Mathematical Biosciences 272 (2016) 34–43

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

New developments in the application of optimal control theory to therapeutic protocols

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ARTICLE INFO

Article history:
Received 16 October 2014
Revised 18 November 2015
Accepted 20 November 2015
Available online 3 December 2015

MSC:
49M05
92B05

Keywords:
Optimal control
Pontryagin's Minimum Principle
Coordinate cyclic descent
Immune response
Pathogenic disease

ABSTRACT

Optimal control theory is one of the most important tools in the development of new therapeutic protocols for treating infections. In this work, we present an algorithm able to deal with high-dimensional problems with bounded controls. The optimal solution is obtained by minimizing a positive-definite treatment cost function. Our method, based on Pontryagin's Minimum Principle and the coordinate cyclic descent method, allows solving problems of varied nature. In this paper, and by way of example, therapeutic enhancement of the immune response to invasion by pathogenic attack is addressed as an optimal control problem. The generic mathematical model used describes the evolution of the disease by means of four non-linear, ordinary differential equations. The model is characterized by the concentration of pathogens, plasma cells, antibodies and a numerical value that indicates the relative characteristic of an organ damaged by disease. From a system theory point of view, drugs can be interpreted as control inputs. Therapies based on separate application of the agents are presented in previous studies. We shall present the more general problem in this paper, considering combined therapies and bounded controls. Finally, we present several numerical simulations.

1. Introduction

The natural human immune system exists to defend our organism against agents such as bacteria, viruses, and our own transformed cells such as tumor cells. Without therapy, the natural immune response depends upon the initial concentration of pathogens. Initially, the innate immune system provides a non-specific tactical response, aimed mainly at killing the pathogen and starting a series of processes like inflammation, vasodilation or blood coagulation which, on one hand, aid the defends and on the other, slow the spread of infection to other parts of the body. Next, a humoral response is initiated, activating B cells to become plasma cells that produce antibodies that bind to the antigens, so as to destroy the pathogens. Finally, the adaptive immune system provides a strategic response that is tailored to the primary attack. Actually, the innate, humoral and adaptive immune responses are coupled. Without any control, four cases of natural response appear: the subclinical case, which does not require medical attention; the clinical case, which warrants medical attention, but is self-healing; the chronic case, which presents an unstable equilibrium with degraded organ health; and the lethal case, which results in death of the organ. When the natural defense mechanism fails, the need for external medication arises. In this paper, therapeutic treatment of a pathogenic disease process is addressed as an optimal control problem.

In [1], the authors study a mathematical model of a disease which, as they themselves state "is only a crude approximation and generally requires further refinement." Certainly, the response of the immune system to intra-cellular microbial attack is a rather complex problem based on producing antibodies customized to the pathogens. We refer to [2] for a better understanding of the associated complex mechanism. Since then, numerous models of immune response to infection have been postulated [3–6]. Based on the idea presented in [1], a model including the effect of various controls is presented in [7] and [8]. This model has proved a good tool for studying therapeutic protocols, and is frequently used in other studies (see for example: [9–11]). Evolution of the disease is characterized by a mathematical model with four non-linear, ordinary differential equations that describes concentrations of pathogens, plasma cells and antibodies, as well as a numerical indication of patient health under the influence of therapeutic treatment. This model of pathogenic attack facilitates the presentation, while more complex control effects could easily be incorporated in the optimization. This is the model that will be considered in this work and is presented in Section 2.

Focusing on the mathematical statement of the problem, several applications of control theory to therapeutic protocols have been presented in the literature from as early as Perelson [12]. An excellent reference for the beginning of the application of control theory to immunology and disease is [13]. Since then, several applications of

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http://dx.doi.org/10.1016/j.mbs.2015.11.013
0025-5564/

control theory to the immune processes have been presented in the literature (see for example: [14–18]). In [7], an optimal solution is obtained by solving the associated two-point boundary value problem using the steepest descent gradient method. In [9], the authors use a linearized neighboring optimal controller based on standard linear quadratic regulator theory. In [7] and [9], the authors consider the effects of each control variable applied and optimized separately (four baseline cases), but do not explicitly present optimizations using all of the therapeutic agents at once. This work is further developed in [8], in which a linear-optimal state estimator is incorporated in the feedback therapy to minimize the effects of measurement error and to account for missing measurements. Another relatively simple nonlinear control method is the dynamic inversion technique, which is essentially based on the philosophy of feedback linearization. This method was used by authors in [10] and [11] in the treatment of infectious diseases. A major drawback of the dynamic inversion approach, however, is its sensitivity to modeling errors and parameter inaccuracies. Moreover, the authors assumed only the availability of drugs that kill the invading microbes and heal the affected organ, but did not consider drugs that enhance the efficacy of the immune system.

In this paper, we propose to use Pontryagin's Minimum Principle (PMP) ([19,20]) and the cyclic coordinate descent method to solve the optimal control problem and provide an optimization algorithm that leads to the determination of the optimal solution of the general problem with several therapies.Unlike some of the other methods, ours is based on the use of Pontryagin's Principle, which makes it particularly suited for the problem at hand. It allows us analyze what happens when a different therapy is applied each time and also to combine several therapies simultaneously. It also allows us to set limits on the controls.

The main objectives of this paper will be: moving from a single-agent therapy to combined therapies, considering four drugs simultaneously, and considering bounded controls, all of it using Stengel's model [7]. The optimal solution is derived by minimizing a positive-definite cost function that penalizes large values of pathogen concentration, poor organ health, and excessive application of therapeutic agents over a fixed time interval. Our method is able to deal with more complex problems and, to illustrate this, Section 2 presents the more realistic case with bounded controls (not considered by other authors). In Section 3, we prove a necessary minimum condition for the optimization problem. Section 4 introduces a numerical relaxation method (the coordinate descent method) for the solution of this problem. In Section 5, we present several numerical simulations. Finally, Section 6 summarizes the main contributions of our paper.

2. A model of enhanced immune response

We consider a simple model for pathogenic attack on an organism and the organism's immunological defense. We refer interested readers to [7,9], and [8] for a better understanding of the associated complex mechanism. The dynamic state comprises four components (the state variables):

$x_1(t)$: concentration of a pathogen
$x_2(t)$: concentration of plasma cells (carriers and producers of antibodies)
$x_3(t)$: concentration of antibodies, which kill the pathogen
$x_4(t)$: relative characteristic of a damaged organ: [0= healthy, 1=dead]

We now add the following idealized therapeutic control agents (the control variables):

$u_1(t)$: pathogen killer
$u_2(t)$: plasma cell enhancer
$u_3(t)$: antibody enhancer
$u_4(t)$: organ healing factor

The four treatments aim, respectively, at killing the pathogen, neutralizing its harmful effects, enhancing the efficacy of immune response and providing healing care to the damaged organs. We seek the best combination of these therapies. The four scalar, non-linear, ordinary differential equations of the dynamic model (the state equations) are (considering no delay):

$$\begin{aligned}
\dot{x}_1(t) &= (a_{11} - a_{12}x_3(t))x_1(t) - b_1u_1(t)\\
\dot{x}_2(t) &= a_{21}(x_4(t))a_{22}x_1(t)x_3(t) - a_{23}(x_2(t) - x_2^*(t)) + b_2u_2(t)\\
\dot{x}_3(t) &= a_{31}x_2(t) - (a_{32} + a_{33}x_1(t))x_3(t) + b_3u_3(t)\\
\dot{x}_4(t) &= a_{41}x_1(t) - a_{42}x_4(t) - b_4u_4(t)
\end{aligned} \tag{1}$$

where $x_2^*(t)$ is the steady-state concentration of plasma cells. a_{ij} and b_i are nonnegative (with $b_i \neq 0$) constants except $a_{21}(x_4)$. This is a non-linear function that describes the immune deficiency triggered by damage to the organ:

$$a_{21}(x_4) = \begin{cases} \cos(\pi x_4) & 0 \le x_4 \le 0.5 \\ 0 & 0.5 \le x_4 \end{cases} \tag{2}$$

This definition expresses the fact that the capacity to generate plasma cells decreases as the damage to the organ increases. Indeed, when the health of the organ reaches a certain point (in this case, $x_4 = 0.5$), the production of plasma cells stops altogether.

Absent the controls, the global behavior of the (uncontrolled) system is a function of the initial conditions. The four cases depending on the initial conditions are: (1) The sub-clinical case, in which the immune system acts and the pathogens are successfully destroyed so that no medical examination is required. (2) The clinical case: if the initial infectious dose is increased, the pathogen compromises the immune system and a medical consultation is required. (3) The chronic case: the pathogen and the health of the organ reach steady-state so that the patient is not completely cured. (4) The lethal case: the antibodies by themselves are unable to overcome the infection, the pathogen concentration diverges and this causes the death of the organ. The chronic case can be defined as the limit between (2) and (4).

The state equations (1) and the sign of the coefficients a_{ij} and b_i have simple interpretations. In the first one, the pathogen has a natural tendency to grow exponentially ($a_{11} > 0$) which is limited by the antibodies x_3 and the pathogen killer ($b_1 > 0$). The second equation describes the evolution of the plasma cells as a non-linear function. The influence of $x_4(t)$, $x_1(t)$, $x_3(t)$ and the steady-state concentration of plasma cells x_2^* is clear. In this case, the control boosts the production of plasma cells ($b_2 > 0$). The third equation shows how the population of antibodies depends on the plasma cells x_2 (producers of antibodies, so $a_{31} > 0$) and also on the balance between births and deaths of cells ($a_{32} > 0$). The pathogen, x_1 has a negative impact and the control u_3 a positive one $b_3 > 0$. In the last equation, the control u_4 with $b_4 > 0$ tries to get a perfectly healthy organ ($x_4 = 0$). From (1) and prior to the pathogen attack, it is immediate to infer that the steady-state value of antibody concentration corresponding to x_2^* is:

$$x_3(0) = (a_{31}/a_{32})x_2^* \tag{3}$$

The state equations can be expressed in the vector form:

$$\dot{\mathbf{x}}(t) = f(t, \mathbf{x}(t), \mathbf{u}(t)) \tag{4}$$

where vector $\mathbf{x}$ is called the state of the system and $\mathbf{u}$ is the control vector, which we will consider bounded:

$$\mathbf{0} \le \mathbf{u}_{\min} \le \mathbf{u}(t) \le \mathbf{u}_{\max};\ \mathbf{u}(t) \in U(t),\ 0 \le t \le t_f \tag{5}$$

being $[0, t_f]$ the fixed time interval. It is worth noting that, in this particular problem, it is not necessary to impose the constraint $\mathbf{x}(t) \ge \mathbf{0}$. This is due to the fact that, in uncontrolled dynamics, the state is never less than zero on its own [7].

The optimal therapeutic protocol is derived by minimizing a positive-definite treatment cost function, J, that penalizes large values of pathogen concentration, poor organ health, and excessive application of therapeutic agents over the fixed time interval:

$$J = \frac{1}{2}\left[p_1 x_1^2(t_f) + p_4 x_4^2(t_f)\right] + \frac{1}{2}\int_0^{t_f}\left[q_1 x_1^2(t) + q_4 x_4^2(t) + r_1 u_1^2(t) + r_2 u_2^2(t) + r_3 u_3^2(t) + r_4 u_4^2(t)\right]dt \quad (6)$$

The problem includes a terminal cost, associated with values of pathogen and organ health at the end of the treatment period, as well as an integral cost of state and control variations during the period. Each value is multiplied by a coefficient (p_1, p_2, q_1, q_2 and $r_i, i = 1, \ldots, 4$) that establishes its relative importance in the cost of treatment.

3. Mathematical formulation: a necessary minimum condition

A standard Lagrange-type optimal control problem (OCP) can be mathematically formulated as follows:

$$\min_{\mathbf{u}(t)} J = S[\mathbf{x}(t_f)] + \int_0^{t_f} F(t, \mathbf{x}(t), \mathbf{u}(t))dt \quad (7)$$

subject to satisfying:

$$\dot{\mathbf{x}}(t) = f(t, \mathbf{x}(t), \mathbf{u}(t)) \quad (8)$$

$$\mathbf{x}(0) = \mathbf{x}_0 \quad (9)$$

$$\mathbf{u}(t) \in U(t),\ 0 \le t \le t_f \quad (10)$$

where J is the *objective functional*, F and S are given functions (*running cost* and *terminal cost*), $\mathbf{x}(t) = (x_1(t), \ldots, x_n(t)) \in \mathbb{R}^n$ is the *state vector*, with initial conditions $\mathbf{x}_0 = (x_{10}, \ldots, x_{n0})$, $\mathbf{u} = (u_1(t), \ldots, u_m(t)) \in \mathbb{R}^m$ is the *control vector* bounded by $\mathbf{u}_{\min}$ ($\mathbf{u}_{\min} \ge 0$) and $\mathbf{u}_{\max}$, U denotes the set of admissible control values, and t is the operation time which starts from 0 and ends at t_f. The *state variables* (or simply the *states*) must satisfy the *state equation* (8) with given initial conditions (9).

In this statement, we consider the final instant to be fixed and the final state to be free. The OCP is referred to as a *constrained* OCP because constraints are imposed on the controls (10), apart from the dynamic equation (8). We say that $\mathbf{x} = (x_1(t), \ldots, x_n(t))$ is admissible if x_i belong to the class $\widehat{C}^1[0, t_f]$ (the set of piecewise C^1 functions).

Let H be the Hamiltonian function associated with the problem:

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = F(t, \mathbf{x}, \mathbf{u}) + \lambda \cdot f(t, \mathbf{x}, \mathbf{u}) \quad (11)$$

where $\lambda = (\lambda_1(t), \ldots, \lambda_n(t)) \in \mathbb{R}^n$ is called the*costate vector*. In our case ($n = m = 4$):

$$\begin{aligned} H(t, \mathbf{x}, \mathbf{u}, \lambda) = {} & \frac{1}{2}[q_1 x_1^2(t) + q_4 x_4^2(t)] \\ & + \frac{1}{2}\left[r_1 u_1^2(t) + r_2 u_2^2(t) + r_3 u_3^2(t) + r_4 u_4^2(t)\right] \\ & + \lambda_1[(a_{11} - a_{12} x_3(t)) x_1(t) - b_1 u_1(t)] \\ & + \lambda_2[a_{21}(x_4(t)) a_{22} x_1(t) x_3(t) - a_{23}(x_2(t) - x_2^*(t)) \\ & + b_2 u_2(t)] \\ & + \lambda_3[a_{31} x_2(t) - (a_{32} + a_{33} x_1(t)) x_3(t) + b_3 u_3(t)] \\ & + \lambda_4[a_{41} x_1(t) - a_{42} x_4(t) - b_4 u_4(t)] \end{aligned} \quad (12)$$

The classical approach involves the use of PMP [19,20] which results in a two-point boundary value problem (TPBVP). In order for $\mathbf{u} \in U$ to be optimal, a nontrivial function, $\boldsymbol{\lambda}$, must necessarily exist, such that for almost every $t \in [0, t_f]$:

$$\dot{\mathbf{x}} = H_\lambda = f;\ \mathbf{x}(0) = \mathbf{x}_0 \quad (13)$$

$$\dot{\lambda} = -H_{\mathbf{x}};\ \ \lambda(t_f) = \frac{\partial S[\mathbf{x}(t_f)]}{\partial \mathbf{x}} \quad (14)$$

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = \min_{\mathbf{v}(t) \in U} H(t, \mathbf{x}, \mathbf{v}, \lambda) \quad (15)$$

In virtue of PMP and Eq. (14), there exists a piecewise C^1 function, $\boldsymbol{\lambda}$ (costate variable), that satisfies:

$$\dot{\lambda} = -H_{\mathbf{x}} = -F_{\mathbf{x}} - \lambda(t) \cdot f_{\mathbf{x}} \quad (16)$$

Operating, we have:

$$\dot{\lambda}_1 = -q_1 x_1 - \lambda_1(a_{11} - a_{12} x_3) - \lambda_2 a_{21}(x_4) a_{22} x_3 + \lambda_3 a_{33} x_3 - \lambda_4 a_{41} \quad (17)$$

$$\dot{\lambda}_2 = \lambda_2 a_{23} - \lambda_3 a_{31}$$

$$\dot{\lambda}_3 = \lambda_1 a_{12} x_1 - \lambda_2 a_{21}(x_4) a_{22} x_1 + \lambda_3(a_{32} + a_{33} x_1)$$

$$\dot{\lambda}_4 = -q_4 x_4 - \lambda_2 a'_{21}(x_4) a_{22} x_1 x_3 + \lambda_4 a_{42}$$

with the boundary conditions:

$$\begin{aligned} \lambda_1(t_f) &= p_1 x_1(t_f) \\ \lambda_2(t_f) &= 0 \\ \lambda_3(t_f) &= 0 \\ \lambda_4(t_f) &= p_4 x_4(t_f) \end{aligned} \quad (18)$$

In virtue of PMP and Eq. (15), we have:

$$\begin{aligned} r_1 u_1 - \lambda_1 b_1 &= 0 \\ r_2 u_2 + \lambda_2 b_2 &= 0 \\ r_3 u_3 + \lambda_3 b_3 &= 0 \\ r_4 u_4 - \lambda_4 b_4 &= 0 \end{aligned} \quad (19)$$

A necessary minimum condition

In the previous section, we have seen that the necessary conditions for optimality are expressed by the three Euler–Lagrange equations [19]: (13), (14) and (15). These equations include: (13), four nonlinear, ordinary differential equations with initial conditions, whose integral is $\mathbf{x}$; (14), four linear, ordinary-differential equations with final boundary condition, whose integral is $\boldsymbol{\lambda}$; and (15), a stationary condition on the control, $\mathbf{u}$.

Due to the complexity of the above mathematical equations, there is no closed-form solution for the Euler–Lagrange equations and they must be solved numerically. There are numerous methods for solving this problem. For example, a quasi-optimal solution is obtained in [7] by solving the associated two-point boundary value problem using the steepest descent gradient method. We propose a new method in this paper, which consists in solving the problem with $n = m > 1$ as the limit of a sequence of problems with $n = m = 1$, based on the use of an equation (coordination equation) which we will obtain in the following theorem. For the sake of simplicity, in this section we first present the necessary minimum condition considering one state variable, $x(t)$ ($n = 1$), and one control variable, $u(t)$ ($m = 1$). The problem to solve is in this case:

$$\min_{u(t)} J = S[x(t_f)] + \int_0^{t_f} F(t, x(t), u(t))dt \quad (20)$$

subject to satisfying:

$$\dot{x}(t) = f(t, x(t), u(t)) \quad (21)$$

$$x(0) = x_0 \quad (22)$$

$$0 \le u_{\min} \le u(t) \le u_{\max},\ 0 \le t \le t_f \quad (23)$$

Prior to proving the theorem, we define the following function.

Definition 1. Let q be a function $q:[0,t_f]->\mathbb{R}$, with $\dot{q}(t)=f(t,q(t),u(t))$. Let us term the *coordination function ofq*, $\mathbb{Y}_q(t)$, the function in $[0,t_f]$, defined as follows:

$$\mathbb{Y}_q(t) := -\frac{F_u(t,q(t),u(t))}{f_u(t,q(t),u(t))}\exp\left(\int_0^t f_x(s,q(s),u(s))ds\right) + \int_0^t\left(F_x(s,q(s),u(s)\exp\left(\int_0^s f_x(z,q(z),u(z))dz\right)\right)ds \quad (24)$$

We now present a necessary minimum condition.

Theorem 1. *Let u_{opt} be the optimal control, let $x_{opt}\in\widehat{C}^1$ be a solution of the above problem. If $f_u(t,x_{opt},u_{opt})>0$ (resp. $f_u(t,x_{opt},u_{opt})<0$) then there exists a constant $K\in\mathbb{R}$ such that:*

$$\begin{aligned} If\ u_{\min}<u_{opt}<u_{\max} &\implies \mathbb{Y}_{x_{opt}}(t)=K\\ If\ u_{opt}=u_{\max} &\implies \mathbb{Y}_{x_{opt}}(t)\geq K (resp.\mathbb{Y}_{x_{opt}}(t)\leq K)\\ If\ u_{opt}=u_{\min} &\implies \mathbb{Y}_{x_{opt}}(t)\leq K (resp.\mathbb{Y}_{x_{opt}}(t)\geq K)\end{aligned} \quad (25)$$

Proof. See Appendix 1. □

The problem in the general -dimensional case will be stated so that what we shall need to solve it will be the holding of the conditions of Theorem 1 in each of the components and this theorem will be applied to each of them, considering all the other constant. We call K the coordination constant and the following equation, the coordination equation

$$\mathbb{Y}_x(t)=K \quad (26)$$

The idea for solving the one-dimensional problem is to find, for each K, the state x such that the function $\mathbb{Y}_x(t)$ that satisfies (1), and from among these states, the one that satisfies the transversality condition. From the computational point of view, the construction can be performed with the same procedure as the simple shooting method, with the use of a discretized version of the coordination equation. This idea will be applied in the next section for the case $n=m=N$, to each of the state variables.

The sufficient condition giving the existence of a minimum holds by Arrow's theorem (see [20]), due to the convexity conditions of the problem in the specific case with which we are dealing.

4. The optimization algorithm

The problem of optimization of the complex system that includes the four state and control variables ($n=m=4$) is highly complex because the associated variational problem is related to solving a boundary-value problem for a system of differential equations. In this section, we present an algorithm of its numerical resolution using a particular strategy related to the *cyclic coordinate descent method* [21]. Using this method, a problem P^N, of the type $n=m=N$, could be solved under certain conditions if we start out from the resolution of a sequence of problems P^1 of the type $n=m=1$.

Let the function:

$$G:\mathbb{R}^n\to\mathbb{R},\ G\in C^1(\mathbb{R}^n) \quad (27)$$

and $\bar{\mathbf{x}}=(x_1,\ldots,x_j,\ldots,x_n)$. The idea underlying the coordinate descent method is to use the coordinate axes as descent directions. The method sequentially searches for the minimum of G in all the directions $\mathbf{e}_j$. Descent with respect to the x_j coordinate means that $G(x_1,\ldots,x_j,\ldots,x_n)$ is minimized with respect to x_j, while the rest remain fixed.We now we adapt the finite-dimensional version of this algorithm to our functional.

4.1. P^N problem

The solution algorithm for the P^N problem is based on the resolution of a succession of problems P^1, each one of them consisting in computing the optimal functioning of a state variable, while the behavior of the rest of the states is assumed fixed. Thus, at each k-th iteration of the algorithm, N stages are performed, one for each state and control variable.For every $\mathbf{q}=(q_1,\ldots,q_N)$ admissible state and $\mathbf{v}=(v_1,\ldots,v_N)$ control vector, we consider the functional $J^i_{\mathbf{q}}$ defined by:

$$\min_{u_i(t)} J^i_{\mathbf{q}}=S^i_{\mathbf{q}}[x_i(t_f)]+\int_0^{t_f}F^i_{\mathbf{q}}(t,x_i(t),u_i(t))dt \quad (28)$$

with:

$$F^i_{\mathbf{q}}(t,x_i,u_i)=F(t,q_1,\ldots,q_{i-1},x_i,q_{i+1},\ldots,q_N,v_1,\ldots,v_{i-1},u_i,v_{i+1},\ldots,v_N) \quad (29)$$

$$S^i_{\mathbf{q}}[x_i]=S[q_1,\ldots,q_{i-1},x_i,q_{i+1},\ldots,q_N] \quad (30)$$

$$\dot{x}_i(t)=f_i(t,x_i(t),u_i(t)) \quad (31)$$

$$0\leq u_{i\min}\leq u_i\leq u_{i\max} \quad (32)$$

where $F^i_{\mathbf{q}}$ and $S^i_{\mathbf{q}}$ represent the functional as a function of the i-th state and the i-th control, under the assumption that the rest of the states and controls remains constants. We call the i-th minimizing mapping the mapping Φ_i, defined in the following way: for every $\mathbf{q}=(q_1,\ldots,q_i,\ldots,q_N)$

$$\Phi_i(q_1,\ldots,q_i,\ldots,q_N)=(q_1,\ldots,q_i^{opt},\ldots,q_N) \quad (33)$$

where q_i^{opt} minimizes $J^i_{\mathbf{q}}$ verifying that for u_i^{opt} :

$$\dot{q}_i^{opt}(t)=f_i\left(t,q_i^{opt}(t),u_i^{opt}(t)\right) \quad (34)$$

and $u_{i\min}\leq u_i^{opt}\leq u_{i\max}$. Beginning with some admissible:

$$\mathbf{q}^0=(q_1^0,\ldots,q_N^0) \quad (35)$$

we construct a sequence of $\mathbf{q}^k$ via successive applications of $\{\Phi_i\}_{i=1}^N$. If we set:

$$\mathbf{\Phi}=(\Phi_N\circ\Phi_{N-1}\circ\ldots\circ\Phi_2\circ\Phi_1)\implies\mathbf{q}^k=\mathbf{\Phi}(\mathbf{q}^{k-1}) \quad (36)$$

the algorithm will search:

$$\lim_{k\to\infty}\mathbf{q}^k \quad (37)$$

Under appropriate conditions in the admissible set (bounded derivatives), the convergence of the above algorithm may be assured using *Zangwill's global convergence theorem of algorithms* [21].

The following proposition is verified, the demonstration of which is identical to that of Theorem 1.

Proposition 1. For all $\mathbf{q}=(q_1,\ldots,q_N)$, with q_i belongs to the class $\widehat{C}^1[0,t_f]$, there exists $K\in\mathbb{R}$ *such that if:*

$$\Phi_i(\mathbf{q})=(q_1,\ldots,q_i^{opt},\ldots,q_N)\ \text{with}\ \dot{q}_i^{opt}(t)=f_i\left(t,q_i^{opt}(t),u_i^{opt}(t)\right) \quad (38)$$

and *if* $f_{u_i}(t,q_i,u_i)>0$ (resp. $f_{u_i}(t,q_i,u_i)<0$)*then:*

$$\mathbb{Y}^i_{\Phi_i(\mathbf{q})}(t) is \begin{cases}\leq K\ (\text{resp.}\geq K) & if\quad u_{i\min}=u_i^{opt}\\ =K & if\quad u_{i\min}<u_i^{opt}<u_{i\max}\\ \geq K\ (\text{resp.}\leq K) & if\quad u_i^{opt}=u_{i\max}\end{cases} \quad (39)$$

4.2. P^1 problem. Formal construction of $\Phi_i(\mathbf{q})$

Given $\mathbf{q}=(q_1,\ldots,q_i,\ldots,q_N)$, with q_i belongs to the class $\widehat{C}^1[0,t_f]$, we shall consider, for each $K\in\mathbb{R}$,

$$\mathbf{q}^i_K=\Phi_i(q_1,\ldots,q_i,\ldots,q_N)=(q_1,\ldots,q_{i_{-1}},q_K,q_{i+1},\ldots,q_N) \quad (40)$$

That is, q_K, for u_i, minimizes the functional $J^i_{\mathbf{q}}$.

The application of every Φ_i involves solving a problem of the type P^1; the optimal functioning of one state calculated at each stage in the following way.

For given$K$,$q_K$the construction is carried out inductively by concatenating inner arcs (inactive restrictions) and boundary arcs (active restrictions). One imposes the boundary conditions $q_K(0) = x_{i0}$ and the conditions of Proposition 1 (See Appendix B). Finally, by varying the coordination constant K, we search for "the extremal" that fulfills the transversality condition:

$$\lambda_{opt}(t_f) = \frac{\partial S[x(t_f)]}{\partial x} \tag{41}$$

The procedure is similar to the shooting method, used to resolve second-order differential equations with boundary conditions, which may be performed approximately using elemental procedures.

The proposed algorithm, specially designed for this problem, shows good convergence properties. Numerical results are presented in the next section.

5. Numerical simulations

A program based on the algorithm presented in the previous section that solves the optimization problem was written using the Mathematica ©package. The values of the parameters used for this study are:

$$a_{11} = a_{12} = a_{23} = a_{31} = a_{41} = a_{42} = 1 \tag{42}$$
$$a_{22} = 3,\ a_{32} = 1.5,\ a_{33} = 0.5$$
$$b_1 = b_4 = b_2 = b_3 = 1$$

These values have been taken from [7] and [8], for the sake of comparison. In the first two cases presented in this section, the unit cost function weights p_1, p_4, q_1 and q_4 are equal to 1, and the r_i, $(i = 1, \ldots, 4)$ are also 1, because we consider all the controls active at once. Later on we shall consider them different, in case 3. Hence, substituting in (1), we have:

$$\dot{x}_1(t) = (1 - x_3(t))x_1(t) + u_1(t) \tag{43}$$
$$\dot{x}_2(t) = 3a(x_4(t))x_1(t)x_3(t) - (x_2(t) - 2) + u_2(t)$$
$$\dot{x}_3(t) = x_2(t) - (1.5 + 0.5x_1(t))x_3(t) + u_3(t)$$
$$\dot{x}_4(t) = x_1(t) - x_4(t) + u_4(t)$$

The treatment interval is 10 time units, and the steady-state concentration of plasma cells is $x_2^* = 2$. Moreover, the initial conditions are:

$$x_1(0) = 3,\ \ x_2(0) = 2,\ \ x_3(0) = 4/3,\ \ x_4(0) = 0 \tag{44}$$

The initial conditions, steady state value and interval of treatment have been chosen based on the results obtained in [7] and [8]. We have chosen an initial value for the pathogen $x_1 = 3$, with which no therapy (uncontrolled) leads to case (4) already presented: the lethal case. The length of the time horizon is enough to reach steady-state.

There are lots of possible combinations of parameters, control variables and cost function weights that could be considered. For the sake of illustration, we present some examples which show the value added of our algorithm. Notice that in all of them, the values of the control, pathogen and organ tend to zero. However, this is not always the case. What happens is that in the examples shown, the organ is always healed because the killer pathogen disappears with the applied therapy. Hence at the end of the needed treatment time the respective controls will tend to zero, as once the illness is cured it is unnecessary to go on with the therapy. Recall that we have considered an initial value for the pathogen $x_1(0) = 3$ which in the uncontrolled case led to the lethal case but that leads to healing with the therapy. However, specific initial levels of the pathogen can give rise to situations incompatible with the healing of the organ and reaching no steady state. This same reasoning works in the case of the pathogen and the indicator of health of the organ, which also tend to zero.

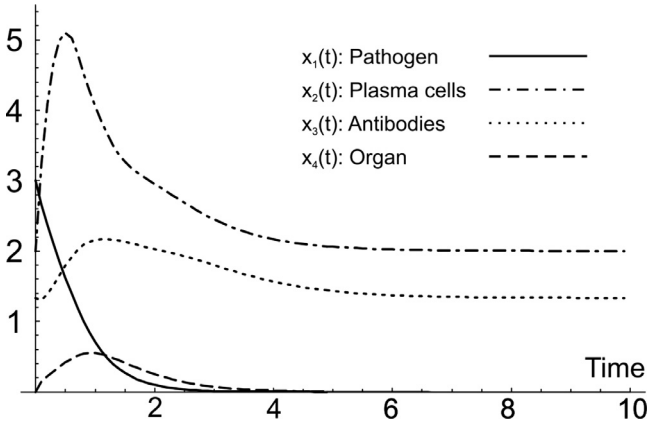

Fig. 1. Optimal response with combined therapies.

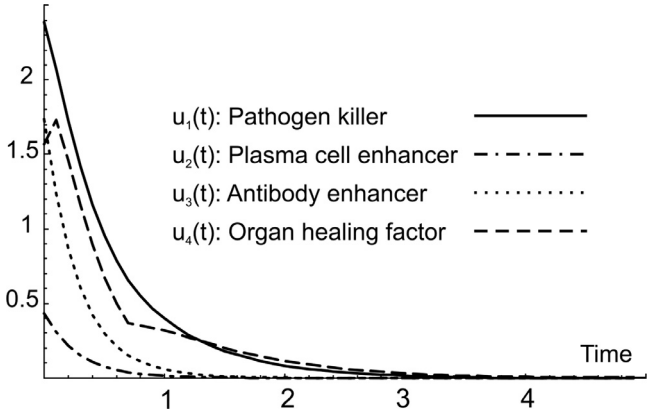

Fig. 2. Optimal therapies.

5.1. Case 1: $0 \leq$ u

We present this case first because it is the case analyzed by other authors ([7] and [9]), who, however, considered the effects of each control variable separately. We shall present the optimization using all of the therapeutic agents at once for its comparison. Optimal solutions computed with these otherwise-lethal initial conditions (44) [7] are presented in Figs. 1 and 2. The values of the controls are presented only for $t \in [0, 5]$ with the aim of providing greater detail.

Some representative values are:

$$x_1(10) = 0.00013;\ \ x_2(10) = 2.0011;$$
$$x_3(10) = 1.3333;\ \ x_4(10) = 0.00021 \tag{45}$$

$$u_1(0) = 2.39004;\ \ u_2(0) = 0.434931;$$
$$u_3(0) = 1.73573;\ \ u_4(0) = 1.56648 \tag{46}$$

We used a discretization of 100 subintervals, the minimum value obtained for the cost functional being: 3.9874. The convergence of the numerical solution is also shown in Fig. 3. We achieve the prescribed tolerance: $tol = 0.001$, in only 15 iterations. For the convergence of the algorithm, the error has been considered as the sum of the differences (in absolute value) of the values of the coordination constant between two consecutive iterations $k-1$ and k of the previous algorithm (36), K^{k-1} and K^k:

$$E(k) = \sum_{i=1}^{N} \left| K_i^k - K_i^{k-1} \right| < tol \tag{47}$$

In this example, the time required by the program was 35.5 s on a personal computer (Intel Core 2/2.66GHz). The reader can now compare this solution with those presented in [7] and [9]. As can be seen,

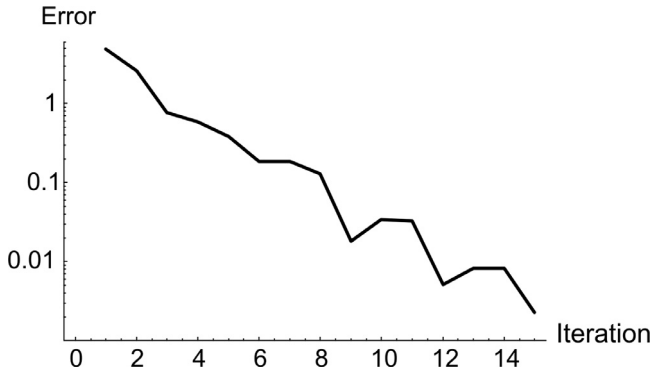

Fig. 3. Convergence of the algorithm.

Table 1
Maximum value of controls with bounds.

	$u_{1\max}$	$u_{2\max}$	$u_{3\max}$	$u_{4\max}$
Free	2.390	0.435	1.735	1.731
$u_{1\,\max} = 0.50$	0.50	0.597	2.257	2.227
$u_{1\,\max} = 1.00$	1.00	0.525	2.039	2.033
$u_{2\,\max} = 0.10$	2.396	0.10	1.745	1.737
$u_{2\,\max} = 0.20$	2.392	0.20	1.740	1.734
$u_{3\,\max} = 0.50$	2.562	0.487	0.50	1.763
$u_{3\,\max} = 1.00$	2.464	0.456	1.00	1.743
$u_{4\,\max} = 0.50$	2.586	0.464	1.801	0.50
$u_{4\,\max} = 1.00$	2.530	0.454	1.788	1.00

the effect of the pathogen killer $u_1(t)$ is dominant, and the form of the solution with combined therapies presented in Fig. 1 is quite similar to that of the pathogen killer alone (see [7]). However, the combined-therapy solution provides a significant improvement in other qualitative aspects, such as cost or time of healing, with respect to the solutions in which single therapies were used separately. For example, if we calculate the cost of the best case reported in [7], i.e. the single therapy employing u_1 ($u_{i\min} = u_{i\max} = 0,\ i = 2, 3, 4$), we obtain $\min J = 4.6954$, whereas in our case, using combined therapies, we have obtained $\min J = 3.9874$.

5.2. *Case 2:* $0 \le \mathrm{u} \le \mathrm{u}_{max}$

We shall now generalize the study, including upper limits for the controls. These bounds could represent physiological limits such as toxicity or discomfort. We think that the imposition of this type of limit is mandatory in any realistic therapy. We start with a one-at-a-time exploration of the upper bounds of the control. Table 1 shows the maximum values now obtained for the other controls u_j ($j \neq i$) when imposing bounds on u_i, compared to the unconstrained solution.

Notice how the more limited a control is, the more the remaining ones must increase in order to attain healing. The most remarkable effect happens for u_1 and the least one for u_2. Noteworthy increases of over 37% can be observed in some cases by limiting u_1.

We analyze them in more detail separately. Table 2 shows the results obtained when imposing different bounds on the controls. The first row in the table represents the unconstrained solution obtained in case 1. In addition to the optimal cost of the functional J, we show two new values that we believe may facilitate the interpretation of the results: the maximum value reached by state x_4 (maximum organ damage) and t^*, which represents the time it takes to reach what could be called complete healing (i.e. $x_4 \le 10^{-2}$). These two parameters can provide a clearer idea about the evolution of the infected organ throughout the entire course of the disease.

The imposed bounds have been chosen in consonance with the values obtained in the unconstrained solution. As can be seen, the influence of control u_2 is negligible, even with high bounds. However, control u_3 can be seen to have a slight influence on the cost, barely perceptible at $\max(x_4)$ and at t^*. The two most important controls are $u_1(t)$, the pathogen killer, and $u_4(t)$, the organ healing factor. We choose the same values for the upper limit for both controls. As can be seen, restricting the killer pathogen, u_1, increases the cost of the final solution notably due to the more elevated use of the other controls, which distorts the final cost. On its part, u_4 has a much lesser effect than u_1 on the minimum cost of the solution. The behavior of both controls is very interesting when analyzing the other two indices in Table 2, as substantial differences arise. Specifically, we see that the bound on u_1 has no effect on the time of treatment, t^*, and a moderate effect on the maximum value reached by x_4, which measures organ damage. However, the effect of u_4 is much more pronounced, both on treatment time, t^*, and above all on the health of the organ. We consider these conclusions to be of major value for subsequent studies on specific diseases.

Table 2
Influence of controls.

$u_{2\max}$	$\min J$	$\max(x_4)$	t^*	$u_{3\max}$	$\min J$	$\max(x_4)$	t^*
–	3.987	0.555	4.4	–	3.987	0.555	4.4
0.20	3.987	0.555	4.4	1.00	3.987	0.557	4.5
0.10	3.988	0.555	4.4	0.50	4.043	0.560	4.5
0.05	3.988	0.555	4.4	0.20	4.129	0.563	4.5
$u_{1\max}$	$\min J$	$\max(x_4)$	t^*	$u_{4\max}$	$\min J$	$\max(x_4)$	t^*
–	3.987	0.555	4.4	–	3.987	0.555	4.4
1.50	4.043	0.573	4.4	1.50	3.988	0.558	4.4
1.00	4.197	0.594	4.4	1.00	3.996	0.679	4.7
0.75	4.338	0.610	4.4	0.75	4.001	0.737	4.7
0.50	4.540	0.627	4.4	0.50	4.038	0.774	4.7
0.25	4.658	0.658	4.4	0.25	4.140	0.894	4.7

How the optimal solution of the state variables changes when restricting the use of these controls is also worth noting. We describe now the influence of the two most important controls, $u_1(t)$ and $u_4(t)$. It can be seen in Fig. 4 that the concentration of plasma cells, $x_2(t)$, decreases as we restrict the use of u_4, the contrary effect being achieved when limiting u_1. On the other hand, the concentration of pathogen, $x_1(t)$, is barely affected by the limitation on u_4, whereas the restriction of u_1 increases its value slightly.

Similar behavior as for $x_2(t)$ can be seen in Fig. 5 for the concentration of antibodies, $x_3(t)$. Finally, $x_4(t)$ shows an increase in the free solution both in the limitation of u_1, and mainly in that of u_4.

The reason for these results is that if u_1 is bounded, the pathogen can develop more, which leads to the generation of more plasma cells and hence antibodies; if u_4 is bounded, the organ is more damaged and less plasma cells are generated.

To conclude this section, we present a study of optimizations with multiple bounds: we simultaneously place upper limits on u_1 and u_4. In Table 3 an analysis of the impact of these bounds on our outputs of interest: $\min J$, $\max(x_4)$ and t^* is presented. We choose 3 values for each bound (free and 2 other values) and cross them.

As can be seen, upon imposing simultaneous limits onu_1 and u_4 the greatest effect regarding the free solution happens for $\max(x_4)$, which undergoes an increase of about 80%. The value of $\min J$ undergoes an increment of approximately 25%, whereas the least affected variable is the time t^* which barely increases by 16%.

We show now, by way of example, the case where the values were: $u_{1\,\max} = 0.50$ and $u_{4\,\max} = 0.50$. The optimal solution of the state variables can be seen in Fig. 6.

What can be observed first in this case is that the optimal solution presents a slightly different pattern: the variables x_2 and x_3, which in the unconstrained solution decreased asymptotically after an initial rapid growth to the initially imposed value, are now seen to fluctuate slightly within these bounds before converging to $x_2(0)$

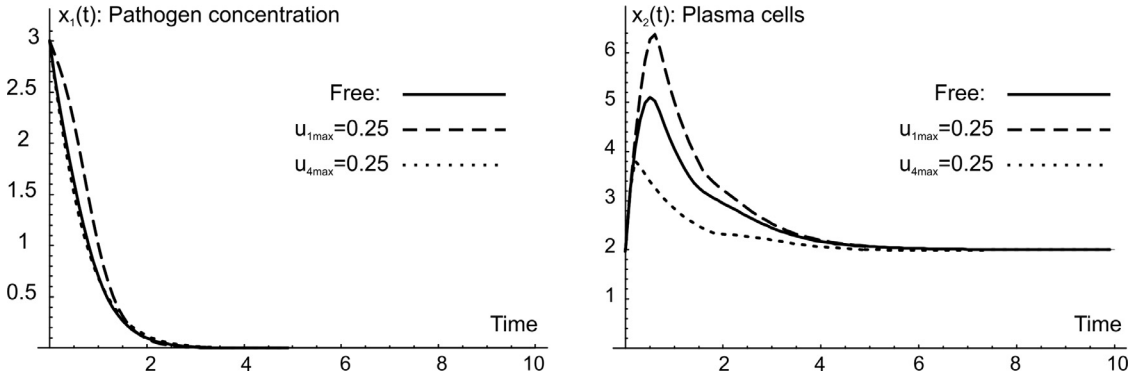

Fig. 4. Optimal $x_1(t)$ and $x_2(t)$ with combined therapies and bounded controls.

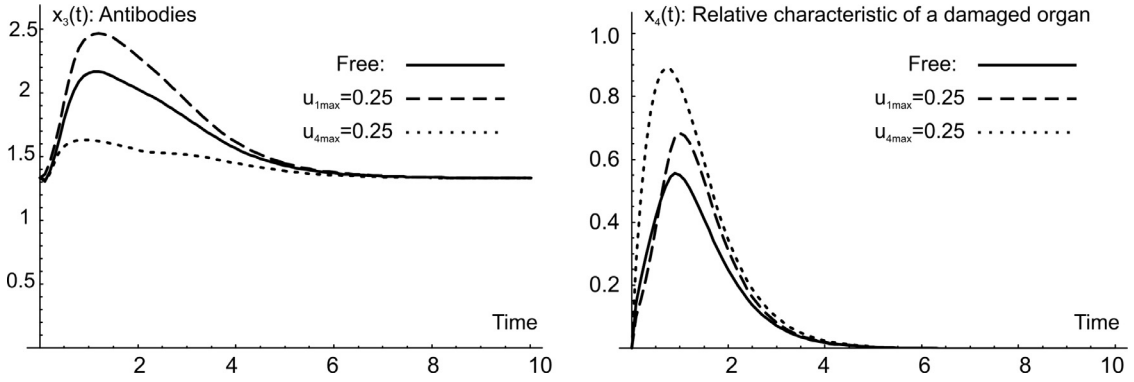

Fig. 5. Optimal $x_3(t)$ and $x_4(t)$ with combined therapies and bounded controls.

Table 3
Analysis with multiple bounds.

$\min J$	u_1 free	$u_{1\max}=1.0$	$u_{1\max}=0.5$
u_4 free	3.9874	4.1976	4.5404
$u_{4\max}=1.0$	3.9960	4.2467	4.7575
$u_{4\max}=0.5$	4.0379	4.3579	4.9513
$\max(x_4)$	u_1 free	$u_{1\max}=1.0$	$u_{1\max}=0.5$
u_4 free	0.5554	0.5945	0.6271
$u_{4\max}=1.0$	0.6796	0.7939	0.8495
$u_{4\max}=0.5$	0.7737	0.9221	0.9938
t^*	u_1 free	$u_{1\max}=1.0$	$u_{1\max}=0.5$
u_4 free	4.4	4.4	4.4
$u_{4\max}=1.0$	4.7	4.8	5.0
$u_{4\max}=0.5$	4.7	4.9	5.1

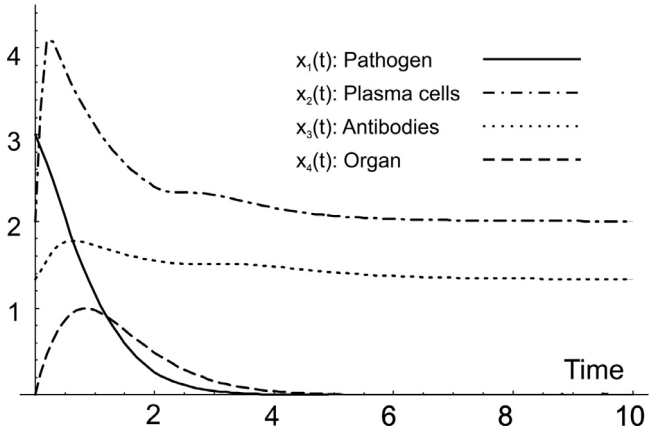

Fig. 6. Combined and bounded therapies.

and $x_3(0)$. On the other hand, if we compare the result now obtained with the values shown in Table 3 when both limits were separately imposed, we observe the following: the final cost increases considerably, specifically to $\min J = 4.951$; the same happens with $\max(x_4)$ which reaches now 0.994; finally, the value of t^* increases now to 5.1. This is related to the pathogen x_1 showing a slower decrease. The organ almost reaches the value 1 (at which it would be considered dead). We believe that maintaining the organ in a diseased condition for so long requires careful consideration and makes the combination of limits in therapies u_1 and u_4 unadvisable, from the clinical point of view.

5.3. Case 3: influence of function weights

Finally, this section presents a variant which, without considering any particular disease, will afford greater importance to curing the disease than the monetary goal. To do so, we simply give more importance to the weight functions q_1, q_4 in our cost functional than to r_i. The chosen values are: p_1, p_4 and r_i, $(i = 1, \ldots, 4)$ equal to 1, while the values of q_1 and q_4 will vary as shown in Table 4. We have included two new parameters which will help us interpret the results. We denote by t^{**} the time taken to achieve the almost complete elimination of the pathogen (i.e. $x_1 \leq 10^{-2}$), and we denote by M_C, the monetary cost of the treatment, calculated as:

$$M_C = \frac{1}{2}\int_0^{t_f} \left[r_1 u_1^2(t) + r_2 u_2^2(t) + r_3 u_3^2(t) + r_4 u_4^2(t)\right] dt \tag{48}$$

which only depends on the u_i. Bear in mind that $\min J$ includes in our statement (6) not only the monetary cost but also other factors which penalize large values of pathogen concentration, or poor organ health.

As can be seen, increasing the weight q_1 associated to $x_1^2(t)$ in the functional, the solution reduces the value of the pathogen as soon as possible. This is apparent in the sudden decrease of t^{**} (38.7%). In

Table 4
Influence of the weight functions q_1 and q_4.

q_1	min$J$	M_C	max(x_4)	t^*	t^{**}	$u_{1\max}$	$u_{4\max}$
1	3.987	1.855	0.555	4.4	3.1	2.39	1.73
2	5.848	2.573	0.469	4.0	2.5	3.41	1.61
3	7.425	3.233	0.451	3.8	2.2	4.3	1.47
4	8.834	3.865	0.438	3.7	2.0	5.0	1.34
5	10.126	4.467	0.432	3.5	1.9	5.7	1.23
q_4	min$J$	M_C	max(x_4)	t^*	t^{**}	$u_{1\max}$	$u_{4\max}$
1	3.987	1.855	0.555	4.4	3.1	2.39	1.73
2	4.166	2.067	0.419	3.6	2.7	2.44	1.84
3	4.273	2.179	0.365	3.2	2.5	2.46	1.90
4	4.352	2.268	0.324	2.9	2.4	2.48	1.95
5	4.414	2.341	0.295	2.7	2.4	2.50	1.99

Table 5
Influence of the weight function r_4.

r_4	min$J$	M_C	max(x_4)	t^*	$u_{1\max}$	$u_{4\max}$
1	3.987	1.855	0.555	4.4	2.39	1.73
1.1	4.022	1.875	0.599	4.5	2.43	1.63
1.2	4.042	1.866	0.647	4.6	2.45	1.50
1.3	4.074	1.896	0.662	4.6	2.48	1.43
1.4	4.080	1.860	0.714	4.8	2.49	1.28
1.5	4.101	1.877	0.727	4.8	2.51	1.22

order to achieve this, it increases remarkably the control associated to the pathogen, this is, u_1, which even doubles its value with respect to the base case and hence the cost shoots up as well. We notice also a remarkable decrease of $u_{4\max}$, as the use of this therapy is not so necessary, and a moderate decrease of the healing time t^* (20.4%).

When the increase takes place in q_4, as this weight affects $x_4^2(t)$ in the functional, now the solution seeks to heal the organ as soon as possible and hence the time which is most affected is precisely t^*, which decreases by 38.6%, whereas the decrease of t^{**} is less noticeable (22.5%). It is interesting to observe how, in order to achieve this, the control u_1 has hardly any influence and the control associated to the organ, u_4 increases its value but very moderately. As a consequence, the cost stays in values near the base case.

The results cannot be considered surprising, although we believe that its detailed study is very interesting. We see that, at the cost of increasing the price of the treatment M_C,we can diminish its duration and organ damage quite considerably. By way of conclusion, the option of increasing q_4 (e.g. to $q_4 = 5$) seems the most reasonable one, getting, at a moderate cost, both a very low damage to the organ max(x_4), and a very low healing time t^*. The last line of the table ($q_4 = 5$) shows how an increment of u_4 reduces the treatment duration and organ damage better than increasing u_1 ($q_1 = 5$).

In view of this result, it seems logical to question what would happen if one now varies the weights r_i and tries to analyze how the price of the treatment of one of the drugs may alter the results (relatively to a basic scenario). The results we obtain are shown in Table 5. As in the previous test we saw how increasing the weight q_4 related to the state x_4 (the health of the organ) seemed interesting, we are now going to study the influence of the weight function r_4, as it is the one associated to the control u_4. The results show how increasing r_4, despite a slight increment of min$J$, does not produce the same effect on the total price of the treatment M_C. Bear in mind that the objective function to minimize is J, not M_C, which makes this result unsurprising. The reason is that the expected decrease of the control u_4 is leveraged with a low increase of the control u_1. The health of the organ (max(x_4)) and the healing time (t^*) worsen, logically, but inside acceptable ranges. Thus, everything seems to indicate that fostering the use of u_4 is a good compromise solution, both from the economic and the sanitary viewpoints.

6. Conclusions

In this paper, we have presented a method based on Pontryagin's Minimum Principle to solve the optimal control problem that arises when therapeutic enhancement of immune response to invasion by a pathogenic attack is considered. Furthermore, we have presented an optimization algorithm based on the cyclic coordinate descent method that leads to determination of the optimal solution of the general problem with several therapies. Our method has certain advantages compared with other methods considered state-of-the-art. First, other authors do not present these combined therapies explicitly. Second, we are able to include more realistic (and complex) problems, such as the possibility of considering upper bounds for the controls. Other effects like those due to treatment duration and terminal cost weights are easy to incorporate but have not been considered in this paper for the sake of simplicity. Precisely this aspect may constitute a possible future line of research: analyzing specific diseases, with more detailed modeling appropriate to each (for example, with more controls or different state variables). We believe that our mathematical tool easily allows these variations in the approach due to the simplicity of the different techniques it employs.

Appendix A. Proof of Theorem 1

Let H be the Hamiltonian associated with the problem:

$$H(t,x,u,\lambda) = F(t,x,u) + \lambda \cdot f(t,x,u) \tag{49}$$

In virtue of PMP, there exists a $\widehat{C}^1$ function, λ_{opt} (costate variable), which satisfies the two following conditions:

$$\dot{\lambda}_{opt}(t) = -H_x(t, x_{opt}(t), u_{opt}(t), \lambda_{opt}(t)) \tag{50}$$

$$\dot{\lambda}_{opt}(t) = -F_x(t, x_{opt}(t), u_{opt}(t)) - \lambda_{opt}(t) \cdot f_x(t, x_{opt}(t), u_{opt}(t)) \tag{51}$$

$$H(t, x_{opt}(t), u_{opt}(t), \lambda_{opt}(t)) \le H(t, x_{opt}(t), u, \lambda_{opt}(t)); \quad \forall u,\ 0 \le u_{\min} \le u \le u_{\max} \tag{52}$$

From (51), it follows that:

$$\lambda_{opt}(t) = \left[K - \int_0^t F_x e^{\int_0^s f_x dz} ds\right] e^{-\int_0^t f_x ds} \tag{53}$$

denoting $K = \lambda_{opt}(0)$ (and omitting the arguments for the sake of simplicity).

From (52), it follows that for each t, $u_{opt}(t)$ minimizes H. Hence, in accordance with the Kuhn–Tucker Theorem, for each t, there exists two real nonnegative numbers, α and β, such that $u_{opt}(t)$ is a critical point of:

$$H^*(u) = F + \lambda_{opt}(t) \cdot f + \alpha \cdot (u_{\min} - u) + \beta \cdot (u - u_{\max}) \tag{54}$$

it being verified that if $u > u_{\min}$, then $\alpha = 0$, and if $u < u_{\max}$, then $\beta = 0$. We hence have:

$$\dot{H}^*(u_{opt}(t)) = F_u(t, x_{opt}(t), u_{opt}(t)) + \lambda_{opt}(t) \cdot f_u(t, x_{opt}(t), u_{opt}(t)) - \alpha + \beta = 0 \tag{55}$$

and the three following cases:

Case i) $u_{\min} < u < u_{\max}$ (t is not a boundary point). In this case, $\alpha = \beta = 0$ and hence:

$$F_u + \lambda_{opt}(t) \cdot f_u = 0 \tag{56}$$

From (53) and (56), we have:

$$F_u + \left[K - \int_0^t F_x e^{\int_0^s f_x dz} ds\right] e^{-\int_0^t f_x ds} \cdot f_u = 0 \tag{57}$$

So:

$$K = -\frac{F_u}{f_u} e^{\int_0^t f_x ds} + \int_0^t F_x e^{\int_0^s f_x dz} ds \tag{58}$$

If we denote $\mathbb{Y}_x(t)$, the second member of the above equation, the following relation is fulfilled:

$$\mathbb{Y}_x(t) = K \tag{59}$$

Case ii) $u = u_{\max}$, then $\beta \geq 0$ and $\alpha = 0$. In this case, If $f_u > 0$ (resp. $f_u < 0$), by analogous reasoning, we have:

$$\mathbb{Y}_x(t) \geq K \text{ (resp. } \mathbb{Y}_x(t) \leq K) \tag{60}$$

Case iii) $u = u_{\min}$, then $\alpha \geq 0$ and $\beta = 0$. In this case, If $f_u > 0$ (resp. $f_u < 0$), by analogous reasoning, we have:

$$\mathbb{Y}_x(t) \leq K \text{ (resp. } \mathbb{Y}_x(t) \geq K) \tag{61}$$

Otherwise, the application of PMP to this Bolza problem leads to the function λ_{opt} having to satisfy the final condition (41).

Appendix B. Concatenation of the extremal arcs

We shall consider:

$$0 = t_0 < t_1 < \cdots < t_p = t_f \tag{62}$$

such that in each (t_{j-1}, t_j) the following is fulfilled:

$$u_{i\min} < u_i < u_{i\max} \text{ or } u_{i\min} = u_i \text{ or } u_i = u_{i\max} \tag{63}$$

We shall carry out p steps, in each of which we shall construct $\omega_j \in C^1[t_{j-1}, t_j]$ such that $\omega_j(t_j) = \omega_{j+1}(t_j)$ and $f_i(t, \omega_j(t_j), u_i) = f_i(t, \omega_{j+1}(t_j), u_i)$ and that the function defined from these as:

$$q_K(t) := \omega_j(t), \text{ where } j \text{ is such that } t \in [t_{j-1}, t_j] \tag{64}$$

satisfies the minimality conditions expressed in Proposition 1.

We shall assume, without loss of generality, that $f_{u_i}(t, q, u_i) > 0$.

Step 1 (the first arc)

(i) If $K \geq -\frac{F_u(t,q_0,u_{i\min})}{f_u(t,q_0,u_{i\min})}$ we set $\omega_1(t)$ such that $\dot{\omega}_1(t) = f(t, \omega_1(t), u_{i\min})$ in the maximal interval $[0, t_1]$, where:

$$K \geq -\frac{F_u(t,\omega_1(t),u_{i\min})}{f_u(t,\omega_1(t),u_{i\min})} \exp\left(\int_0^t f_x(s,\omega_1(s),u_{i\min})ds\right) + \int_0^t \left(F_x(s,\omega_1(s),u_{i\min}) \exp\int_0^s f_x(z,\omega_1(z),u_{i\min})dz\right)ds \tag{65}$$

(ii) If $K \leq -\frac{F_u(t,q_0,u_{i\max})}{f_u(t,q_0,u_{i\max})}$ we set $\omega_1(t)$ such that $\dot{\omega}_1(t) = f(t, \omega_1(t), u_{i\min})$ in the maximal interval $[0, t_1]$, where:

$$K \leq -\frac{F_u(t,\omega_1(t),u_{i\max})}{f_u(t,\omega_1(t),u_{i\max})} \exp\left(\int_0^t f_x(s,\omega_1(s),u_{i\max})ds\right) + \int_0^t \left(F_x(s,\omega_1(s),u_{i\max}) \exp\int_0^s f_x(z,\omega_1(z),u_{i\max})dz\right)ds \tag{66}$$

(iii) If $-\frac{F_u(t,q_0,u_{i\max})}{f_u(t,q_0,u_{i\max})} < K < -\frac{F_u(t,q_0,u_{i\min})}{f_u(t,q_0,u_{i\min})}$ then $\exists u^* \in (u_{i\min}, u_{i\max})$ such that $K = -\frac{F_u(t,q_0,u^*)}{f_u(t,q_0,u^*)}$, and we set $\omega_1(t)$ the arc of the extremal in its maximal domain $[0, t_1]$ (with $\omega_1(0) = q_0, \dot{\omega}_1(0) = f(t, q_0, u^*)$) which satisfies:

$$K = -\frac{F_u(t,\omega_1(t),u(t))}{f_u(t,\omega_1(t),u(t))} \exp\left(\int_0^t f_x(s,\omega_1(s),u(s))ds\right) + \int_0^t \left(F_x(s,\omega_1(s),u(s)) \exp\int_0^s f_x(z,\omega_1(z),u(z))dz\right)ds \tag{67}$$

j-th Step (j-th arc)

(A) If ω_{j-1} has an interior extremal arc in $[t_{j-2}, t_{j-1}]$, there are two possibilities:

(I) If $\dot{\omega}_{j-1}(t_{j-1}) = f(t, \omega_{j-1}(t_{j-1}), u_{i\min})$, we set $\omega_j(t)$ in the maximal interval $[t_{j-1}, t_j]$ which satisfies the differential equation $\dot{\omega}_j(t) = f(t, \omega_j(t), u_{i\min})$ with the initial condition $\omega_j(t_{j-1}) = \omega_{j-1}(t_{j-1})$ and:

$$-\frac{F_u(t,\omega_{j-1}(t_{j-1}),u_{i\min})}{f_u(t,\omega_{j-1}(t_{j-1}),u_{i\min})} \geq -\frac{F_u(t,\omega_{j-1}(t_{j-1}),u_{i\min})}{f_u(t,\omega_{j-1}(t_{j-1}),u_{i\min})} \exp\left(\int_{t_{j-1}}^t f_x(s,\omega_j(s),u_{i\min})ds\right) + \int_{t_{j-1}}^t \left(F_x(s,\omega_j(s),u_{i\min}) \exp\int_{t_{j-1}}^s f_x(z,\omega_j(z),u_{i\min})dz\right)ds \tag{68}$$

(II) If $\dot{\omega}_{j-1}(t_{j-1}) = f_u(t, \omega_{j-1}(t_{j-1}), u_{i\max})$, we set $\omega_j(t)$ in the maximal interval $[t_{j-1}, t_j]$ which satisfies the differential equation $\dot{\omega}_j(t) = f(t, \omega_j(t), u_{i\max})$ with the initial condition $\omega_j(t_{j-1}) = \omega_{j-1}(t_{j-1})$ and:

$$-\frac{F_u(t,\omega_{j-1}(t_{j-1}),u_{i\max})}{f_u(t,\omega_{j-1}(t_{j-1}),u_{i\max})} \leq -\frac{F_u(t,\omega_{j-1}(t_{j-1}),u_{i\max})}{f_u(t,\omega_{j-1}(t_{j-1}),u_{i\max})} \exp\left(\int_{t_{j-1}}^t f_x(s,\omega_j(s),u_{i\max})ds\right) + \int_{t_{j-1}}^t \left(F_x(s,\omega_j(s),u_{i\max}) \exp\int_{t_{j-1}}^s f_x(z,\omega_j(z),u_{i\max})dz\right)ds \tag{69}$$

(B) If $[t_{j-2}, t_{j-1}]$ is the boundary interval, we set $\omega_j(t)$ the arc of the interior extremal (with $\omega_j(t_{j-1}) = \omega_{j-1}(t_{j-1})$) in its maximal domain $[t_{j-1}, t_j]$, in a similar way to the described in item (iii) of step 1.

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