OPTIMIZATION OF THE THERAPY OF VIRAL INFECTIONS USING FUZZY TECHNIQUES

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

KEYWORDS

Optimization, Fuzzy Criteria, Numerical Methods, Simulation, Virus Infection

ABSTRACT

This work concerns the optimization of treatment schemes for viral infections using drugs that stimulate the humoral immune response. The dynamics of the disease is based on Marchuk's formulation of the behavior of immune systems. 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, that should be traded off against quantities that can be objectively measured, such as cost of medication. The admissible controls are assumed to belong to the class of piecewise constant functions. A numerical example using influenza dynamics show a considerable improvement of the optimized drug administration policy, when compared to non-optimized policies, in terms of reduction in the achieved performance index.

1. INTRODUCTION

The immune system provides defense against genetically 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 the optimization of 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. The drug employed is ionol (BUTYLATED HYDROXY TOLUENE), an antioxidant which has been tested in the treatment of influenza (Meringova *et al*. 1996) to stimulate the humoral immune response.

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.

2.THE INFECTION MODEL

In this work, it is used the model proposed in Asachenkov *et al.* 1994, which describes an influenza infection and is also suitable to analyze the therapeutic action of administered drugs.

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

According to the authors, in order to simplify the identification of the parameters, the model was rewritten in the following form:

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

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

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

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

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

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

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

where

V(t) : concentration of virus
Le(t) : effector lymphocytes
Lp(t) : lymphocyte precursor cells
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.

3. 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:

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

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

$$m(t_H)$$

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 $\mu_3(m(t_H))$ reflexted the criteria (a), (b) and (c). The logical conective AND was implemented by using the function MIN.

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 t_0

(application time), w (width) and hu (height), as shown in figure 2. Due to the low-pass characteristic of the dynamics involved, a rectangular pulse can be regarded as an approximate model for a "period of intensive therapy".

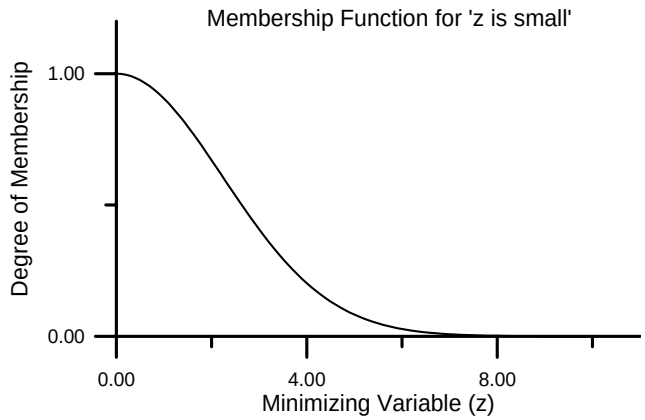

Figure 1 Shape of the Membership Functions representing the fuzzy set 'z is small'

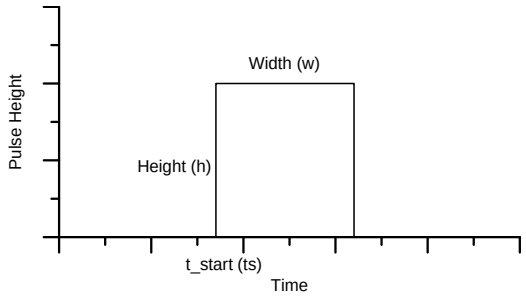

Figure 2 Drug dose versus time, where the pulse is characterized by the parameters to be optimized: starting time (ts), width (w) and height (h)

The performance index to be maximized is, therefore:

$$J(ts, w, h) = \min\{\mu_1(t_H), \mu_2(u\_total), \mu_3(m(t_H)\} \qquad (8)$$

4. 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 local maximum and may not globally maximize J.

5. 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.

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.

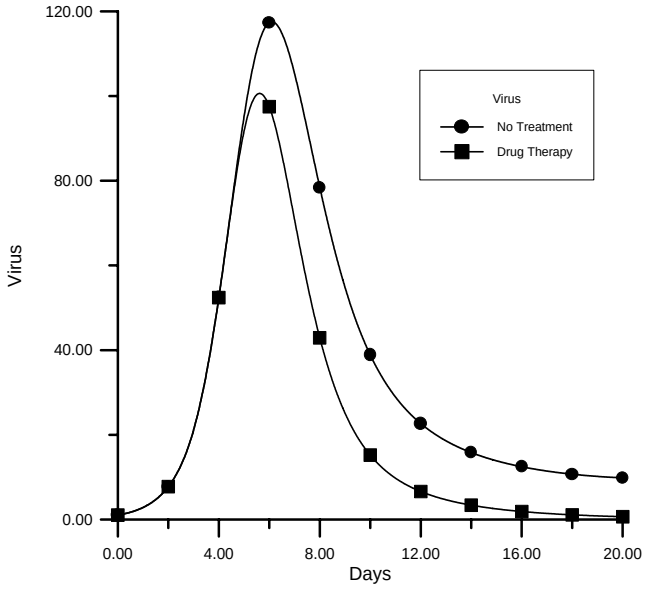

Figure 3 Surge of Virus for the cases with and without drug therapy.

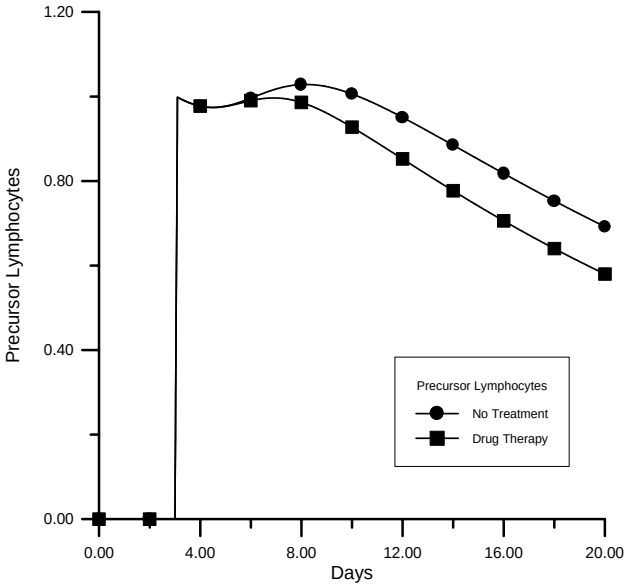

Figure 4 Dynamics related to the activation of resting precursors for the cases with and without drug therapy.

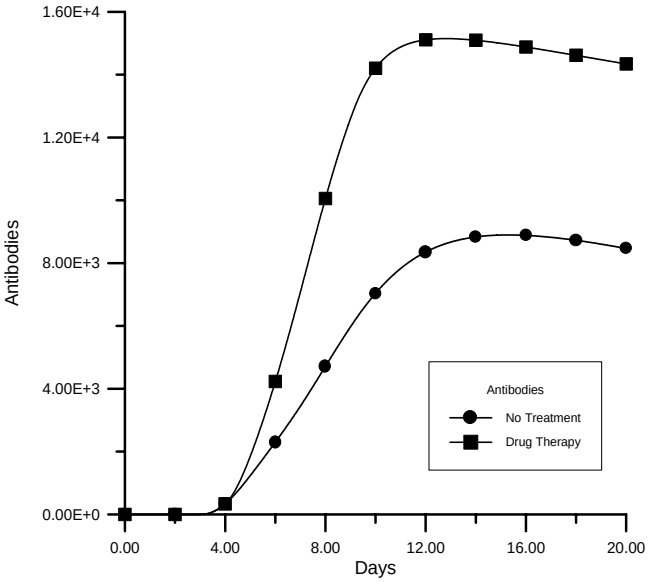

Figure 5 Dynamics of Antibodies for the cases with and without drug therapy.

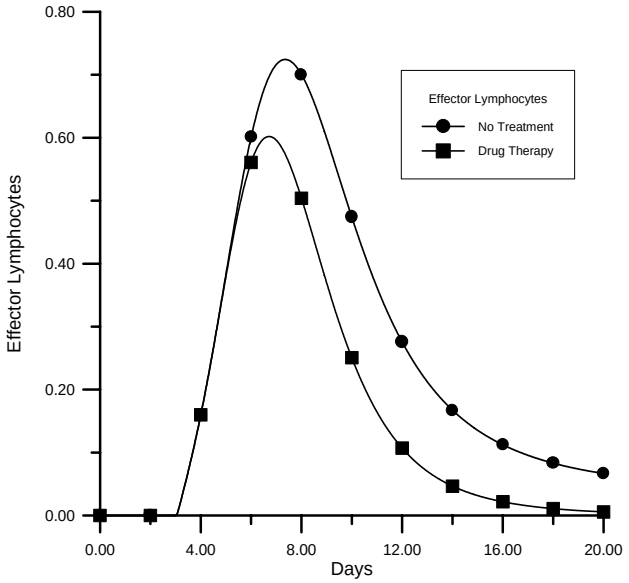

Figure 5 Dynamics of Effectors for the cases with and without drug therapy.

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.

6. 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.

It is interesting to remark that the optimal application time (5 days) coincides with the appearance of the first symptoms of influenza (people become sick 3-10 days after

being exposed to the virus). Thus, the results suggest that, for this particular infection, therapeutic benefits are not enough to justify the adoption of preventive measures (that is, administering drugs before the symptoms appear).

Further research is needed in order to determine how close to the minimum of the cost surface is the solution found in this work. The model could also be extended to include non-linearities (such as saturation) in the control input u.

7. ACKNOWLEDGMENTS

This work was sponsored by the program PET/CAPES and FAPESP. The authors would like to thank Prof. Carmelinda Unterkircher for help and their valuable suggestions.

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 fuzzy logic - a case study. *Automatica*, Vol. 29, No.2, pp.549-554.

Meringova, L. F. et al. 1996. Effects of the antioxidanti ionol on humoral immune response in experimental influenza. *Vestnik Rossiskoi Akademii Meditsinskikh Nauk.*, Vol. 3, pp. 34-37.

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 .