SIMULATION ANALYSIS OF DOSE RESPONSE IN THE TREATMENT OF AIDS

José A. M. Felippe de Souza*, Marco Antonio Leonel Caetano and Takashi Yoneyama*****

**Department of Electromechanical Eng.*
UBI - Universidade Beira Interior
6201-001 - Covilhã
PORTUGAL
felippe@demnet.ubi.pt

***Department of Statistics, Comp.& Applied Maths*
UNESP - Univ. Estadual Paulista
Rio Claro - SP
BRAZIL
malc@netvale.com.br

****Electronics Eng. Division*
ITA - Instituto Tecnol. Aeronáutica
12228-900 - São José Campos - SP
BRAZIL
takashi@ele.ita.cta.br

Keywords: Control systems, dynamic programming, identification, optimization.

Abstract

This work concerns the problem of optimizing the drug doses in the treatment of AIDS by looking for a balance between the therapeutic response and the side effects. Extensive computer simulation and comparison with the constant dose scheme evaluate the results. For some few cases the results are also compared with actual clinical data. A mathematical model describing the dynamics of HIV virus and CD4 cells is initially fitted to actual published clinical data. The identified model is then used to compute the sub-optimal drug doses for the treatment of AIDS by a direct method of optimization using a performance index of Bolza type. The sub-optimal treatment scheme is shown to achieve a therapeutic response close to the constant dose strategy, but with lower cost, as measured by the proposed performance index.

INTRODUCTION

Mathematical models of dynamical systems in the form of differential equations are used extensively, for example, in computer simulations for investigation of the dynamics of viral and lymphocyte populations. The model used in this work is an adapted version of the one proposed by Tan and Wu, 1998. A performance index which takes into account the number of non-infected CD4 cells and the administered doses of the drugs evaluate the effectiveness of a particular treatment scheme. The optimal control problem resulting by combining the mathematical model and the performance index is solved numerically by direct optimization techniques.

MATHEMATICAL MODELS

A number of mathematical models have been proposed in the field of immunology, which can be found, for instance, in Murray *et al, 1998*, Mittler *et al*, 1998, Wick , 1999, Behrens *et al*, 1999, Tan and Wu, 1998, Tan and Xiang, 1999, Nowak *et al*, 1996, Nowak *et al*, 1991, Nowak *et al*, 1997, Nowak *et al*, 1995, Regoes *et al*, 1998 and Wein *et al*, 1998, among other works. The model in Nowak *et al.* (1991) considers a system of ordinary differential equations with four variables x_i, y, v_i and z_i which denote respectively strain-specific CD4 cells, total CD4 cells, virus population and cross-reactive CD4 cells. The authors simulate the mathematical model with immunotherapy starting at different times after infection. Nowak and Bangham (1996) compare three dynamic models of HIV infection. The first is the simpler and contains three variables x, y and v denoting, respectively, uninfected cells, infected cells and free virus. Another model uses four variables where the first three variables are again x, y, v as before and the fourth variable z represents CTL lymphocytes. The last model has four variables and includes the variability of virus. The model in Philips, (1996) involves four differential equations in variables R, L, E and V which represent, respectively, uninfected CD4, latently infected cells, infected cells and free viruses. This model can be used to simulate the initial phase of infection. Nowak *et al.* (1995) presented a new model that considers the interaction between CTL and the multiple epitopes of a genetically variable pathogen. The version proposed in Nowak *et al.* (1997) includes the population of mutant virus, and provides analytic approximation for the rate of emergence of resistant viruses. This model comprises five equations and the results match the experimental data of three infected patients treated with Neverapine (NVP). In Murray *et al.* (1998) the proposed model uses eight differential equations with the variables such as: naïve cells; cells that do not recognize HIV but are only activated by other antigen; cells that recognize HIV and are stimulated by its presence to divide and produce activated cells; memory cells specific to HIV; free viruses and viruses that have lost their ability to attach to CD4 T cells.

Wick (1999) proposed a model of T cell dynamics in which rising activation rates produced falling T-cell counts and showed that apoptosis and proliferation must nearly balance. His model has four differential equations composed by: naïve T cells and memory cells in activated and resting states. The model in Zaric *et al.* (1998) focuses on the simulation of protease inhibitors and development of drug-resistant HIV strains. The model is composed of eleven differential equations and there is a coupling between organisms that are infected with resistant and non-resistant HIV strains. The analysis shows that multi-drug therapy can lead to significantly high prevalence of multi-drug-resistant

HIV strains. Tan and Wu, (1998, 1999) proposed a discrete stochastic model for the HIV pathogenesis under treatment by antiviral drugs. The model has four differential equations and stochastic terms in the variables that represent the number of latently infected T cells. It has also stochastic components on infectious free HIV and non-infectious free HIV variables.

The mathematical model presented by Tan and Wu, (1998) with deterministic terms was adopted here. The dynamics is described by the differential equations

$$\begin{aligned}
\dot{x}_1 &= S(x_4) + \lambda(x_1, x_2, x_3)x_1 - x_1\{\mu_1 + k_1(m_1)x_4\} \\
\dot{x}_2 &= \omega k_1(m_1)x_4 x_1 - x_2\{\mu_2 + k_2(m_2)\} \\
\dot{x}_3 &= (1-\omega)k_1(m_1)x_4 x_1 + k_2(m_2)x_2 - \mu_3 x_3 \\
\dot{x}_4 &= N(t)\mu_3 x_3 - x_4\{k_1(m_1)x_1 + \mu_v\}
\end{aligned} \tag{1}$$

where $\dot{x}$ represents dx/dt,

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

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

$$N(t) = \beta_2 - (\beta_2 - N_0)e^{-\mu_3 t} \tag{4}$$

with $x_1 = x_1(t) \equiv$ uninfected cells $CD4^+$ T; $x_2 = x_2(t) \equiv$ infected cells $CD4^+$ T latently; $x_3 = x_3(t) \equiv$ infected cells $CD4^+$ T active; $x_4 = x_4(t) \equiv$ free virus HIV; s: rate of generation of x_1 from precursors; r: rate of stimulated growth of x_1; T_{max}: maximum T cells population level; μ_1: death rate of x_1; μ_2 : death rate of x_2; μ_3 : death rate of x_3; μ_v: death rate of x_4; k_1: infection rate from x_1 to x_2 by virus; k_2: conversion rate from x_2 to x_3; N: number of infectious viruses produced by an actively infected T cell; θ: viral concentration needed to decrease.

In the model by Tan and Wu, 1998, x_1 cells are stimulated to proliferate to generate new x_1 cells with rate $\lambda(x_1, x_2, x_3)$ in the presence of antigen and HIV (Eq. 3). Without the presence of HIV, the rate of generation is $S(x_4)$ (Eq. 2). In the presence of free HIV (x_4), uninfected cells x_1 can be infected to become x_2 cells and x_3 cells, depending of probability of cells become actively or latently infected with rate ω. The x_2 cells can be activated to become x_3 cells. The activation rate is k_2. The x_3 cells are short lived and will normally be killed upon activation with death rate μ_3. The x_1, x_2 cells and x_4 free virus have finite life and the death rate in this model is μ_1, μ_2 and μ_v respectively. When x_3 cells die free viruses x_4 are released with rate N(t) described by (4). Drugs such as reverse transcriptase inhibitors (*zidovudine* and *lamivudine)* and protease inhibitors (*saquinavir*, *indinavir* and *ritonavir*) affect the parameters k_1 and k_2.

THE SUB-OPTIMAL CONTROL

The objective in a general optimal control problem is to find a control-input m(t) that minimizes the cost function

$$J[m] = h(x(t_f), t_f) + \int_{t_0}^{t_f} g(x(t), m(t), t)dt \tag{5}$$

where t_0 and t_f are the initial and final times; h and g are given positive scalar functions. Moreover, x(.) and m(.) are constrained by the state equation

$$\dot{x} = f(x(t), m(t), t) \tag{6}$$

In the specific problem treated in this work, $x = [\, x_1\ x_2\ x_3\ x_4\,]^t \in R^n$ and $u = [\, u_1\ u_2\,]^t$

$$f(x,m,t) = \begin{bmatrix} S(x_4) + \lambda(x_1, x_2, x_3)x_1 - x_1\{\mu_1 + k_1(m_1)x_4\} \\ \omega k_1(m_1)x_4 x_1 - x_2\{\mu_2 + k_2(m_2)\} \\ (1-\omega)k_1(m_1)x_4 x_1 + k_2(m_2)x_2 - \mu_3 x_3 \\ N(t)\mu_3 x_3 - x_4\{k_1(m_1)x_1 + \mu_v\} \end{bmatrix} \tag{7}$$

$$\epsilon_1(t) = k_{10}e^{-\alpha_1 m_1 t} \tag{8}$$

$$k_2(t) = k_{20}e^{-\alpha_2 m_2 t} \tag{9}$$

$$h(x(t_f), t_f) = \frac{\gamma_1}{x_1(t_f)} \tag{10}$$

$$\begin{aligned} g(x(t), m(t), t) = {} & \phi_1\left[1 - \exp\left(-\varepsilon_1 m_1(t)^2\right)\right] + \\ & + \phi_2\left[1 - \exp\left(-\varepsilon_2 m_2(t)^2\right)\right] + \frac{\gamma_2}{x_1(t)} \end{aligned} \tag{11}$$

where k_{10}, k_{20}, α_1, α_2, ϕ_1, ϕ_2, γ_1, γ_2, ε_1 and ε_2 are constants.

Optimal control problems can be solved by indirect or direct methods. In the solution using an indirect method, one is required to solve a boundary value problem with 2n equations corresponding to n state and n adjoint variables if Maximum Principle is invoked or to solve a partial differential equation if Dynamic Programming is used (Kirk, 1970; Lewis, 1986, Bulirsh, 1980). In the solution using a direct method, one attempts to minimize directly the performance measure (7) after a suitable parameterisation of the admissible control inputs u(t). Here, a direct method proposed by Jacob, (1972) is used. The parameterisation of the input functions u(t) involves, in the present case, a subset of the coefficients of expansion in sine functions and only approximations to the actual optimal u(t) are obtained. However, those sub-optimal control inputs are found to provide improved treatment results when compared to fixed drug doses.

Three cases are considered in this work: monotherapy (either reverse transcriptase inhibitor or protease inhibitor) and combination of both.

First Case

Sub-optimal administration of reverse transcriptase inhibitor

In this case k_2 is assumed to be constant ($m_2(t) = 0\ \forall t$) while k_1 depends on the drug dose:

$$k_1^*(t) = k_{10}e^{-\alpha_1 m_1 t} \tag{12}$$

Second Case

Sub-optimal administration of protease inibitor

In this case k_1 is assumed to be constant ($m_1(t) = 0\ \forall t$) while k_2 depends on the drug dose:

$$k_2^*(t) = k_{20}e^{-\alpha_2 m_2 t} \tag{13}$$

Third Case

Sub-optimal administration of a combination of reverse-transcriptase and protease inhibitors

In this case, both k_1 and k_2 are allowed to vary simultaneously

$$k_1(t) = k_{10}e^{-\alpha_1 m_1 t} \tag{14}$$

$$k_2(t) = k_{20}e^{-\alpha_2 m_2 t} \tag{15}$$

PARAMETERISATION OF THE CONTROL INPUT

This work uses a direct method to minimize the cost function (5) based on the numerical algorithm proposed by Jacob, (1972), available in the form of a computer program called EXTREM.

$$\begin{aligned} m_i(t) = {} & c_{1,i} + c_{2,i}\sin(t\pi/t_f) + \\ & + c_{3,i}[2\sin(t\pi/t_f)\cos(t\pi/t_f)] + \\ & + c_{4,i}[3\sin(t\pi/t_f)\cos(t\pi/t_f)^2 - \\ & + \sin^3(t\pi/t_f)] + \\ & + \ldots + \\ & + c_{n,i}\{(n-1)\sin(t\pi/t_f)\cos^{n-2}(t\pi/t_f) - \\ & + [(n-1)/3]\sin^3(t\pi/t_f)\cos^{n-4}(t\pi/t_f) + \\ & + [(n-1)/5]\sin^5(t\pi/t_f)\cos^{n-6}(t\pi/t_f) - \ldots \\ & + \ldots\} \end{aligned} \tag{16}$$

Eq. 16 shows the form of each component of the control input m(t) which is represented by an expansion over the interval $[0, t_f]$.

SIMULATION RESULTS

The actual clinical data were extracted from Tan (Tan and Wu, 1998) and refers to a patient that contracted HIV at the age of 11 years and his T cell counts were measured on 16 occasions.

Years	3.2	3.9	4.7	5.2	5.9	6.6	7.2	7.6
T cell counts/mm^3	1254	1005	1022	1105	372	432	520	660
Years	8.2	8.6	9.2	9.6	10.3	10.7	11.2	11.7
T cell counts/mm^3	686	357	440	584	508	583	328	345

Table -1- Clinical data of CD4 T Cells of an HIV-Infected Patient (Tan and Wu, 1998)

S	R	Tmax	μ_1	μ_2	μ_3	μ_v	K_1	K_2	N_0
10	0.52	1700	0.4	0.5	0.03	2.4	2.410^{-5}	3.10^{-1}	1400
θ	ω	β_1	β_2	$x_1(0)$	$X_2(0)$	$x_3(0)$	$x_4(0)$	t_f (days)	
10^6	1	10^{-1}	65470	357	10	100	133352	224	

Table -2- Parameters used in the simulations

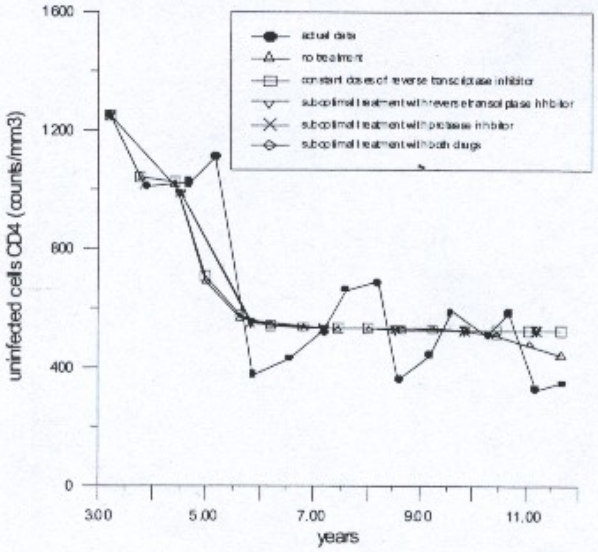

Figure 1

The data are reproduced in Table 1. Firstly the model parameters were adjusted by an identification procedure to match the available data. Simulation results in the figures 1-5 correspond to the present case study. In the figures the actual data set is shown to fit the simulated model using the identified parameters and without treatment.

The control variables were constrained to be in the range (300 mg) $\leq m_1(t) \leq$ (900 mg) {reverse transcriptase inhibitor} and (300 mg) $\leq m_2(t) \leq$ (900 mg) {protease inhibitor}, respectively, in the case of patient A.

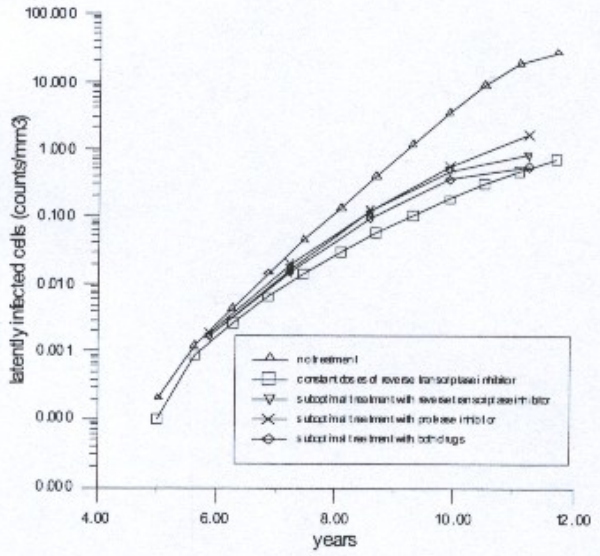

Figure 2

For others patients the constraints were relaxed to (0 mg) $\leq m_1(t) \leq$ (1500 mg) and (0 mg) $\leq m_2(t) \leq$ (1500 mg). In all cases the expression of the control variable was where the constants $\alpha_1 = \alpha_2 = 0.005$ can be interpreted as the activity of the drugs.

These controls $m_1(t)$, $m_2(t)$ were found by applying an optimization method for minimizing the performance index (5).

It is worth noting that the optimal drug doses varies from patient to patient, because of the differences on the actual models parameters.

Figure 6 shows typical trajectories (projections on x_4, x_1 plane) under sub-optimal and constant dose treatment schemes.

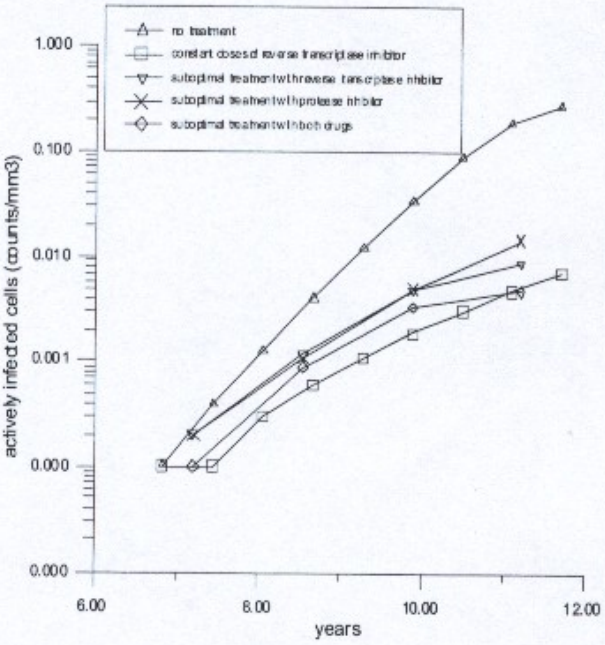

Figure 3

CONCLUSION

The new performance index help the numerical method to solve the problem and to found a solution fitted of actual data. Of all patients, only one case shows the same final result with actual data. All others treatment (theoretical) were better than the conventional treatment with the constant administration of drugs.

The polynomial approach was good using degree 5 and seven terms in the representation of controls variables and the optimal solutions run about 10 times in all cases studied. We use three types of control in the administration of drugs: only reverse transcriptase inhibitor, only protease inhibitor and cocktail of drugs with two types of inhibitors.

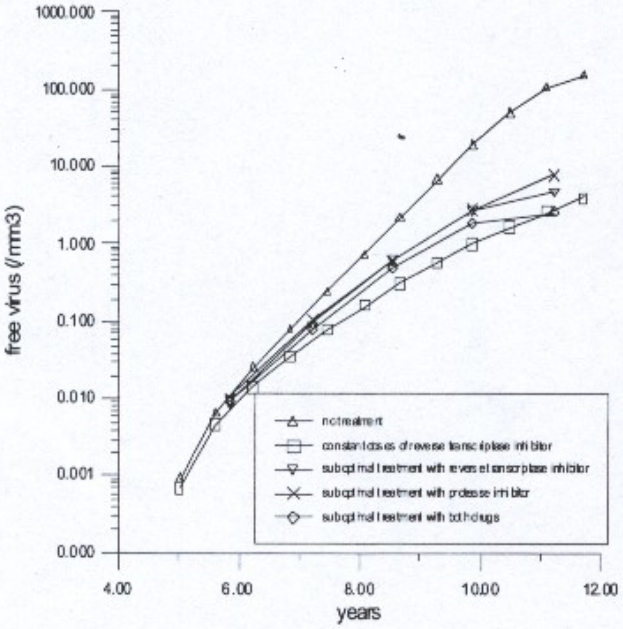

Figure 4

The results indicate that the best situation is with the use of cocktails, but when we use the optimal control in the performance index, the results with cocktail in optimal administration was better than the one without it. This is important because there is some relation between the performance index and side effects of drugs in the patients.

This article showed a method to design of treatment schemes using optimal control theory for patients with AIDS.

References

Behrens, D.A.; Caulkins, J.P.; Tragler, G.; Haunschmied, J.L.; Feichtinger, G. A dynamic model of drug initiation: implications for treatment and drug control. 1999. v 159. 1 - 20 pp.

Bulirsh, R.; Stoer, J. *Introduction to Numerical Analysis.* Springer-Verlag. 1980. 609 p.

Jacob, H.G. An Engineering Optimization Method with Application to Stol Aircraft Approach and Landing Trajectories. Langley. NASA TN-D 6978. 1972. 38 p.

Kirk, D.E. *Optimal Control Theory: an Introduction.* New Jersey. Prentice-Hall. 1970. 452 p.

Lewis, F.L. *Optimal Control.* John Wiley. 1986. 362 p.

Mittler, J.E.; Sulzer B.; Neumann, A.U.; Perelson, A.S. Influence of delayed viral production on viral dynamics in HIV-1 infected patients. Mathematical Biosciences. 1998. v 152. 143 - 163 pp.

Murray, J.M.; Kaufmann, G.; Kelleher, A.D.; Cooper, D.A. A Model of primary HIV-1 infection. Mathematical Biosciences. 1998. 57-85 pp.

Nowak, M.A.; Anderson, R.M.; McLean, A.R.; Wolfs, T.F.; Goudsmit, J.; May, R.M. Antigenic Diversity Thresholds and the Development of AIDS. Science. 1991. 963 - 969 pp.

Nowak, M.A.; Bangham, C.R.M. Population Dynamics of Immune Responses to Persistent Viruses. Science. 1996. v 272. 74 - 79 pp.

Nowak, M.A.; Bonhoeffer, S.; Shaw, G.M.; May, R.M. Anti-viral Drug Treatment: Dynamics of Resistance in Free Virus and Infected Cell Populations. Journal of Theoretical Biology. 1997. v 184. 203 - 217 pp.

Nowak, M.A.May, R.M.; Phillips, R.E.; Jones, S.R.; Lalloo, D.G.; McAdam, S.; Klenerman, P.; Köppe, B.; Sigmund, K.; Bangham, C.R.M.; McMichael, A.J. Antigenic oscillations and shifting immunodominance in HIV-1 infections. Nature. 1995. v 375. 606-611 pp.

Phillips, A. Reduction of HIV Concentration during acute infection; Independence from a Specific Immune Response. Science. v 271. 1996. 497 - 499 pp.

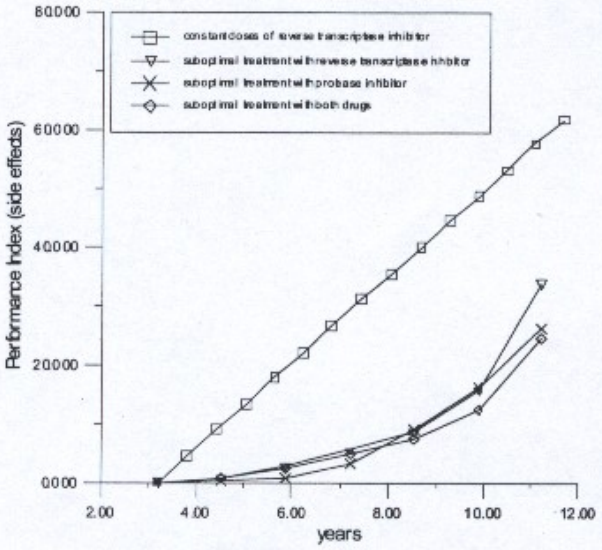

Figure 5

Pontesilli, O.; Kerkhof-Garde, S.; Pakker, N.G.; Notermans, D.W.; Roos, M.T.L., Klein, M.R.; Danner, S.A.; Miedema, F. Immunology Letters. 1996. v 66. 213 - 217 pp.

Regoes, R.R.; Wodarz, D.; Nowak, M.A. Virus Dynamics: the Effect of Target Cell Limitation and Immune Responses on Virus Evolution. Journal of Theoretical Biology. 1998. v 191. 451 - 462 pp.

Tan, W.Y.; Wu, H. Stochastic Modelling of the Dynamics of $CD4^+$ T-Cell Infection by HIV and Some Monte Carlo

Studies. Mathematical Biosciences. v 147 .1998. 173 - 205 pp.

Tan, W.Y.; Xiang, Z. Some state space models of HIV pathogenesis under treatment by anti-viral drugs in HIV-infected individuals. Mathematical Biosciences. 1999. v 156. 69 - 94 pp.

Wein, L.M.; D'Amato, R.M.; Perelson, A. Mathematical Analysis of Antiretroviral Therapy Aimed at HIV-1 Eradication or Maintenance of Low Viral Loads. Journal of Theoretical Biology. 1998. v 192. 81 - 98 pp.

Wick, D. On T-cell dynamics and the hyperactivation theory of AIDS pathogenesis. Mathematical Biosciences.1999.127-144 pp.

Zaric, G. S.; Bayoumi, A.M.; Brandeau, M.L.; Owens, D.K. The Effects of Protease inhibitors on the Spread of HIV and Development of Drug-Resistant HIV Strains: A Simulation Study. Simulation. 1998. V. 71:4. 262-275 pp.

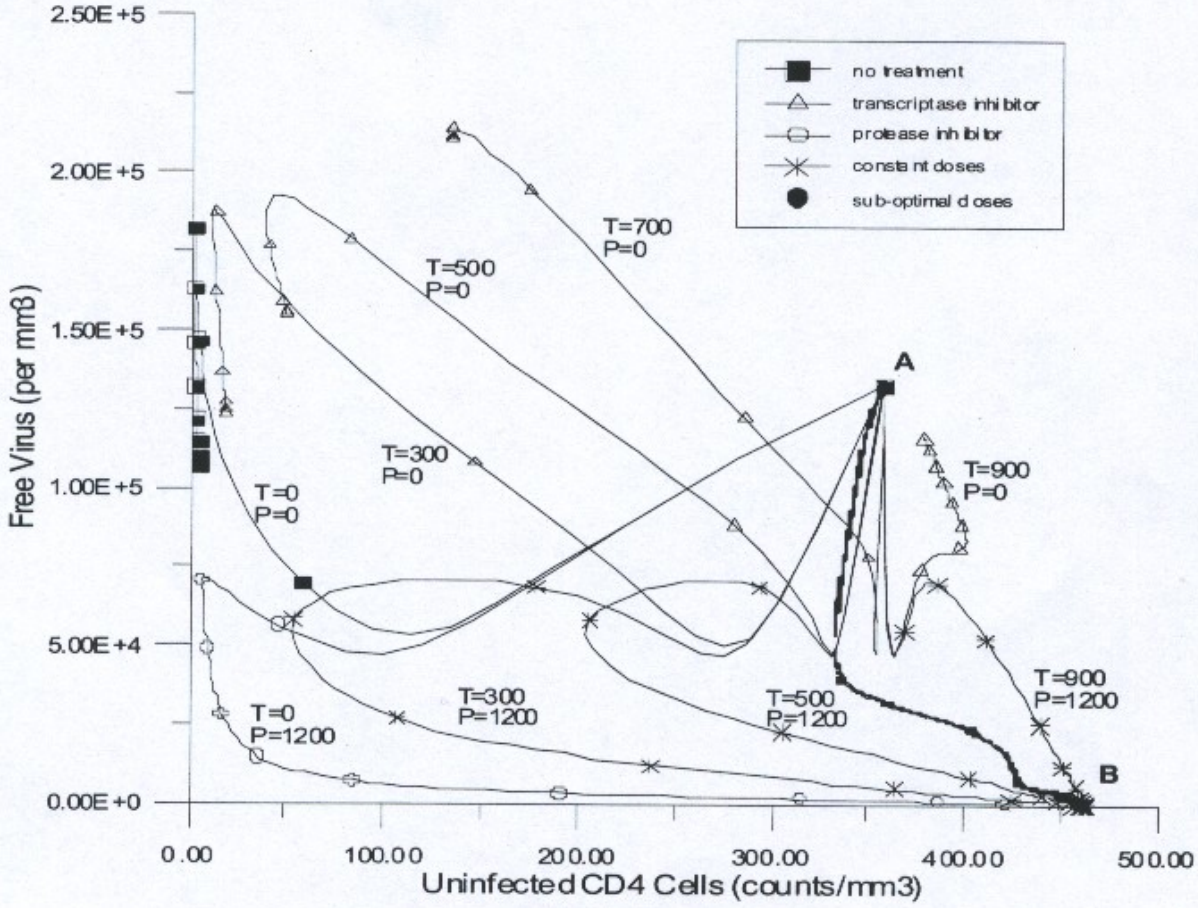

Figure 6 - Typical trajectories (projections on x_4, x_1 plane) under sub-optimal and constant dose treatment schemes