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AN APPLICATION OF OPTIMAL CONTROL THEORY TO THE DESIGN OF THEORETICAL SCHEDULES OF ANTICANCER DRUGS

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A system of differential equations for the control of tumor growth cells in a cycle non-specific chemotherapy is analyzed. Spontaneously acquired drug resistance is taken into account by means of a mutation rate non-decreasingly dependent on time and the drug kill rate is supposed to depend on the growth rate of sensitive cells. For general tumor growth and drug kill rates the optimal treatment consists in maximizing the allowable drug concentration throughout.

Keywords: chemotherapeutic treatments, drug resistance, optimal control.

1. Introduction

The modelling of the onset, development and treatment of tumors containing drug resistant cells can be mathematically addressed by several means. One kind of study is based on probabilistic models like in Coldman and Goldie (1983, 1986), Harnevo and Agur (1992), Kimmel and Axelrod (1990), Kimmel *et al.* (1992). However, this approach usually engenders models that are rather difficult to analyze. Thus, when it is intended to study the average behavior of the erratic nature of tumor cell growth and to have a qualitative understanding of the phenomena involved in chemotherapeutic protocols, a deterministic approach, which is usually easier to analyze, can serve as a guide to determine the relevant aspects captured by the model. Besides, when confronted with experimental results, it can suggest possible corrections of some aspects on a qualitative basis.

In this paper, we will employ this approach to study certain questions concerning the design of chemotherapeutic protocols. More specifically, we will apply the deterministic optimal control theory to examine theoretical models dealing with the continuous delivery of a cycle nonspecific anticancer drug in a setting to be described next.

The first important aspect to be considered is the modelling of the drug effect on tumor growth. This is usually handled with by means of a perturbation term which is added to the differential equation describing the evolution of tumor cells, and in many

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cases this effect is conveyed by the product of the drug concentration and the number of tumor cells. However, Norton and Simon (1977; 1986) observed that "clinical experience suggests that some tumors may be less sensitive to therapy when they are very small or very large than when they are of intermediate size" (Norton and Simon, 1977, p.1307). Backed up by this clinical evidence, they proposed an alternative way of describing drug induced mortality, relying on the fact that the growth-inhibiting effect of treatment in those tumors can be proportional to the tumor growth rate instead of just being proportional to the tumor population level. This proposal will be one of the major hypotheses in our analysis.

The second aspect relevant to the design of chemotherapeutic protocols is the phenomenon of spontaneously acquired drug resistance (Coldman and Goldie, 1983). This can be handled by considering a compartmental model where one of the variables is associated with the drug resistant cells, with an influx mediated by a certain mutation rate. In several works this mutation rate is taken to be constant in time. However, as evidenced in clinical practice (Tan, 1989, p.146), the mutation rate can actually increase with time. Our analysis will encompass this situation.

The third important aspect is drug toxicity (Vietti, 1980). There are several possibilities of modelling this item in the context of optimal control theory (each one with its own advantages and drawbacks from the clinical point of view), but in this work we will consider the simplest instance and model toxicity just as a cumulative term in the performance index.

Needless to say, the interplay among all those three factors already makes the design of appropriate protocols a difficult task. There is, however, a fourth aspect to be considered in an optimal control approach: the choice of the final-time of treatment. In this study, we chose to analyze a free final-time optimal control problem, i.e. the final time must also be found to minimize the performance index. Certainly, in order to possibly carry over the results of such an analysis to clinical practice, they should be subjected to scrutiny, especially concerning the practicability of the calculated final time of treatment and total cumulative toxicity. However, previous analyses led us to argue that this approach is reasonable and can sometimes yield better theoretical results than those obtained by optimal control problems with *ad hoc* fixed final-time of therapies.

Briefly, in this work we analyze the mathematical problem of designing optimal chemotherapeutic protocols using a rather simple model that retains all the above aspects, namely, toxicity, the fact that the mutation rate to drug resistance is nondecreasingly dependent on time, and the assumption that the growth-inhibiting effect of treatment is proportional to the growth rate of sensitive cells.

The work is outlined as follows. In the next section, we present a mathematical model which describes a possible dynamics of tumor cells under drug action and poses the related optimal control problem. A subsection is entirely devoted to the derivation of the optimal protocol, where we only formulate the lemmas pertaining to the mathematical analysis and briefly comment on the results so as to highlight their biological significance. A discussion of the results follows and lastly, technical proofs are deferred to the Appendix.

2. Optimal Chemotherapy

2.1. Problem Statement

In order to carry out the analysis of tumor growth subjected to chemotherapy, the following assumptions are taken:

a) The tumor will be viewed as a cell population undergoing a spatially homogeneous growth, i.e. it does not depend on the cell position within the tumor.

b) The tumor will also consist of drug-resistant cells whose growth rate depends not only on the size of its own population, but also on the size of the sensitive cells. This latter dependence is due to a randomly spontaneous mutation during mitosis towards drug resistance, which will occur according to a time increasing rate. In this way, no sensitive cell becomes drug resistant during its life time; only their daughter cells may acquire drug resistance by spontaneous mutation during mitosis. A biological validation of this kind of drug resistance was performed by 'in vitro' experiments with the T-cell lymphoblastic cell line CCRF-CEM. A description of these experiments can be found in (Vendite, 1988). (The importance of drug resistance in designing chemotherapeutic protocols is emphasized in (Skipper, 1983).)

c) The kill rate of the drug (number of killed cells/unit drug concentration) will be considered as a function of the *growth rate of the sensitive cells population.* This is in accordance with clinical observations as pointed out by Norton and Simon (1977; 1986).

d) The mutation rate from sensitive tumor cells to resistant cells is modeled as a nondecreasing function of time, since it is evidenced that "as cancer progresses, the tumor cells show increased genetic instability and the tumor cell population becomes more heterogeneous. This implies that the mutation rates from sensitive tumor cells to resistant mutants may increase with time" (Tan, 1989, p.146).

The following system is a model for the behavior of tumoral cells submitted to chemotherapy when the assumptions mentioned above are taken into account:

$$\begin{cases} \dfrac{dx}{dt} = xf(y) + \alpha(t)f(y)(y-x) \\ \dfrac{dy}{dt} = yf(y) - u(t)f(y)g(y-x) \\ x(0) = x_0, \quad y(0) = y_0 \end{cases} \tag{1}$$

Here $t \geq 0$ represents the elapsed time, $y(t) \in \mathbb{R}$ stands for the total number of tumor cells at time t, while $x(t) \in \mathbb{R}$ stands for the number of drug-resistant cells within the tumor. Clearly, any initial condition (x_0, y_0) is such that $x_0 < y_0$; $f(y)$ is a specific growth rate for the tumor cells; $\alpha(t)$ is the fraction per unit of time of the drug sensitive cells that mutate into drug resistant cells; $0 \leq u(t) \leq u_m$ is the drug

concentration at the tumor site (assumed to be limited, i.e., $u_m < +\infty$); $f(y)g(y-x)$ gives the kill rate of the drug per unit of drug concentration, and can represent, amongst others, the growth rate of the drug-sensitive cells (take e.g. $g(y-x) = y-x$), as considered by Norton and Simon (1977; 1986). The technical conditions required for the above functions will be described later on.

The objective function to be minimized is as follows:

$$J(u, t_f) = y(t_f) + c \int_0^{t_f} u \, dt \tag{2}$$

The first term of (2) represents the final tumor level and the second one, the drug accumulation in the patient's body, where $c > 0$ is introduced to take care of the physical dimensionalization of the problem and also serves as a penalization factor.

In the light of the cell dynamics described by (1), the factors that make up the objective function J (2) are contradictory. Indeed, the action of the drug to minimize the overall cell population y increases concomitantly the amount of toxicity, defined here as the accumulated drug in the body. On the other hand, the periods of the absence of drug concentration ($u = 0$) allow for a tumor growth, although toxicity (considered as a cumulative process) remains constant during the same period.

We will be interested in studying questions associated with the following Free Final-Time Optimal Control Problem related to (1), (2):

$$\text{Infimum}\Big\{ J(u, t_f), \quad 0 \leq t_f < +\infty, \quad u \in A(t_f) \Big\} \tag{3}$$

where $A(t_f) = \{u \in BV[0, t_f^*)\colon \ 0 \leq u(t) \leq u_m \text{ for } 0 \leq t \leq t_f\}$. The notation $BV[0, t_f^*)$ signifies the set of functions $u : [0, t_f^*) \longrightarrow \mathbb{R}$ such that for any $0 \leq \tau < t_f$ the restriction of u to $[0, \tau]$ is in $BV[0, \tau]$, i.e., u is of bounded variation on the interval $[0, \tau]$. The functional J is defined as in (2).

As regards the functions f, g that appear in (1), we will consider the following natural assumptions:

$$\begin{cases} f, g \in C^0[0, \infty) \cap C^1(0, \infty) \\ g(0) = 0, \quad g(s) > 0, \quad g'(s) > 0 \text{ when } s > 0 \end{cases} \tag{4}$$

and

$$\text{there exists } y_m > 0 \text{ such that } f(y_m) = 0 \text{ and } f(y) > 0 \text{ for } 0 \leq y < y_m \tag{5}$$

or

$$f(y) > 0 \text{ for } y \geq 0, \text{ and } g \text{ is globally Lipschitz} \tag{6}$$

In (4) the second expression indicates that the drug effect is strictly related to the existence of sensitive cells and the third one states that a part of the drug effect increases as the level of sensitive cells increases. In (5) it is stated that the tumor exhibits a density dependent growth, where y_m is the maximum attainable level of tumor cells.

Remark 1. In this case, when the tumor achieves its maximum size, the drug will have no more effect, which simulates the clinical evidence (Norton and Simon, 1977) that certain large tumors are much less sensitive to the drug effect than medium size ones. It is important to stress that condition (5) together with the term $u(t)g(y-x)$ in the second equation of (1) conveys the insensitivity of large tumors as opposed to their sensitivity in the same situation under a logkill hypothesis (that is, the drug kill rate linearly proportional to the tumor cells populational level).

In (6) it is assumed that there is no maximum attainable level of tumor cells and that the relative increment of the part of the kill rate per unit concentration dependent on the sensitive cells population is bounded.

As for the conditions on $\alpha(t)$, we will assume:

$$\alpha(\cdot) \text{ is a } C^1 \text{ function satisfying } 0 < \alpha(t) < 1 \text{ and } \frac{\mathrm{d}\alpha(t)}{\mathrm{d}t} \geq 0 \tag{7}$$

This last condition is in accordance with observations in (Tan, 1989).

The behavior of the system (1) without drug concentration for all t ($u(t) = 0$, $\forall\ t \geq 0$) is similar to the dynamics obtained in (Goldie and Coldman, 1979, p.1732) describing the evolution of resistant cells in relation to the number of tumoral cells.

2.2. Derivation of the Optimal Strategy

In the sequel, we formulate some lemmas and a theorem that establish a mathematical analysis. For those which are not purely technical, we give a brief explanation of their significance.

First, we present a lemma that states, in particular, the positivity of the populations involved, thus, ensuring the biological consistency of the model.

Consider the following open set Ω in $\mathbb{R}^2$:

$$\begin{cases} \text{i)} & \Omega = \{(x,y) \in \mathbb{R}^2 : \ 0 < x, \quad 0 < y, \quad x < y\} \\ & \text{if assumptions (4) and (6) hold} \\ \\ \text{ii)} & \Omega = \{(x,y) \in \mathbb{R}^2 : \ 0 < x, \quad 0 < y < y_m, \quad x < y\} \\ & \text{if assumptions (4) and (5) hold} \end{cases}$$

Lemma 1. *Consider $u(t) \geq 0$ a function of bounded variation. The trajectories corresponding to the solution $(x(t), y(t))$, $t \geq 0$, of (1) with initial conditions $(x_0, y_0) \in \Omega$ do not cross the boundary of Ω in finite time.*

For further use, we stress that this lemma implies in particular that for initial conditions in Ω, $0 < x(t) < y(t)$ for all finite times $t \geq 0$.

Now we proceed with the analysis of the optimal control problem itself.

According to the optimal control theory (Sage, 1968) we define the Hamiltonian as

$$H(x,y,t,\lambda_1,\lambda_2,u) = \lambda_1(xf(y) + \alpha(t)f(y)(y-x)) + \lambda_2(yf(y) - uf(y)g(y-x)) + cu \tag{8}$$

where λ_1 and λ_2 are the adjoint variables.

In turn, the adjoint variables are given by the following differential equations with their respective final conditions:

$$\begin{cases} \dot{\lambda}_1 = -\dfrac{\partial H}{\partial x} = -\Big[\lambda_1 f(y)\big(1-\alpha(t)\big) + \lambda_2 u f(y) g'(y-x)\Big] \\ \dot{\lambda}_2 = -\dfrac{\partial H}{\partial y} = -\Big[\lambda_1\big(xf'(y) + \alpha(t)f'(y)(y-x) + \alpha(t)f(y)\big) \\ \qquad\qquad x + \lambda_2\big(yf'(y) + f(y) - u\big(f'(y)g(y-x) + f(y)g'(y-x)\big)\big)\Big] \\ \lambda_1(t_f) = 0, \quad \lambda_2(t_f) = 1 \end{cases} \tag{9}$$

We remark that throughout this work '$\cdot$' and 'd/dt' will be used interchangeably. Also, for simplicity of notation, we will denote the values of the Hamiltonian along a fixed optimal trajectory, that is, the values of $H(x(t),y(t),t,\lambda_1(t),\lambda_2(t),u(t))$, simply by $H(t)$.

Since we have a free final-time problem, it is known that on an optimal trajectory the Hamiltonian is zero at the final time t_f (Sage, 1968):

$$H(t_f) = 0 \tag{10}$$

However, the Hamiltonian is not necessarily identically zero along optimal trajectories because our system is not necessarily autonomous (i.e., it may depend on time). Thus, we will have to obtain more information on the behavior of $H(t)$ in order to accomplish our analysis.

Since the Hamiltonian is linear in u, we find the following *Optimal Control Law*:

$$u = \begin{cases} 0 & \text{if} \quad c - \lambda_2 f(y)g(y-x) > 0 \\ u_m & \text{if} \quad c - \lambda_2 f(y)g(y-x) < 0 \\ \text{undetermined} & \text{if} \quad c - \lambda_2 f(y)g(y-x) = 0 \end{cases} \tag{11}$$

The next lemma states that optimal treatments must end up with the application of the maximum drug concentration.

Lemma 2. *Any optimal trajectory must end up with* u_m.

The next three lemmas are technical and deal with the determination of the signs of the adjoint variables and the Hamiltonian.

Lemma 3. *In any optimal strategy* $\lambda_1(t) > 0$ *for all* $t \in [0, t_f)$.

Lemma 4. *In any optimal strategy* $\lambda_2(t) > 0$ *for all* $t \in [0, t_f]$.

Lemma 5. *For any* $t \in [0, t_f]$, $H(t) \leq 0$.

The following lemma rules out any optimal strategy whose drug concentration may depend on the level of the cells (that is to say, the existence of singular controls is ruled out). Moreover, it does not allow for abrupt interruption or a start of the effect of drug concentration.

Lemma 6. *In any optimal strategy singular controls cannot exist. Moreover, switchings from* $u = 0$ *to* u_m *or vice-versa are not allowed.*

As a consequence of the above lemmas, we will now show that any optimal strategy consists in the administration of the maximum drug concentration throughout the whole treatment.

Theorem 1. *In an optimal strategy* $u(t) = u_m$ *for all* t.

Proof. It follows immediately from the previous lemmas, since an optimal strategy must end up with u_m, and can have neither switchings nor a singular control. ∎

The importance of this theorem is mainly related to the independence of the optimal strategy with respect to the cell growth and drug kill rates.

Remark 2. The mathematical analysis remains valid for the case of a constant mutation rate (i.e., $\dot{\alpha} = 0$), wherein the proofs could be simplified.

3. Discussion

A dynamical model of spontaneously acquired drug resistance has been presented in order to describe the evolution of a heterogeneous tumor. The growth-inhibiting effect of the treatment has been modeled according to the assumption made by Norton and Simon (1977; 1986), which presupposes that the cell loss due to the cytotoxic action of the drug is directly proportional to the growth kinetics of the tumor. In addition, the mutation rate to drug resistance is supposed to be nondecreasing with time according to clinical observations (Tan, 1989). The objective of the treatment has been set to minimize a sum of the final tumor level and the cumulative toxicity (modeled as an integral of the drug concentration at the tumor site, see eqn. (2)) incurred from the therapy. Within this context, the optimal strategy against a general tumor growth consists in administering a maximum drug concentration throughout the protocol. Regarding this result, some comments are in required. As argued in (Boldrini and

Costa, 1997) (the setup of a time varying mutation rate and a growth-inhibiting effect of the treatment directly proportional to *the number of sensitive cells*, that is, in eqns. (1), $\dot{y} = yf(y) - u(t)g(y-x)$, with $g(y-x) = y - x$), the mutation rate is nondecreasing with time, so the resistant cells grow faster and the lack of controllability of the overall cell population increases. Moreover, the components of the objective function (minimization of the final tumor level and toxicity) are conflicting by virtue of the dynamical model equations. These points, in their own right, might indicate that alternation between rest periods and variable levels of the drug could form an optimal protocol. To corroborate this possible scenario, there still exists the fact that the drug kill rate proposed in this work does not change monotonically with the tumor size. To wit, e.g. in a Gompertzian growth, the influence of the therapy on the tumors with sensitive cells significantly above the 'inflection point' level (corresponding to 37% of the maximum tumor size) is markedly lessened. It might then be expected that the optimal strategy would take this feature into account (at least for the initial sensitive cells levels above the 'inflection point') and vary accordingly the amount of the drug to be injected, since the maximum drug concentration (which, in terms of the proposed objective function, increases most rapidly the incurred toxicity) would not prove useful in this instance. As regards this speculation of a possible drug schedule, it is worthwhile to mention that variations in drug administration can be found in (Norton and Simon, 1977) where, under the proposed growth-inhibiting effect of treatment, a successful strategy for eradicating a single homogeneous tumor obeying a Gompertzian growth (without drug resistance) consists in a therapy level sufficient to maintain a steady volume regression, and applying an intensive schedule of an anticancer agent towards the end of the protocol.

At this stage, it is worthwhile to recall that the mathematical analysis presented in this work is also valid for the instance of a constant mutation rate (i.e., α =constant in eqns. (1)). Therefore, the above discussion remains in force in view of the fact that the corresponding model with a constant mutation rate and a growth-inhibiting effect linearly proportional to the number of sensitive cells, yields a maximum drug concentration throughout as an optimal strategy (Costa *et al.*, 1992).

Hence, in the face of the previous arguments, the result found in this work is unexpected to some extent, since variations of the drug schedule along time may prove effective as shown in (Norton and Simon, 1977), although without drug resistance.

Several conjectures could be raised. The maximum drug concentration throughout as an optimal strategy may be due to the free final-time formulation of the optimal control problem. In fact, previous works suggested this drug regimen, but there remains some evidence that the defective modeling of other aspects of the phenomenon, such as the acquired drug resistance mechanism, toxicity (Costa *et al.*, 1992; 1995), as well as the drug kill rate (Costa *et al.*, 1994) might have significantly contributed to the derivation of the protocol with that structure. On the other hand, when considering a certain recuperation mechanism from toxicity effects in the setting of a free final-time (Costa and Boldrini, 1997), it is proved that there are instances where the corresponding optimal strategy consisted of the maximum drug concentration interspersed with rest periods, rather than the maximum drug concentration throughout. Although, in general terms, one could wonder whether the free final-time setup for

optimal chemotherapy fits in the clinical context, we argue that it can yield useful information. In fact, in specific situations, the final-time t_f^*, which represents the length of the optimal treatment, can be calculated numerically, just by recalling from optimal control theory that it is given by the relation $H(t_f^*) = 0$, thus implying $\mathrm{d}y(t_f^*)/\mathrm{d}t = -cu_m$ (in the exponential cell growth case an analytical expression for t_f^* can be easily obtained). With such an estimate for t_f^*, one could assess the duration of the treatment, the cumulated toxicity (proportional to $u_m t_f^*$), as well as the corresponding value of the performance index, and then check them with the acceptably required standard values. In the case of a failure of such a procedure, one could resort to therapies derived by *ad hoc* fixed final-time optimal control problems. In other words, the free final-time setup could be employed as a first step in a tuning process in the derivation of theoretical optimal protocols. As a matter of fact, results obtained in (Boldrini and Costa, 1998), where the above process was implemented (although in models without drug resistance), showed that in most cases the simple optimal strategy obtained by the free final-time optimal control setup had a shorter duration and a lower value for the performance index than those values corresponding to the complex, tumor size dependent optimal strategies given by fixed *ad hoc* final-time optimal control schedules.

Another conjecture to explain the prevalence of the maximum drug concentration as the optimal protocol in our settings is the possibility of defectively modeling the drug resistance mechanism. The result seems to indicate that with this model of drug resistance, the recruitment of resistant cells is so intense that it makes any strategy of drug administration other than the maximum drug concentration, superfluous. One could think that a mechanism like back-mutation could lead to different results. However, our previous analysis could easily be extended to simple forms of modeling back-mutation (for instance, the inclusion of the term $-\beta(t)f(y)x$ in the first equation of (1), where $\beta(t)$ is the time varying back-mutation rate and satisfies $0 < \beta(t) < \alpha(t)$), leading exactly to the same conclusions. Thus, if back-mutation has led to different optimal strategies, it would probably have not been modeled in such a simple way. In a more general context, the inclusion in the model of *an acquired drug sensitivity* (Usher and Henderson, 1996) could generate optimal strategies other than maximum drug concentration throughout.

Finally, in our opinion, one of the main reasons for the prevalence of the maximum drug concentration as an optimal strategy, in the presence of drug resistance and free final-time setting, may be ascribed to the lack of an appropriate modeling of toxicity. However, as mentioned in (Costa *et al.*, 1995), in the same frame of drug resistance and free final-time optimal control problems, exchanging the cumulative criterion of toxicity used above for a noncumulative one, like, say, a required minimum level of normal cells (which themselves are mathematically described by a dynamical equation), did not modify the structure of the optimal drug regimen with respect to the regimen found in this work.

In conclusion, this analysis showed the role that some aspects can play in the modeling of sensitive and resistant tumor cells under drug action. It is hoped that the above speculations may shed some light on the processes involved so as to give some alternative ways that lead to more refined models of chemotherapeutic protocols.

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Appendices

A. Proof of Lemma 1

First, we will prove that the referred trajectories cannot touch the boundary of Ω corresponding to $x = y$ in finite time (and in fact that the set given by $x = y$ is invariant). Suppose by contradiction that this is not so, and consider the first positive time τ such that $x(\tau) = y(\tau)$. Then $y(t) > x(t)$ for all $t \in [0, \tau)$. On the other hand, it is easy to observe that $x(t) = y(t) = w(t)$ with $w(t)$ satisfying $\mathrm{d}w/\mathrm{d}t = wf(w)$ and $w(\tau) = x(\tau)$ is also a solution to (1) passing through $(x(\tau), y(\tau))$. Since we have conditions for the uniqueness of the solutions to initial value problems for (1), we obtain a contradiction that proves that the trajectories starting inside Ω never touch the line $x = y$ in finite time. Thus the referred solution satisfies $y(t) > x(t)$ for all finite times t.

Now, using the previously obtained information, we conclude that the right-hand side of the first equation in (1) is positive for $x > 0$. Thus, for initial conditions inside Ω, the solutions $(x(t), y(t))$ have increasing $x(t)$, and therefore $x(t) > 0$ for all $t > 0$ and the referred trajectories never touch the line $x = 0$.

If we are in Case (i) of Ω, the above results imply the statement of the lemma. If we are in Case (ii), we have to verify that the trajectories starting inside Ω do not touch the line $y = y_m$. When $u \equiv 0$, this is done by contradiction with the uniqueness of the solutions to the initial value problem as in the first part, just by observing that (x, y_m) is also a solution to (1). Therefore in Case (ii) for $u \equiv 0$ the trajectories of (1) remain in Ω for a finite time t.

As for $u > 0$, suppose that for an initial condition (x_0, y_0) there is a τ such that $y(\tau) = y_m$. We know already that in a finite time $g(y(t) - x(t)) > 0$, hence for $t \in [0, \tau]$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = y(t)f\big(y(t)\big) - u(t)f(y)g\big(y(t) - x(t)\big) \leq y(t)f\big(y(t)\big) \tag{A1}$$

On the other hand, if $(x_1(t), y_1(t))$ denotes the solution to (1) with $u \equiv 0$ and the same initial conditions, we have for every $t \in [0, \tau]$

$$\frac{\mathrm{d}y_1(t)}{\mathrm{d}t} = y_1(t)f\big(y_1(t)\big) \tag{A2}$$

Thus, by the result of differential inequalities (Hale, 1980, p.30), we conclude that $y(t) \leq y_1(t)$ for every $t \in [0, \tau]$. In particular, $y_m = y(\tau) \leq y_1(\tau)$, and so $(x_1(\tau), y_1(\tau)) \notin \Omega$. But this yields a contradiction to the fact that the trajectories for $u \equiv 0$ in Case (ii) remain in Ω for a finite time t.

B. Proof of Lemma 2

Suppose that either $u(t_f) = 0$ or $u(t)$ is singular. Then, at t_f, the Hamiltonian reduces to $H(t_f) = y(t_f)f(y(t_f)) = 0$ (from (10)). Since from Lemma 1 $y(t_f) > 0$, (5) or (6) guarantee that $f(y(t_f)) > 0$, and we have a contradiction. So the only possibility is $u(t_f) = u_m$.

C. Proof of Lemma 3

From (9) and Lemmas 1 and 2, we observe that $\dot{\lambda}_1(t_f^-) < 0$. Thus, in a left neighborhood of t_f, λ_1 is positive. Suppose, by contradiction, that there exists $\hat{t}$ such that $\lambda_1(\hat{t}) = 0$ for the first time going backwards from t_f (i.e., $0 \leq \hat{t} < t_f$). Now, we observe that after some algebraic manipulations it holds $\dot{H} = \lambda_1 \dot{\alpha}(t) f(y)(y - x)$ (Sage, 1968); as $\lambda_1(t) > 0$ for $t \in (\hat{t}, t_f)$, we then conclude that $\dot{H} \geq 0$ for $t \in (\hat{t}, t_f)$. Since $H(t_f) = 0$, this implies that $H(t) \leq 0$ for $t \in [\hat{t}, t_f]$.

Now we prove that in the interval $[\hat{t}, t_f]$, $\lambda_2(t) > 0$. Since $\lambda_2(t_f) = 1$, the continuity of $\lambda_2(t)$ implies that λ_2 is positive in a left neighborhood of t_f. Suppose, by contradiction, that $\lambda_2(t)$ is not positive on $[\hat{t}, t_f]$. Then, there exists a first t^* (going backwards from t_f) such that $\hat{t} \leq t^* < t_f$ and $\lambda_2(t^*) = 0$. By the optimal control law (11), we know that $u(t^*) = 0$, and, since $u(t_f) = u_m$, there is at least one $\tilde{t}$, with $t^* \leq \tilde{t} < t_f$, for which a switching occurs. But at the switching time $\tilde{t}$, we have $H(\tilde{t}) = \lambda_1(\tilde{t})\dot{x}(\tilde{t}) + \lambda_2(\tilde{t})y(\tilde{t})f(y(\tilde{t})) > 0$, since $\lambda_1(\tilde{t}) > 0$ (by the definition of $\hat{t}$) and $\lambda_2(\tilde{t}) > 0$ (by the definition of the optimal control law (11)). But this is a contradiction because we had concluded that $H(t) \leq 0$ for $t \in [\hat{t}, t_f]$ and, in particular, $H(\tilde{t}) \leq 0$. So $\lambda_2(t) > 0$ for $t \in [\hat{t}, t_f]$.

Returning to the proof of the main statement of the lemma, we observe that by calculating the right derivative of $\lambda_2(t)$ at $\hat{t}$ (by using (9)), we obtain $0 \leq \dot{\lambda}_1(\hat{t}^+) = -[\lambda_2(\hat{t}^+)u(\hat{t}^+)g'(x(\hat{t}^+) - y(\hat{t}^+))]$. When $u(\hat{t}) > 0$, the contradiction is immediately established since the left-hand side of the above expression is negative. On the other hand, when $u(\hat{t}) = 0$, there will be at least one $\bar{t}$ for which a switching occurs, with $\hat{t} < \bar{t} < t_f$, since $u(t_f) = u_m$ (by Lemma 2). Hence, at $\bar{t}$, $H(\bar{t}) = \lambda_1(\bar{t})\dot{x}(\bar{t}) + \lambda_2(\bar{t})y(\bar{t})f(y(\bar{t})) > 0$. But again, this is a contradiction with $H(t) \leq 0$ for $t \in [\hat{t}, t_f]$.

D. Proof of Lemma 4

The argument is similar to the one used in the proof of the last lemma. We already know that λ_2 is positive in a left neighborhood of t_f, since it is continuous and $\lambda_2(t_f) = 1$. Suppose, by contradiction with the statement of the lemma, that there exists a first t^* (going backwards from t_f and $\hat{t} \leq t^* < t_f$) such that $\lambda_2(t^*) = 0$. By the optimal control law (11), $u(t^*) = 0$ and, since $u(t_f) = u_m$, there is at least one $\tilde{t}$, with $t^* \leq \tilde{t} < t_f$, for which a switching occurs. But at the switching time $\tilde{t}$, it holds $H(\tilde{t}) = \lambda_1(\tilde{t})\dot{x}(\tilde{t}) + \lambda_2(\tilde{t})y(\tilde{t})f(y(\tilde{t})) > 0$, since $\lambda_1(\tilde{t}) > 0$ (by Lemma 3) and $\lambda_2(\tilde{t}) > 0$ (by the definition of the optimal control law (11)). But this is a contradiction, since arguing as in the previous lemma we know that $H(t) \leq 0$ for $t \in [\hat{t}, t_f]$. Therefore $\lambda_2 > 0$ for $t \in [0, t_f]$.

E. Proof of Lemma 5

As in the proof of Lemma 3, we observe that after some computations one obtains (Sage, 1968) $\dot{H}(t) = \lambda_1(t)\dot{\alpha}(t)f(y(t))(y(t)-x(t))$. Due to Lemma 3, the condition (7), either (5) or (6), and Lemma 1, the right-hand side of the above equality is nonnegative for $t \in [0, t_f]$. Since $H(t_f) = 0$, (according to (10)), we conclude that $H(t) \leq 0$ for all $t \in [0, t_f]$.

F. Proof of Lemma 6

We will prove the first result of Lemma 6 by contradiction. Suppose that there is a singular control during a certain time interval. Then, according to the optimal control law (11), we must have $c - \lambda_2 f(y)g(y-x) = 0$ during the same time interval. But the fact that $c > 0$ and Lemma 1 (positivity of $g(y-x)$) imply that $\lambda_2 > 0$ in the singular control.

Thus, in the singular control interval we have $H = \lambda_1 \dot{x} + \lambda_2 y f(y) > 0$, since $\lambda_2 > 0$ and $\lambda_1 > 0$ (by Lemmas 3 and 4), in contradiction with the result of Lemma 5.

Suppose now that there is a switching from $u = 0$ to $u = u_m$ at $t = \tau$. Then, the continuity in time of the state and adjoint variables and the optimal control law (11) imply that we must have $c - \lambda_2(\tau)f(y(\tau))g(y(\tau) - x(\tau)) = 0$. Again, the fact that $c > 0$ and Lemma 1 ($g(y-x) > 0$) yield $\lambda_2(\tau) > 0$. Thus, at the instant of switching we have $H(\tau) = \lambda_1(\tau)\dot{x}(\tau) + \lambda_2(\tau)y(\tau)f(y(\tau)) > 0$, since $\lambda_2(\tau) > 0$ and $\lambda_1(\tau) > 0$ (Lemmas 3 and 4), in contradiction with the result of Lemma 5. The same reasoning holds for the switching from $u = u_m$ to $u = 0$.

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