A SUB-OPTIMAL TREATMENT SCHEME FOR VIRAL INFECTIONS USING FUZZY CRITERIA

J.A.M. Felippe de Souza
Universidade da Beira Interior
Departamento. de Engenharia Electromecânica, 6200 - Covilhã - Portugal
e-mail: felippe@ubi.pt

R. K. H. Galvão and T. Yoneyama
Instituto Tecnológico de Aeronátutica
Divisão de Engenharia Eletrônica, 12228-900 - S. J. dos Campos - Brazil
e-mails: kawakami@ele.ita.cta.br, takashi@ele.ita.cta.br

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ABSTRACT

This work concerns the optimization of treatment schemes for viral infections using drugs that affect the rate of production of antibodies. The dynamics of the disease is based on Marchuk's formulation of the behavior of the immune system. The model is extended to include the effect of treatment and to allow a representation of the pathological consequences of the infection and the side effects of the drugs on the patient. The performance index uses the concept of fuzzy sets to model non-exact subjective quantities, such as patient well-being and provide means to represent a compromise in terms of other quantities such as cost of medication, that can be objectively measured. The admissible controls are assumed to belong to the class of piecewise constant functions. A numerical example using influenza dynamics shows a considerable improvement of the optimized drug administration policy, when compared to non-optimized policies, in terms of reduction in the achieved performance index.

INTRODUCTION

The immune system provides defense against alien agents that do not contain genetically coded segments which makes them recognizable as part of the organism (such as bacteria, viruses, alien tissue or tumors).

Upon detection of an alien agent (*antigen*), the organism reacts generating special cells and molecules (*antibodies*) to neutralize it or destroy it.

From primitive cells found on the bone marrow, two populations of cells evolve: lymphocytes T and B. Both populations, being stimulated by the antigen, proliferate and suffer morphological alterations. B lymphocytes generate the effecter-cells, which synthesize and segregate antibodies; T Lymphocytes evolve to lymphoblasts which, by segregating several soluble factors, establish the cell-type immune response (T-helper cells), actuating primarily on the macrophages. A subpopulation of activated T lymphocytes (T-killer cells) also acts directly on infected cells, segregating citotoxic substances which cause their destruction.

Several authors have worked on models that describe quantitatively the complex phenomena of the immune response (Mohler *et al.* 1980, Asachenkov *et al.* 1970, Bell 1970).

This work proposes a methodology for improving the pharmacological treatment of viral infections based on the sub-optimal solution of an optimal control problem. The problem is formulated to allow a numerical selection of a set of drug administration strategy parameters that yields a good compromise between therapeutic and side effects.

In order to simplify the statement of the problem specifications, fuzzy performance indexes are used, involving the total amount of medicine expended, the patient recovery time and the damage inflicted to the organism during infection.

THE INFECTION MODEL

This work uses the model proposed in Asachenkov *et al.* 1994, which describes an influenza infection

The model consists on a system of ordinary differential equations which describe the dynamics of the the virus, the antibody concentration and the populations of defense cells in the infected organism.

The model, which was originally of autonomous form was modified to include an external input (administration of drugs). The seric concentration is assumed to follow a first order dynamic equation with inputs that correspondes to the administered drug doses:

$$\frac{d}{dt}V = \left(a_1 + \frac{a_2}{1 + a_3 F} + a_4 Le\right)V$$

$$\frac{d}{dt}Lp = Lp^0\delta(t - t^*) + a_5[1 - \exp(-a_6 V)]Lp$$

$$\frac{d}{dt}Le = a_7[1 - \exp(-a_6 V)]Lp - a_8 Le$$

$$\frac{d}{dt}F = a_9 \exp(-Us)Le - \left(\frac{a_{10}V}{1 + a_3 F} + a_{11}\right)F$$

$$\frac{d}{dt}m = a_{12}V + a_{13}F + a_{14}Us$$

$$\frac{d}{dt}Us = -a_{15}Us + a_{16}u$$

$$V(0) = V_0\, Lp(0) = Le(0) = F(0) = 0$$

where

V(t) : concentration of virus
Le(t) : effector lymphocytes
Lp(t) : precursor lymphocyte
F(t) : concentration of generalized antibodies.
m(t) : accumulated damage
Us(t) : drug concentration
u(t) : external drug input

and $\delta(.)$ is a Dirac impulse. The coefficients a_1, ... , a_{16} are constants.

The coefficients a_i were extracted from Asachenkov *et al.*, 1994, where the identification was carried out using data from experiments in which F1 mice were infected intranasally with influenza virus A/PR8/34. In order to evaluate the organism deterioration during the infection, a variable m(t) is introduced, representing the overall damage due to the infection and to the side effects of the drugs. It is interesting to note that not only the viruses, but also the antibodies themselves inflict damage to the infected organism.

MULTI-CRITERIA OPTIMIZATION

Having modeled the influence of the drug administration on the evolution of the infection, the next step is the proposal of some criteria to allow the actual computation of an optimal treatment policy. One would be concerned, therefore, with issues such as:

- which is more effective: apply a single concentrated 'one-shot' scheme of the drug or carry out the treatment in a continuous way during a longer period with low dosages?
- When the doses should be administered?
- How much medicine should be administered per dose?

One way to consider those issues is to propose performance indices and apply the techniques of optimal control theory. The indices shoud reflect:

- The cost of the medicine
- The side effects caused by large doses
- The physical and psychological stress on the patient

However, except for the first one, it is difficult to translate these aspects in analytical specifications such as an LQ performance index. It would be more natural to define a cost based on linguistic concepts like “good” and “bad”, “better” or “worse”. Thus, fuzzy logic arises as a convenient tool for the problem of defining a performance index (Kienitz 1993).

An informal description of the desired result for the treatment would be:

Criterion (a): 'Patient recovery is fast'.

AND

Criterion (b): 'Total amount of drug expended is small'.

AND

Criterion (c): 'The damage to the patient's organism during infection is small'.

The criteria (a), (b) and (c) can be related to the minimization of the following variables:

$$t_H \quad \text{s.t.} \quad V(t_H) = \lambda \max_{t \in [0, t_f]} V(t)$$

$$u\_total = \int_0^{t_H} u(t)dt$$

$$m(t_H)$$

where λ is a constant.

For computational simplicity, gaussian functions were adopted as the membership functions for the

variables given above, as shown in figure 1. The 'standard deviations' were adjusted in such a way that for each of $z = t_H$ or $z = u\_total$ or $z = m(t_H)$, the corresponding membership functions $\mu_1(t_H)$, $\mu_2(u\_total)$ and $\mu_3(m(t_H))$ reflected the criteria (a), (b) and (c).

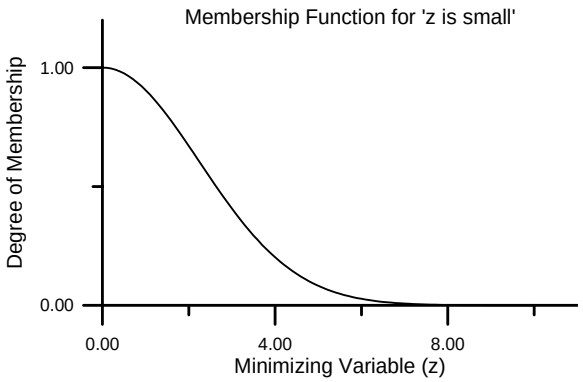

Figure 1 Shape of the Membership Functions representing the fuzzy set 'z is small'

Since, from a practical point of view, it would be difficult to implement a drug administration programme with continuously varying drug doses, the admissible controls are assumed to belong to the class of piecewise constant functions. In order to further simplify the optimization problem, the number of switches from one level of the drug dosage to another is kept small. In particular, the application example in this work will consider only the case of pulse therapy, so that the control function adopted is a rectangular pulse with parameters ts (starting time), w (width) and h (height), as shown in figure 2.

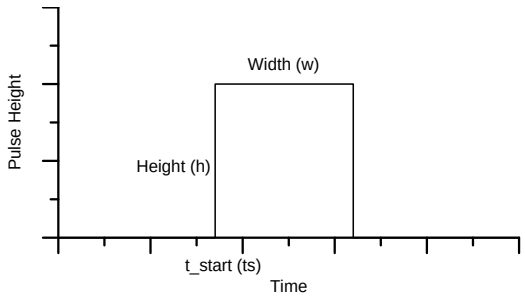

Figure 2 Drug dose versus time, where the pulse is characterized by the parameters to be optimized: starting time (ts), width (w) and height (h)

The performance index to be maximized is, therefore:

$$J(ts, w, h) = \min\{\mu_1(t_H), \mu_2(u\_total), \mu_3(m(t_H))\}$$

A NUMERICAL EXAMPLE

The combination of non-linear state equations and fuzzy performance indexes yields a problem of formidable complexity. So, instead of searching an analytical solution, a numerical optimization algorithm is used.

The simulations of the system were carried out using MATLAB/SIMULINK© package and the maximization of the function $J:R^3 \rightarrow R$ was performed by the flexible polyhedron algorithm with simulated annealing. The modification of the original flexible polyhedron (Nelder-Mead) algorithm was necessary to search for the global maximum (Yoneyama and Cardozo 1994).

A sub-optimal point (denoted with $[.]^*$) was found after 36 iterations:

$$(ts^*, w^*, h^*) = (4.7, 5.2 , 1.9)$$
$$J^* = 0.97$$

with tol = 10^{-3}. The actual optimal point should be the global maximum point of J. Although the simulated annealing mechanism suggests that J* is a good point, eventually it may achieve only a local maximum and may not globally maximize J.

SIMULATION RESULTS

Figures 3 to 6 present the evolution of V(t), Lp(t), Le(t) and F(t) for the cases with and without treatment.

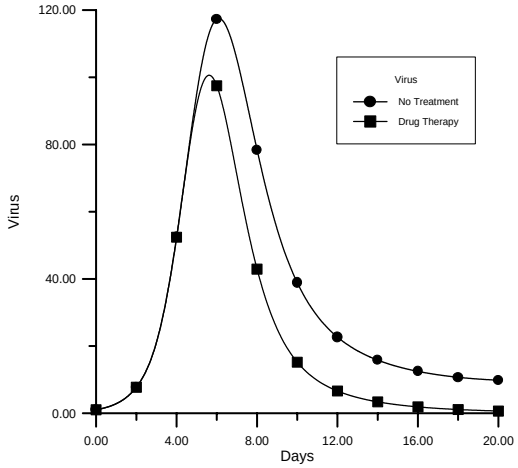

Figure 3 Surge of Virus for the cases with and without drug therapy.

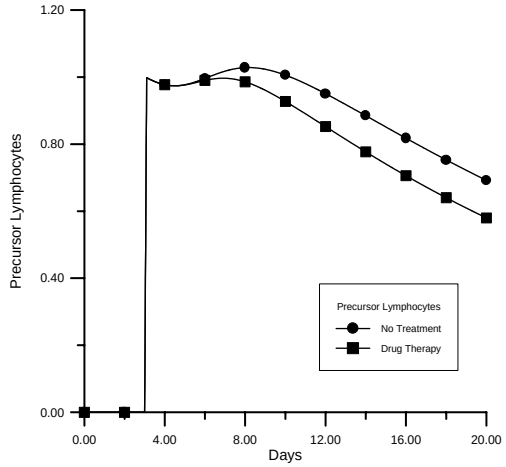

Figure 4 Dynamics related to the activation of resting precursor cells for the cases with and without drug therapy.

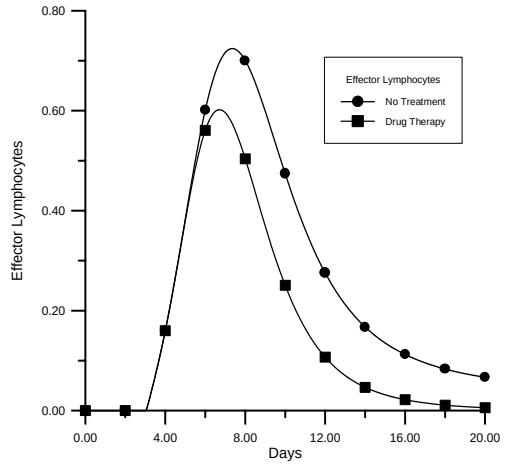

Figure 5 Dynamics of effector cells for the cases with and without drug therapy.

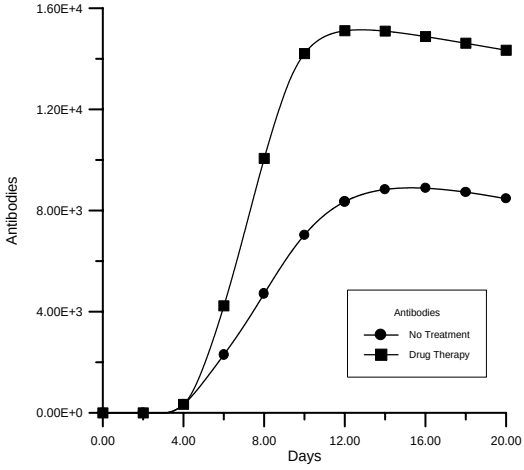

Figure 5 Dynamics of Antibodies for the cases with and without drug therapy.

It is interesting to note that the optimal starting time is posterior to the activation of the resting precursors. In fact, administration of drugs that stimulates the production of antibodies becomes effective only when immuno competent lymphocytes are already present. Prior administration of this type of drugs just increases the side effects. Other types of drugs with different mechanisms (such as interferon, enzime inhibitors, etc...) act on different stages of the immuno response (by protecting lymphocytes, reducing viral replication rate, etc...) so that the proposed method requires modification of the infection model to accomodate these cases. It can also be noted that in many cases, the appearance of clinical symptoms occurs close in time in relation to the optimal starting time for the treatment.

Because the drug does not attack the virus itself in a direct way, it presents a rather delayed response. Hence, the example could be adapted to other longer lasting viral infections.

The example used in this work is a self-limited viral infection, so that the patient would recover even without treatment. Therefore, if the side-effects of the drug were very large, the optimal policy would be to use very small doses. However, if the infection were related to a life-threatening desease, the performance index and the 'damage equation m(t)' should be adjusted to reflect the necessity of intensive treatment.

CONCLUSIONS

The main difficulty with the proposed framework is that the model parameters can vary considerably from one specific patient to another while identification procedures may be impractical in many cases because of urgency or discomfort. The present example used “averaged” parameters and may be useful in 'what if' simulations so as allow development of intuitive feeling on how a therapeutic procedure can be tuned by the physician for each patient.

In principle, the optimal control problem could be solved for more general control inputs u, invoking, for example, dynamic programming equations which might be solved by numerical methods such as multiple-shooting or quasi-linearization (Tolle 1975). However, the continuously time-varying curve for the drug doses offers considerable difficulty in terms of actual implementation. Moreover, due to the difficulty in obtaining accurate estimates for the model parameters corresponding to a specific patient, it may be advisable to use a simpler and more robust therapeutic scheme than an optimal but more sensitive treatment policy.

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REFERENCES

Asachenkov, A.L., Marchuk, G.I., Mohler, R.R. and Zuev, S.M. 1994. Immunology and disease control: a systems approach. *IEEE Transactions on Biomedical Engineering*, Volume 41, No.10, pp.943-953.

Asachenkov, A.L., Marchuk, G.I., Mohler, R.R. and Zuev, S.M. 1994. *Disease Dynamics*. Birkhäuser, Boston.

Bell, G.I. 1970. Mathematical model of clonal selection and antibody production. *Journal or Theoretical Biology*, No.29, pp.191-232.

Felippe de Souza, J.A.M.; Galvão, R.K.H.; Yoneyama, T. 1997. Therapy Optimization for Viral Infections using Fuzzy Performance Index. In *Proceeding of the IFAC Biom. Symp. Modelling and Control*, (Warwick, U.K., Mar, 23-6).

Kienitz, K.H. 1993 .Controller design using uzzy logic - a case study. *Automatica*, Vol. 29, No.2, pp.549-554.

Mohler, R.R., Bruni, C. and Gandolfi, A. 1980. A systems approach to immunology. *Proceedings of the IEEE*, Vol.68, No.8, pp.964-990.

Tolle, H. 1975. *Optimization Methods*. Springer Verlag, Berlin, 1975.

Yoneyama, T. and Cardozo, E. 1994. Randomized search methods for optimization of controller parameters. In *Proceedings of the VI CLACA e 10^0 CBA*, (Rio de Janeiro, Brazil), 584-590 .

BIOGRAPHY

José A.M. Felippe de Souza graduated in Electrical Engineering from Pontificia Universidade Católica, Rio de Janeiro, Brazil, in 1978. He obtained his PhD degree at University of Warwick, England, in 1983. He is presently an Associate Professor and Head of the Department of Electro-Mechanical Engineering at University of Beira Interior, Portugal.

Roberto K.H. Galvão graduated 'summa cum lauda' in Electronics Engeneering at Instituto Tecnológico de Aeronáutica, Brazil, in 1995, where he also obtained his MSc degree and is currently about to complete his doctoral studies.

Takashi Yoneyama graduated in Electronics Engineering at Instituto Tecnológico de Aeronáutica (ITA), in 1975 and in Medicine at University of Taubaté, Brazil, in 1993. He obtained his MSc degree at Instituto Tecnológico de Aeronáutica and PhD degree from Imperial College of Science, Technology and Medicine, London, England, in 1983. He is currently a Professor of Control Theory, ITA, Brazil.

Simulation Diagram for the Infection Model (MATLAB/SIMULINK©)