A NEW MATHEMATICAL INDEX FOR THE OPTIMAL CONTROL OF DRUG DOSES

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Abstract: A new quantitative index is proposed to assign a numerical value that reflects the compromise between the therapeutic and side effects during treatment of AIDS using drugs that are active against HIV. The model considers that the clinical conditions are related to the values of $CD4^+T$ cell counts and viral load. The therapeutic effect is associated with increase in the $CD4^+T$ cell counts, while the side effects are assumed related to the drug doses. The proposed index might be useful in computer programs for numerical evaluation and optimization of different types of drug administration schemes.

Keywords: Biomedical systems, Biomedical control, Optimization, Modelling.

1. INTRODUCTION

Quantitative descriptions of the clinical dynamics exhibited by AIDS is now available as a consequence of intense research, together with advances in the mathematical modeling methods: (Nowak & Bangham, 1996; Phillips, 1996; Perelson *et al.,* 1993; Tan & Wu, 1998).

These descriptions are usually mathematical models that are provided in the form of differential equations and can be used to optimize the drug doses that are best suited in terms of a criterion that can represent the efficacy of the treatment.

The model used in this work was proposed by Tan & Wu (1998), and is similar to the one in Perelson *et al.* (1993).

In works such as Kirschner *et al.* (1997), Caetano & Yoneyama, (1999a), Caetano & Yoneyama (1999b), de Souza *et al (*2000), the problem of optimizing the doses of drugs for treatment of AIDS was tackled using classical numerical methods (Bulirsh, 1980; Kirk, 1970; Jacob, 1972; Lewis, 1986).

In Caetano & Yoneyama (2002), it is shown that it is possible to obtain results using optimal theory for treatment of AIDS that are very similar to the schemes recommended by Health World Organization, when the comparison is carried out in terms of $CD4^+T$ Cells Count and Viral Load, using actual data of sero-positive patients from *Centro de Referência e Tratamento em DST/AIDS* at São Paulo in Brazil.

The experience gained with the previous work using numerical simulations led to the proposal of a new mathematical index that reflects the compromise between the therapeutic and side effects.

Thus, the objective of this work is to discuss its biological and medical aspects, correlating them with the symptoms reported by patients.

The patients of this work were also provided by the *Centro de Referência e Tratamento em DST/AIDS* at São Paulo city, Brazil.

2. DYNAMIC MODEL

Dynamic models describe the time evolution of the relevant variables and are important in computer simulations to analyze the efficacy of the treatment scheme.

The usual form of dynamic models involves differential equations with some parameters.

One important task is, thus, to determine the numerical values of these parameters, i.e., fit the model with actual data.

So, the model must be validated and this is done by comparing the numerical solutions of the differential equations with the observed clinical evolution of the patient.

There are many different mathematical models for AIDS in the literature, each one focusing on the representation of some specific aspects (Mittler *et al.,* 1998, Wick, 1999, Beherens, 1999, Tan & Xiang, 1999, Nowak *et al.,* 1991, Nowak *et al.,* 1995, Nowak *et al.,* 1997, Wein *et al.,* 1998, Nowak & Banghan, 1996, Phillips 1996, Perelson *et al.* 1993, Wick, 1999 and Zaric, 1998).

In this work, the attention is directed to the effects of treatments using reverse transcriptase and protease inhibitors.

The adopted model was adapted from a more general version that includes stochastic terms, as originally presented by Tan & Wu (1998, 1999).

The model consists of four coupled ordinary differential equations as follows:

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

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

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

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

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

with $x_1 = x_1(t) \equiv$ uninfected $CD4^+$ T cells; $x_2 = x_2(t) \equiv$ latent infected $CD4^+$ T cells ; $x_3 = x_3(t) \equiv$ active infected $CD4^+$ T cells ; $x_4 = x_4(t) \equiv$ free viruses 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 viruses; k_2: conversion rate from x_2 to x_3; N: number of infectious "virions" produced by an actively infected T cell; θ: viral concentration that tends to decrease s.

The coefficients k_1 and k_2 are functions of the drug doses

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

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

where k_{10}, k_{20}, α_1 and α_2 are constants.

The negative exponential functions model the effect of saturation of the drug activity, so that increase in the administered doses does not yield proportional increase of the therapeutic effects.

Basically, x_1 cells are stimulated to proliferate with rate $\lambda(x_1,x_2,x_3)$ in the presence of antigen and HIV (equation 3).

Without the presence of HIV, the rate of generation would be $S(x_4)$ (equation 2).

However, in the presence of free HIV (x_4), uninfected cells x_1 can be infected to become x_2 cells or x_3 cells, respectively actively or latently infected forms, depending on probability expressed by the 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 living and will normally be killed upon activation with death rate μ_3.

The x_1, x_2 cells and x_4 free viruses have finite life and the death rates in this model are 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 dynamics via parameters k_1 and k_2.

3. THE PERFORMANCE INDEX

The proposed mathematical index was conceived to indicate a compromise between the therapeutic effect and the undesirable dose-related side effects. The expression for the proposed index is

$$\begin{aligned}
J = \int_{t_0}^{t_f} \Big\{ & \phi_1\left(1 - e^{\alpha_1 m_1(t)}\right) + \\
& + \phi_2\left(1 - e^{\alpha_2 m_2(t)}\right) + \\
& + \frac{\gamma_1}{(CD4(t))^2} + \\
& + \gamma_2 (\text{viral load}(t))^2 \Big\} dt
\end{aligned} \tag{7}$$

The heuristic interpretation of the proposed cost functional is that the first two terms in the summation represent the side effects due to m_1 and m_2, respectively. Here m_1 is the reverse transcriptase inhibitor and m_2 is the protease inhibitor.

Clearly the two last terms out of integral represent the target of maximising non-infected CD4 (x_1) and viral load (x_4) along the pre-specified time horizon.
Analogously to the therapeutic effect, the side effect is also assumed to present saturation and, hence, modeled by a negative exponential. The coefficients α_1, α_2, ϕ_1, ϕ_2, γ_1 and γ_2 are constants.
After numerical evaluations with clinical data corresponding to several patients and despite the considerable variability from individual to individual, some typical nominal values for constants α_1, α_2, ϕ_1, ϕ_2, γ_1 and γ_2 were adopted for the sake of computational simulations:

$$\phi_1 = 100, \quad \alpha_1 = 10^{-9}, \quad \gamma_1 = 250{,}000$$

$$\phi_2 = 100, \quad \alpha_2 = 10^{-9}, \quad \gamma_2 = 10^{-8}$$

The proposed index was then used to compare several drug administration schemes, including those based on the optimal control theory.
As expected, the numerical simulations show that improved clinical results can be achieved in terms of a compromise between the side effects, reduction of the viral load and increase in the $CD4^+$ T cell counts.

4. NUMERICAL RESULTS

The actual data was obtained from *Centro de Referência e Tratamento em DST/AIDS* at São Paulo city, Brazil, after the approval of the protocol by the State Ethical Review Board.

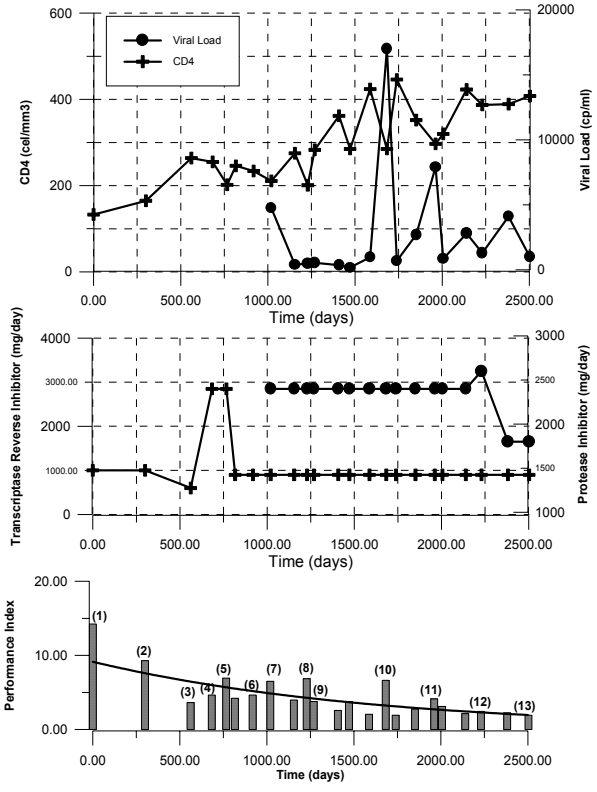

Fig. 1. CD4, viral load and performance index for PATIENT 14.

In order to select the patients for inclusion in the present study, some eligibility criteria were adopted. Also, In order to avoid complications related to senility or growing phase, patients were required to be in the range of 18 to 60 years of age.

It is worth mentioning that the patients from this Center had been receiving treatment with the help of Ministry of Health under the public system SUS. Overall, the Center has around 5000 patients receiving treatment over 10 years.

The sample consisted of 43 patients and for illustration purposes, 3 patients (identified by numbers 14, 22 and 39) were selected for presentation of the specific numerical results.

In Figure 1 one can see the actual clinical data for patient 14. It is possible to observe, in the first picture, the CD4 cells count and viral load (copies/ml).

The second picture shows the administered doses of reverse transcriptase and protease drugs.

This patient started receiving 900 mg of reverse transcriptase inhibitor (zidovudine) and after 1000 days begun receiving protease inhibitor (indinavir and ritonavir) 2400 mg/day.

The third picture shows the graph of the performance index (7) when the clinical data corresponding to patient 14 are inserted.

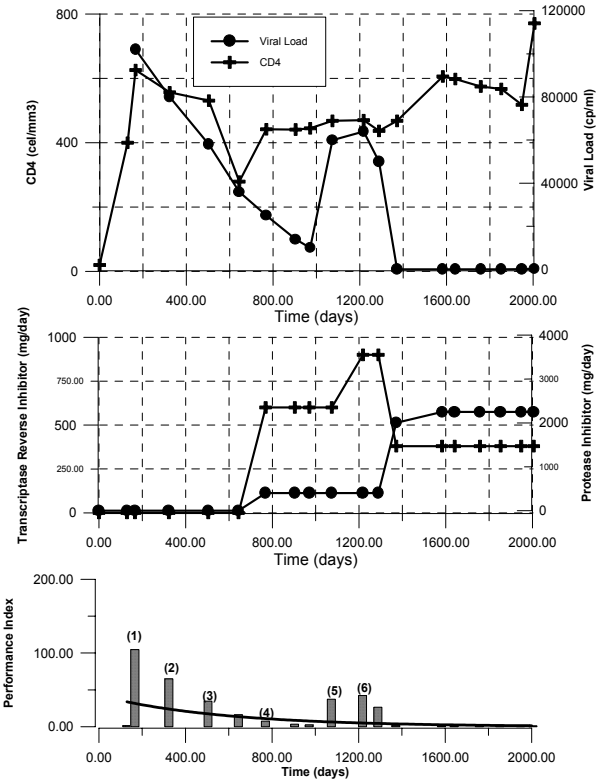

Fig. 2. CD4, viral load and performance index for PATIENT 22.

The figures in the graph are used to make associations with the table 1 with the reported side effects of patient 14.

The trend curve shows that the index decreases when the adopted treatment scheme has a good response.

The entry marked number (1) in the table (beginning of the treatment) corresponds to the record that the patient was having a serious tuberculosis and diarrhea.

The same patient, at the final period considered in this study, reported only minor problems in the ear. In the beginning the index had the value 14.23 and on the last day only 1.91.

Figure 2 shows results for other patient who had serious problems: hepatitis C, pneumonia, and cerebral syndrome with lesions (see table 2).

This patient had also severe depression. In terms of the proposed index, it is possible to note that it starts with value 1.5 but upon manifestation of the hepatitis, the value jumps to 104.67.

In the final period when the patient has recovered, the index is only 0.94. For this patient, the doses were 600 mg/day of transcriptase reverse inhibitor (zidovudine) and 400 mg of protease inhibitor (DDI), most of the time.

However, some adjustments were made during the treatment, so that for a period he received 2250 mg of protease inhibitor (nelfinavir).

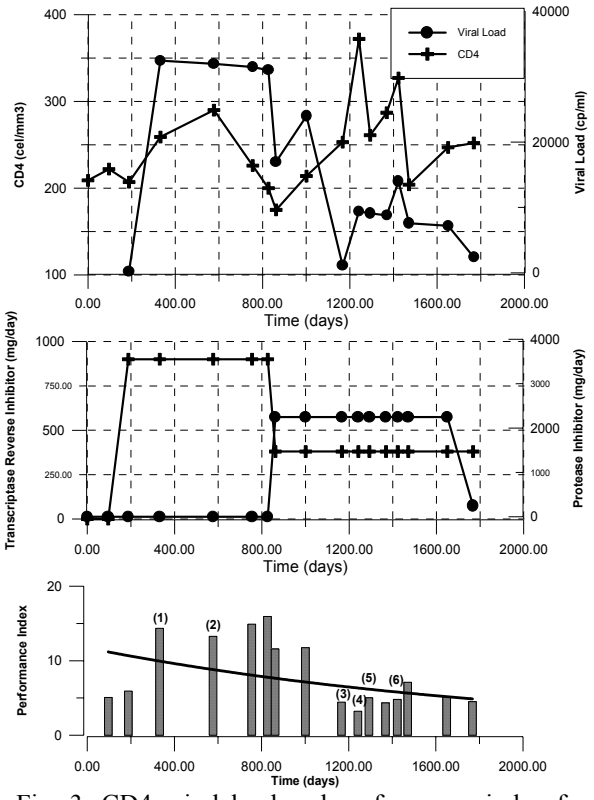

Fig. 3. CD4, viral load and performance index for PATIENT 039.

Table 1 Side effects reported by PATIENT 14

No.	*Side effects- P014*
1	Diarrhoea; Tuberculosis
2	Backache; Leg ache
3	Liquid Diarrhoea; Colic
4	Headache; High Fever; weight loss
5	
6	Diarrhoea; Pulmonary Tuberculosis
7	Stain in the Face
8	Emesis
9	Throat pain
10	Vertigo dizziness
11	Atypical Pneumonia ; Influenza
12	Throat pain
13	Ringing in the hear

Figure 3 shows the clinical history of patient 39. In the beginning the patient had bacterial pneumonia and after that, herpes and hepatitis C (see table 3).

These events can be related to markings in first picture with number (1) and (2). The values of performance index were 14.35 and 13.28 respectively.

Around day 1500, the patient reported only backache. An interesting fact is that around day 1200 he received vaccination for hepatitis B and pneumonia and the viral load that was 1,100 copies/ml increased rapidly to 9,400 copies/ml.

Again, the index presents a decrease compatible with the described clinical evolution, varying from 4.43 to 3.21. That is numbers (3) and (4) in the third picture.

5. CONCLUSION

In order to provide a quantitative means to indicate the clinical state of AIDS patients, this work provided a new mathematical index.

It can be used to help monitor the clinical response of the patient to the several treatment schemes for AIDS.

The main idea is to balance the intensity of side effects and therapeutics-effects by including model variables closely related to them.

Table 2 Side effects reported by PATIENT 22

No.	*Side effects- P022*
1	Hepatitis C
2	Hepatitis C
3	Hepatitis C
4	Cephalea; Dyspepsia
5	Brainstem lesion
6	Strabismus; Depression; Vertigo Dizziness

Table 3 Side effects reported by PATIENT 39

No.	*Side effects- P039*
1	Bacterial Pneumonia
2	Herpes + Hepatitis C
3	Vaccination (Hepatitis B + Pneumonia) 1^{th} dose
4	Vaccination (Hepatitis B +Pneumonia) 2^{th} dose
5	Vaccination (Hepatitis B +Pneumonia) 3^{th} dose
6	Backache

The proposed index can also be used to optimize the doses administered to the AIDS patients.

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