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

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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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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].