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Optimal medication in HIV seropositive patient treatment using fuzzy cost function

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Abstract— **This work concerns the optimization of medication doses using fuzzy relations to represent the compromise between the side-effects and therapeutic effects in the clinical treatment of HIV (Human Immunodeficiency Virus) seropositive patients. The optimization process is carried out using a mathematical model which relates immunological variables such as the number of CD4+T helper cells (immune cells) and the viral load. The control variables used in the optimization process are the doses of reverse transcriptase inhibitor and protease inhibitor. The cost function uses fuzzy logic rules because clinical states are well expressed by linguistic variables by the medical staff. The results are illustrated with a model fitted to the actual data clinical data of an HIV seropositive patient.**

I. INTRODUCTION

The optimal control theory has different applications in many biological areas such as in the study of population growth, disease dissemination, genetics, ecology, etc. In terms of medical applications, several papers have appeared in the literature dealing with diseases such as malaria, dengue, schistosomiasis and Aids, among others.

The object of this work is the use the concept of fuzzy logic to propose a cost function for quantifying linguistically the magnitude of side-effects and the therapeutic effects during treatment. Numerical descriptions of the dynamics exhibited by AIDS is now available due to intense clinical research, together with advances in the mathematical modeling methods ([1]-[4]). These mathematical models can be used together with appropriate cost functions to optimize the drug doses required in the treatment. The model used in this work was proposed Tan and Wu [4], and is similar to Perelson [3].

When the viruses invade our immunological system it has as goal to attack CD4+T helper cells. The process is controlled by using two types of inhibitors for HIV. The reverse transcriptase inhibitors block the entrance of virus in the CD4+T cell and the protease inhibitors block the exit of virus of cells. The first group of inhibitors is composed by drugs as Zidovudine (AZT), Neverapine, Didanosine (DDI), Epivir (3TC) and others. The second group is composed by Indinavir, Saquinavir, Ritonavir and others. In last decade they have been using both simultaneously and today are known as anti-aids cocktail, also known scientifically as HAART (**H**ighly **A**ctive **A**ntiretroviral **T**herapy) scheme. There are many different effects for patients with long term treatment. Both single and severe effects have been observed in sero-positives patients such diarrhea, backache, headache, high fever, weight loss, tuberculosis, pneumonia, influenza, stain in the face, vertigo, throat pain, etc. The actual data used to tune the model parameters in this work were provided by the *Centro de Referência e Treinamento em DST-AIDS* in São Paulo, Brazil. The mathematical model consists of four differential equations representing the dynamics of uninfected CD4+T cells, latently infected CD4+T cells, actively infected CD4+T cells and viral load. The compromise between the therapeutic outcomes and the intensity of the side-effects is expressed by rules of fuzzy logic. This approach is an alternative with respect to the use of numerical indices ([5],[6]) and tries to capture the medical staff's assessment of the patient's condition such as “good health state”, “count of CD4+T is somewhat low”, etc. In terms of optimal control, the method of solution is unchanged, as a deffuzification block is used to convert the linguistic output to a numerical value ([7]-[9]).

II. THE MATHEMATICAL MODEL FOR AIDS

The use of parameterized differential equations is a standard way to construct dynamic models. One important task is, thus, to determine the numerical values of these parameters, i.e., to fit the model with the actual data. So, the model must be validated by comparing the numerical solutions of the differential equations with the observed clinical evolution of the patient.

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 and Wu [4]. The model consists of four coupled ordinary differential equations as follows:

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

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

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

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

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

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; σ: 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 variables m_1 and m_2 represents the drug doses. The negative exponential functions model the effect of saturation of the drug activity, so that large increases in the administered doses do not a yield proportional gain of the therapeutic effects.

The various relations between the variables which appears in the dynamic model (equations 1 to 4) can be graphically represented as in figure 1.

The x_1 cells are stimulated to multiply themselves with rate $\lambda(x_1, x_2, x_3)$ (which is described by equation 3), in the presence of antigen and HIV (equation 3). Without the presence of HIV, the rate of generation would be $S(x_4)$ (described in equation 2). However, in the presence of 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 the probability which is expressed by the rate ω. Also x_2 cells can be activated to become x_3 cells.

The activation rate is k_2. On the other hand, 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, pieces of viruses x_4 are released with rate N(t) described by (4). Drugs such as reverse transcriptase inhibitors (m_1) and protease inhibitors (m_2) affect the dynamics via parameters k_1 and k_2, described by equation 5 and equation 6.

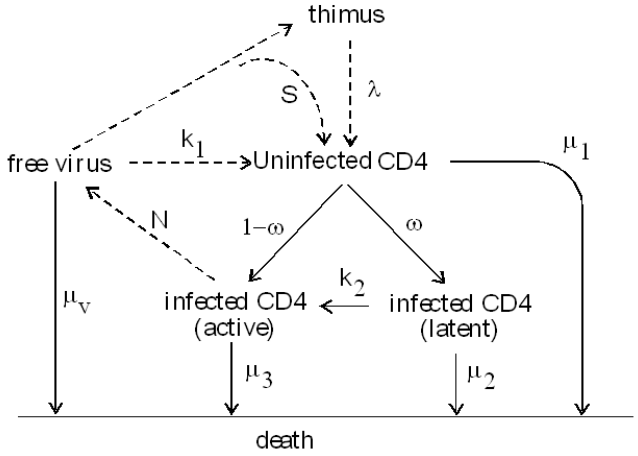

Figure 1 Relations between the state variables

I. THE COST FUNCTION

In Medicine, linguistic variables that are related to actual numerical data are quite useful in representing the clinical state of patients. Therefore, fuzzy relations can be used in a cost function to represent the effectiveness of the chosen treatment schemes. The proposed fuzzy index was conceived to indicate a compromise between the therapeutic effects and the undesirable dose-related side effects. Figure 2 shows the scheme used for computing the cost function and to feedback the control to apply in dynamic system. The treatment consists of administration of m_1 and m_2 that are constants during a fixed interval T (such as 3 months, 6 months or 1 year).

$$m_j(t) = m_j(t_i) \quad t \in [t_i, t_{i+1}) \tag{7}$$

where t = 1, 2, 3… and $t_{i+1} - t_i = T$.

The process is initialized with a sequence of random positive doses. These doses are used to simulate the dynamic system of ordinary differential equations (equation 1 – equation 4).

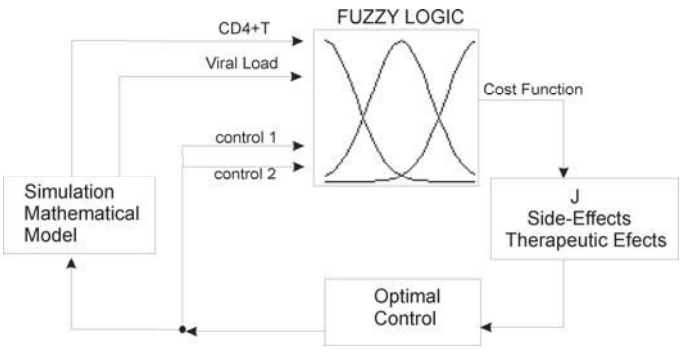

Figure 2 Proposed optimization setup

The simulation results of CD4+T, viral load and doses of m_1 and m_2 are fed into the fuzzy logic block. The fuzzy block computes the value of the cost function that indicates, in a normalized scale, the effectiveness of the attempt to balance the possible side-effects and the therapeutic effects. The obtained result for cost function is used by an optimization algorithm (such as Nelder-Mead) to search for the optimal doses for the minimum cost.

The logic rules for the fuzzy block were built based on the clinical reports of 45 patients treated at *Centro de Referência e Tratamento DST/AIDS of Vila Mariana in* São Paulo city. However each patient requires a process of fine tuning of the model parameters in order to represent the individual specifities.

A set of 14 rules were built to generate the output for the cost function. Each fuzzy rule has four conditions, namely the number of CD4+T per mm^3, the viral load, the dose of the transcriptase inhibitor ($m_1(t)$) and the dose of the protease inhibitor ($m_2(t)$) . For instance a fuzzy logic rules may use the structure:

"IF <CD4 is low> AND <viral load is high> AND <m_1 is high> AND <m_2 is high> THEN <cost function is high>".

Table 2 presents the complete set of fuzzy logic rules used in this work as designed based on the knowledge provided by the clinical staff. No supervised training was used so that the membership function was tuned by hand. The time horizon [t_o , t_F] is partitioned into N subintervals and let

$$t_i = t_{i-1} + \frac{t_F - t_0}{N}$$
$$i = 1,\ldots,N$$

For each t_i , let the cost function $J_i\left(m_1^i, m_2^i\right)$ as the output of the fuzzy inference machine and define the cost function as

$$J(m_1, m_2) = \sum_{i=1}^{N} J_i\left(m_1^i, m_2^i\right)$$

where (m_1,m_2) are functions that are piecewise constant assuming values m_1^i, m_2^i, in each interval (see Figure 5). The problem is to search for (m_1^*, m_2^*) that minimize $J(m_1,m_2)$.

Figure 3 shows the membership functions for the four inputs (CD4+T, viral load, $m_1(t)$ and $m_2(t)$) and the only output (cost function). The membership functions are of Gaussian type divided in low, mean and high (linguistic variables) for both, input and output data. For deffusification the Center of Mass method was used .

II. RESULTS

In order to illustrate the application of the proposed methodology, "patient 22" was selected. Firstly, the model parameters for the *patient 22* were identified yielding an adequate fitting, as can be seen in figure 4. The parameters fitted are in table 1. The final time for observation of this patient was 1840 days. The total period was divided in five intervals in order to use a finite dimensional optimizer.

The result in terms of the cost function can be seen in figure 4. This figure is a comparison between the constant doses (recommended by the World Health Organization) and simulation using table 1 with the same doses from actual data. The initial conditions for this simulation are in table 3. It is possible to observe that the cost function using optimal control with fuzzy logic is lower than with constant doses in the figure 5. The evaluation of both strategies (constant doses and optimal doses) are made by the fuzzy cost function.

Figure 6 shows the results for the immunological variables (CD4+T and viral load) and the administered medications (control). The doses adopted were 1400 mg of m_1 (reverse transcriptase inhibitor) and 2000 mg of m_2 (protease inhibitor) for the simulation using constant medications. It is possible to see that the results for CD4+T is lower (using optimal control) than fitted curve (dashed line) but the results for the viral load are the same, showing that is possible to control the HIV using lower and variable doses of drugs. The optimal doses for reverse transcriptase inhibitor ($m_1(t)$) were between 1100 and 1200 mg (the actual doses was 1400 mg). Also the protease inhibitor ($m_2(t)$) were lower (between 900 mg and 1400 mg) than actual doses (2000 mg). Matlab © 6.5 software was used in order to apply the Nelder-Mead search optimization algorithm, via the function *fminsearch.m*; and also to implement the Runge-Kutta method for simulation via the function *ode45.m.*

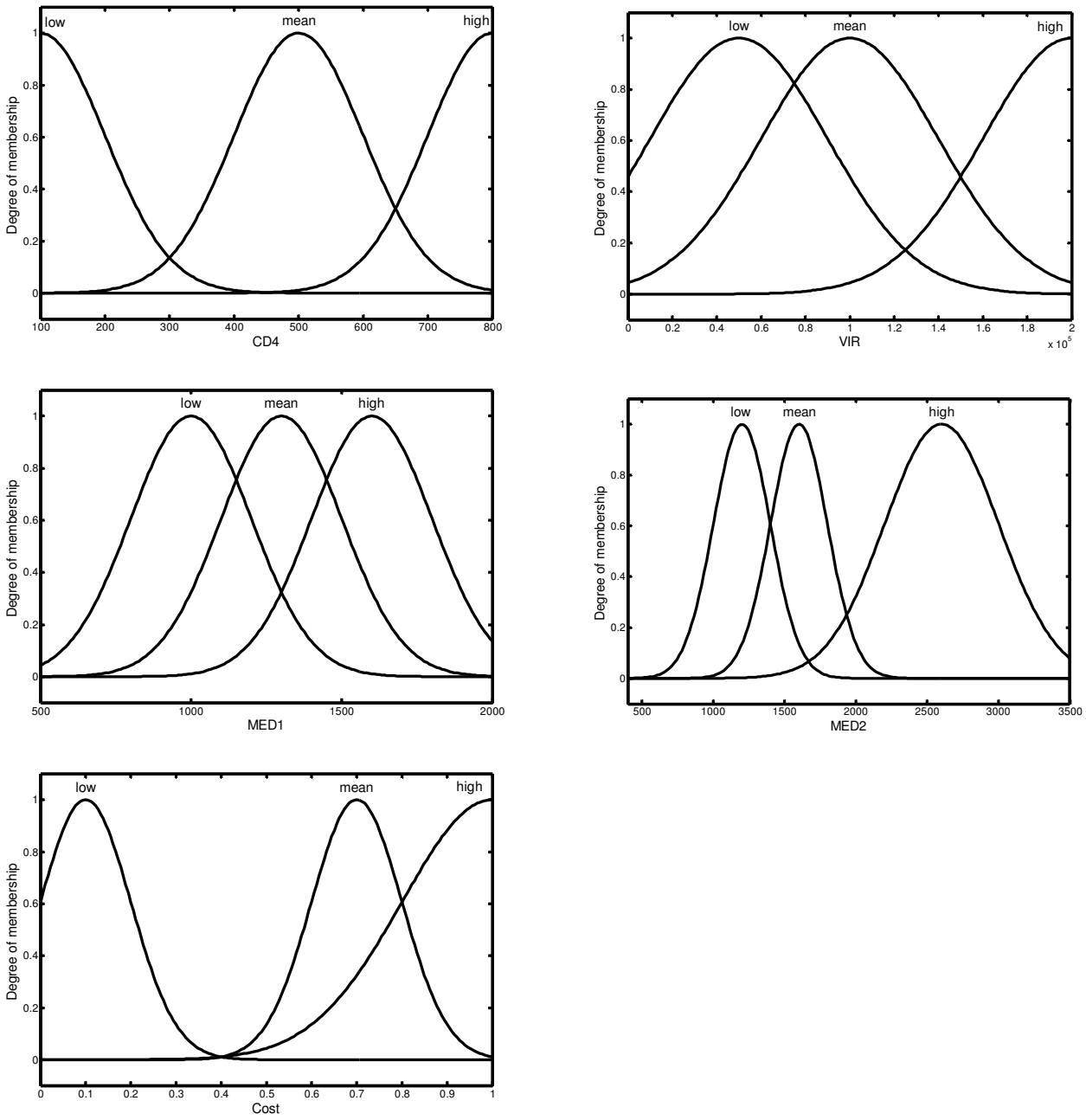

Figure 3 Membership functions for CD4+T, Viral Load, Medication Doses and Normalized Cost

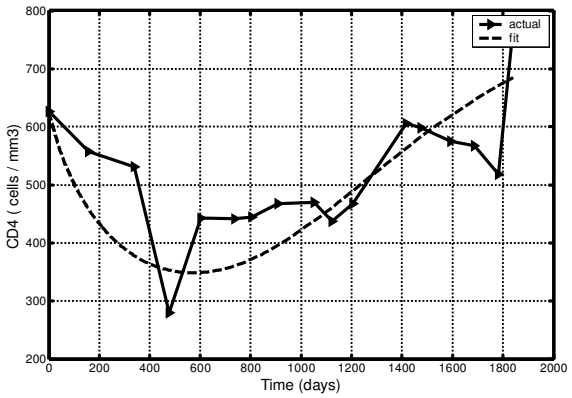

Figure 4 Parameters fit for actual data

V. CONCLUSION

The present work shows the use of fuzzy logic in the cost function to optimize the treatment of HIV seropositive patients. A set of 14 rules were built to generate the output for the cost function based in medical report. The actual data set of a patient from *Centro de Referência e Treinamento em DST-AIDS* in São Paulo city, Brazil was used to compare the results. The fuzzy logic was seen to describe, in a natural way, the accessment of the quality of treatment, as made by the medical staff, by combining the side-effects and therapeutic effects. The membership functions were built based in clinical experience and comments of doctor medical in report about the side-

effects of patient. The optimal doses and variable were compared to the scheme with constant doses applied used by an actual patient (recommended by the World Health Organization).

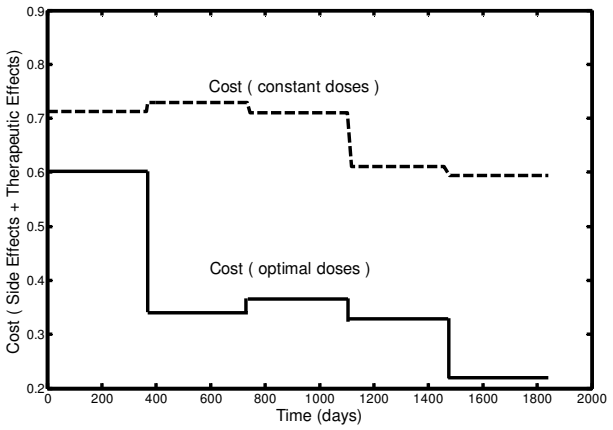

Figure 5 Intermediate values of the cost function for optimal doses and fixed doses of (1400 mg of m_1 and 2000 mg of m_2)

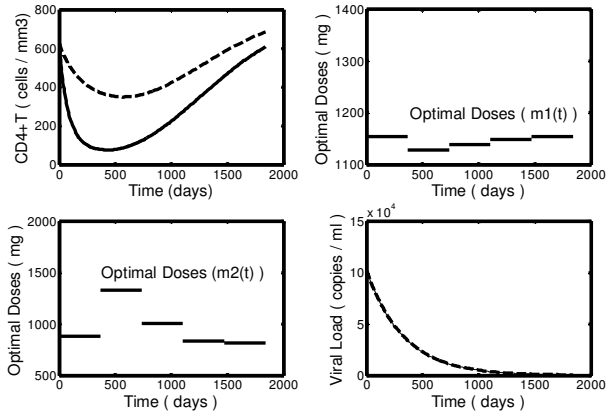

Figure 6 - Evolution of the variables used in the fuzzy rules

Obviously, a larger sample of patients is needed to obtain a medically reliable result with adequate statistical confirmation.

However, the present results are consistent with other works related to the effectiveness of the treatments of HIV seropositive patients, as long period of administration of large doses can lead to a significant manifestation of side-effects. For instance, the work [10] present results using "start-stop" methodology with tests *in vivo* with ten patients. The patients use HAART scheme with periodical interruptions. The authors mention that the viral load rebounces when the treatment is interrupted, but up to level lower than the previous values.

Table 1 – Model Parameters

σ	1.2 mm^{-3}
R	0.001day^{-1}
T_{max}	1200 mm^{-3}
μ_1	1E-4 day^{-1}
μ_2	1.4E-2 day^{-1}
μ_3	1E-7 day^{-1}
μ_v	0.003 day^{-1}
k_{10}	0.01 mm^3/day
k_{20}	0.007 mm^3/day
N_0	1000 cell/mm^3
θ	10000
ω	0.97
β_1	0.01
β_2	1000
α_1	0.01
α_2	0.01

Table 2 – Rules for fuzzy logic

CD4+T	VIRAL LOAD	m_1	m_2	Cost
low	high	high	high	high
low	high	low	high	high
low	high	low	low	high
low	high	high	low	high
medium	high	high	high	high
medium	medium	high	high	high
medium	medium	medium	high	medium
medium	medium	medium	medium	medium
high	medium	medium	medium	low
high	medium	low	low	low
high	low	low	low	low
high	low	high	low	medium
high	low	low	high	medium
low	low	low	low	medium

Table 3 – Initial Conditions

Variables	Values
$x_1(0)$	626 cells/mm^3
$x_2(0)$	1000 cells/mm^3
$x_3(0)$	2000 cells/mm^3
$x_4(0)$	102000 copies/ml
Final time	1840 days

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