruses  $x_4$  are released with rate  $N(t)$  described by

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

The  $x_1, x_2$  cells and  $x_4$  (free viruses) also have finite life and the death rates in this model are  $\mu_1, \mu_2$  and  $\mu_v$  respectively.

The effects of drugs such as reverse transcriptase inhibitors and protease inhibitors are considered via the parameters  $k_1$  and  $k_2$ .

The standard treatment of sero positive patients includes two classes of drug to block the action of HIV.

The first class includes drugs that blocks *reverse transcriptase* enzyme involved in exchange of viral-RNA and viral-DNA. Some of the available reverse transcriptase inhibitors are: *zidovudine* (AZT), *didanosine* (ddI), *lamivudine* (3TC), *zalcitabine* (ddc), *stavudine* (D4T), *Abacavir* (Ziagen), *Viramune* (nevirapine), *Rescriptor* (delavirdine) and *Sustiva* (efavirenz), among others.

The second class includes drugs that inhibit the protease enzyme: *Invirase* (saquinavir), *Norvir* (ritonavir), *Crixivan* (indinavir), *Viracept* (nelfinavir), *Agenerase* (amprenavir) and others.

The World Health Organization proposes tables for the administration of these drugs which should be followed by the medical staff. However they may change the used drugs when patients develop resistance or present intense side effects.

In the present work the parameters in Tan's model takes the form

$$k_1(m_1) = k_{10}e^{-\alpha_1 m_1} \quad (5)$$

$$k_2(m_2) = k_{20}e^{-\alpha_2 m_2} \quad (6)$$

where  $k_{10}$  and  $k_{20}$  are natural rate for conversion of uninfected CD4 cells into latently infected CD4 cell and natural rate for conversion of latently infected CD4 cell

into actively infected cell, respectively. Also, the parameters  $\alpha_1$  and  $\alpha_2$  are the efficiency of drugs for reverse transcriptase and protease inhibitors, respectively.

The variables  $m_1(t)$  and  $m_2(t)$  are the doses from drugs administrated to reverse transcriptase and protease inhibitors respectively, while  $\alpha_1$  and  $\alpha_2$  are constants.

In [7,11] one can see other works dealing with the control of the viral load using a mathematical modeling and simulations by computer.

The numerical method used here was proposed by Jacob in [4] and is available in the form of a computer program called EXTREM. The objective is to find a control input

$$m(t) = [m_1(t) \ m_2(t)]^T$$

that minimizes the cost function

$$\begin{aligned} J(m) = & \frac{\gamma_1}{x_1^2(t_f)} + \gamma_2 x_4^2(t_f) + \\ & + \int_{t_0}^{t_f} \left\{ \phi_1 \left( 1 - e^{-\varepsilon_1 m_1^2(t)} \right) + \right. \\ & + \phi_2 \left( 1 - e^{-\varepsilon_2 m_2^2(t)} \right) + \\ & \left. + \gamma_2 x_4^2(t) \right\} dt \end{aligned} \quad (7)$$

The chosen performance index tries to make a compromise between the side effects and the therapeutic effects, reflected by the CD4 count and the viral load and it has been used before in [3]:

The biological interpretation of the proposed cost functional is that the two first terms out of integral represent the target of maximizing non-infected CD4 cells and also to minimize the viral load after a pre-specified time horizon.

The coefficients  $\phi_1$  and  $\phi_2$  of the terms in the integrand are weights that reflect the dose-related side effects of the two drugs ( $m_1(t)$  and  $m_2(t)$ ) which must be adequately balanced.

The two last terms are included to force  $x_1$  (uninfected CD4<sup>+</sup>T cells) to increase and  $x_4$  (viral load) to decrease with treatment.

Finally,  $\varepsilon_1$  and  $\varepsilon_2$  are sensibilities of the patient with respect to reverse transcriptase inhibitors and protease inhibitors respectively. To fit these parameters is very difficult and only are possible with a controlled experiment.

The control input  $m(t)$  in this optimization method [4] is represented by an expansion over the interval  $[0, t_f]$  with the following form (for  $i = 1, 2$ )

$$m_i(t) = \frac{c_{i1} - c_{i4}}{2} \tanh\left(\frac{0.08(t - c_{i3})}{|c_{i2}|}\right) + \frac{c_{i1} + c_{i4}}{2} + \frac{c_{i4} - c_{i7}}{2} \tanh\left(\frac{0.08(t - c_{i5})}{|c_{i6}|}\right) - \frac{c_{i4} - c_{i7}}{2} + \frac{c_{i7} - c_{i10}}{2} \tanh\left(\frac{0.08(t - c_{i9})}{|c_{i8}|}\right) - \frac{c_{i7} - c_{i10}}{2} \quad (8)$$

where the coefficients  $c_{ij}$  are to be determined by minimizing (7).

Here, after fitting the parameters the obtained values were:

$$\begin{aligned} \varepsilon_1 &= 7.5E-9 & \gamma_1 &= 250,000 & \phi_1 &= 100 \\ \varepsilon_2 &= 0 & \gamma_2 &= 1E-8 & \phi_2 &= 0 \end{aligned}$$

To illustrate we present here one case studied (Figures 1-3). During the period presented in Fig-1 the patient had manifested symptoms of AIDS. The CD4 count and the viral load are represented by the “*triangles*” and the “*plus signs*”, respectively.

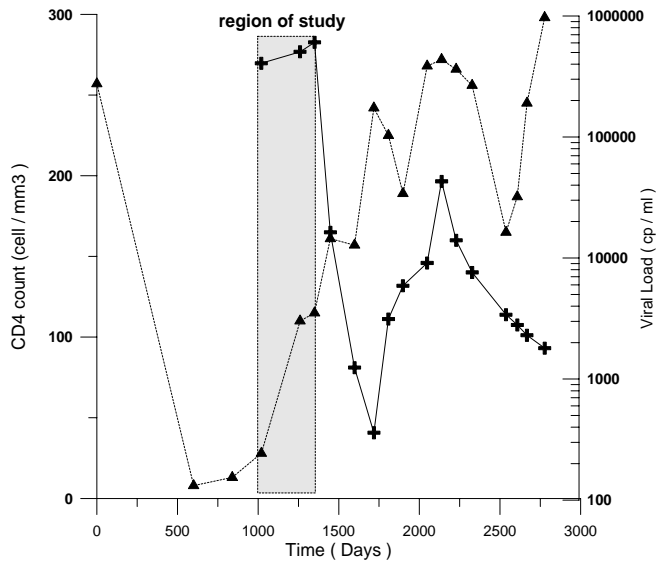


Fig-1 - Historical data of a patient.

The corresponding parameters that were used in the simulations are presented in Tables I and II.

For this simulations it was used the constant control

$$\begin{aligned} m_1 &= 900 \text{ (AZT = 600 mg plus 3TC = 300 mg)} \\ m_2 &= 0 \text{ (none protease inhibitor).} \end{aligned}$$

The *patient* illustrated in Fig-1 had a typical immunological resistance with the viral load increase tending to be very high in this period (340 days).

The initial CD4<sup>+</sup>T cells count was 30 cells/mm<sup>3</sup> and in the final period was around 110 cells/mm<sup>3</sup> (healthy individuals have CD4 cells counts about 1,000 cells/mm<sup>3</sup>).

The initial viral load for this patient was 407,000 copies/ml. During the period the viral load (slowly) increases (to about 500,000 copies/ml).

When more infected cells become latent their actions may have a longer time horizon and hence, more difficult to combat.

Table I - Parameters fitted

$\alpha_1$	$\alpha_2$	$\beta_1$	$\beta_2$
0.002	0	0.01	1,000

$\mu_1$	$\mu_2$	$\mu_3$	$\mu_v$
0.05	0.14	0.006	1E-6

$K_{10}$	$k_{20}$	$N_0$	$\theta$
3E-7	0.007	1,000	10,000

$r$	$s$	$T_{\max}$	$\omega$
0.102	0.01	700	0.97

Table II - Initial conditions

$t_f$	$x_1$	$x_2$	$x_3$	$x_4$
340	28	300	110	40,700

After the fitting of curves to the actual data the direct method described in the last section is used to solve the optimal control problem for this patient.

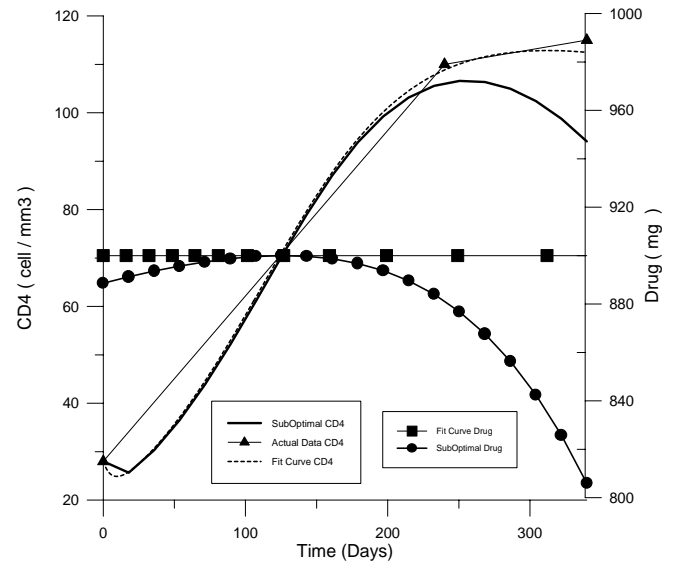


Fig-2 - Optimal and standard treatment.

In Fig-2 it is possible to see that for this patient the optimal treatment would be improved by starting using around 880 mg of drugs and gradually decreased until the final period (340 days) to end up around 800 mg.

Also in Fig-2 the results for CD4 which are similar to the actual data.

The optimal control problem was then solved with the numerical direct method described earlier. It is possible

to observe the better results for sub-optimal control than the actual data (Fig-3). But the solution is almost the same for constant use of drugs.

An important fact related to the use of the optimal (sub-optimal) strategy lies in the probability of CD4 infected cells transforming from latent to active forms. For this patient this probability was

$$\omega = 0.97 \text{ (97\%).}$$

It is interesting to observe that the chance of infected CD4 cells to become latent under the optimal control is almost 50% smaller than HAART scheme.

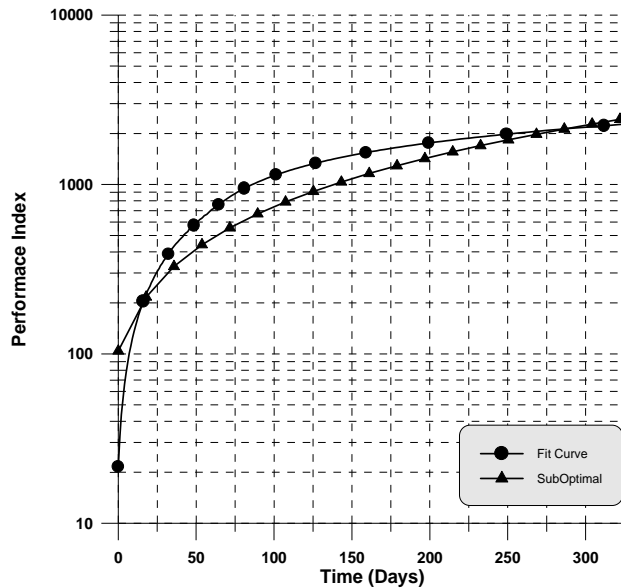


Fig-3 - Performance index.

The mathematical solutions show that treatments can be improved in terms of side effects, although further studies are required to establish the adequacy of the therapeutic results.

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