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Optimal control for a combination of cancer therapies in a model of cell competition*

Pauline Mazel[1], Walid Djema[2], Frédéric Grognard[3]

***Abstract*— We present a simple mathematical model of ordinary differential equations that describes the interaction between a healthy cell population and cancerous cell population. This model includes the effects on cell populations of chemotherapy and targeted therapy, which are two bounded control variables. We study this model and seek to optimize the fraction of healthy cells within the total cell population over a given therapy period. We apply the Pontryagin Maximum Principle (PMP) and establish the expressions of singular solutions in different interaction cases between healthy and cancer cells. Then, we use a direct optimization method to validate and illustrate our theoretical results.**

***Key words*— Optimal control, differential equations, cancer, chemotherapy, targeted therapy.**

I. Introduction

Cancer treatment is complex, and this disease remains a leading cause of death worldwide [1], [2]. In light of this, improving treatments is crucial, with many studies investigating its evolution under combined therapies.

In the following, we study a generic mathematical model as an initial step towards developing a more specific model of acute myeloid leukemia, which has one of the lowest survival rates among different leukemia types [3]. This disease, originating from hematopoietic cells, is primarily treated with chemotherapy. However, due to the resistance of cells to this treatment, alternatives must be considered [3]. Thus, with a better genomic understanding of cancers, recent years have seen the development of targeted therapies aimed at inhibiting the processes underlying cell formation and proliferation [4], [5].

The first model to utilize optimal control theory for chemotherapy in human tumors, developed by Swan and Vincent in 1977 [6], [7], has paved the way for the widespread study of combined treatment approaches, including chemotherapy, in cancer research. The combination of immunotherapy and chemotherapy has thus been studied by Ledzewicz et al. and Rihan et al. to model the interactions between the immune system and the tumor [8], [9]. Other combinations such as chemotherapy and tumor anti-angiogenesis have been proposed, the advantage of the latter being that it does not lead to drug resistance development [10]. Additionally, the use of chemotherapy and a ketogenic diet has been explored [11], [12]. Feizabadi et al. have, on the other hand, taken a more general interest in chemotherapy and its drug resistance by integrating other drugs that combat resistant cells [13].

Many works have focused on modeling two cell populations with different characteristics using ordinary differential equations [14], [15], [16]. We consider a similar approach here, by modeling a healthy cell population coexisting with a cancerous one. Our model is widely inspired by the PDE model in [17] (but see also [18], [19]), which was specifically designed to account for phenotypic heterogeneity in cell populations. However, as an initial step, we do not include cell heterogeneity in this work. Instead, we focus on analyzing the impact of a combination of treatments on cancer cells through a simpler mathematical model that includes two controls: chemotherapy and targeted therapy. These two treatments have proved indeed to be an interesting therapeutic approach [3], [20]. To derive optimal treatment strategies, we apply the Pontryagin Maximum Principle, which is a powerful theoretical tool to investigate this type of problems in cancer (see e.g. [16]).

The paper is organized as follows. In section II, we firstly introduce the competition system describing the dynamics of healthy cells and cancerous cells, we highlight its features and state main assumptions on the model parameters. Then, in section III, we formulate the optimal control problem and apply the Pontryagin Maximum Principle. Moreover, we analyze the singular solutions in section IV. Finally, we utilize direct optimization to illustrate our theoretical results and discuss the observed turnpike phenomenon in section V.

II. Development of the mathematical model

A. Description of the model

We consider a model describing the dynamics of two cell populations, a population of healthy cells x_h and a population of cancerous cells x_c, involving two anticancer treatments represented by the bounded control variables u_1 and u_2. The first one, u_1, stands for cytotoxic drugs (chemotherapy) while the second one, u_2, represents cytostatic drugs (targeted therapy). We assume that the u-values represent the effect of the associated drugs at their site of action.

To describe the dynamics of healthy and cancerous cells, we will consider the following generic model, which repre-

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[1]Pauline Mazel with Université Côte d'Azur, Inria MACBES Project-team, France pauline.mazel@inria.fr

[2]Walid Djema with Université Côte d'Azur, Inria BIOCORE Project-team, France walid.djema@inria.fr

[3]Frédéric Grognard with Université Côte d'Azur, Inria MACBES Project-team, France frederic.grognard@inria.fr

sents a generalized Lotka-Volterra system with inputs,

$$\begin{cases} \dot{x}_h = R_h(x_h, x_c, u_1, u_2)x_h, \\ \dot{x}_c = R_c(x_h, x_c, u_1, u_2)x_c, \end{cases} \tag{1}$$

where R_h and R_c represent the respective growth rates of x_h and x_c. These terms can be decomposed into: a term for the growth rate which depends on the treatments u_1 and u_2; and a term of competition dependent on x_h and x_c, as follows,

$$R_h(x_h, x_c, u_1, u_2) = M_h(u_1, u_2) - F_h(x_h, x_c),$$
$$R_c(x_h, x_c, u_1, u_2) = M_c(u_1, u_2) - F_c(x_h, x_c).$$

The controls involved in these dynamics are assumed to be bounded by maximum tolerated doses $u_1^{\max}$ and $u_2^{\max}$:

$$\forall t \geq 0, \quad 0 \leq u_1(t) \leq u_1^{\max} \quad \text{and} \quad 0 \leq u_2(t) \leq u_2^{\max}.$$

Following [17], we focus on the specific case where:

$$M_h(u_1, u_2) = \frac{\mu_h}{1 + \kappa_h u_2} - s_h u_1,$$
$$M_c(u_1, u_2) = \frac{\mu_c}{1 + \kappa_c u_2} - s_c u_1,$$

and

$$F_h(x_h, x_c) = p_{hh}x_h + p_{hc}x_c,$$
$$F_c(x_h, x_c) = p_{ch}x_h + p_{cc}x_c.$$

which leads to the dynamic system,

$$\begin{cases} \dot{x}_h = \left(\frac{\mu_h}{1 + \kappa_h u_2} - p_{hh}x_h - p_{hc}x_c - s_h u_1 \right) x_h, \\ \dot{x}_c = \left(\frac{\mu_c}{1 + \kappa_c u_2} - p_{ch}x_h - p_{cc}x_c - s_c u_1 \right) x_c. \end{cases} \tag{2}$$

The parameters are described in Table I. More precisely:

- The parameters $\mu_h > 0$ and $\mu_c > 0$ are the proliferation rates of the cell populations. These proliferation rates are reduced by cytostatic drugs u_2 and the parameters $\kappa_h > 0$ and $\kappa_c > 0$ represent the sensitivity to this drug.
- Competition within and between the populations is incorporated to this model with the terms $(p_{hh}x_h + p_{hc}x_c)x_h$ and $(p_{ch}x_h + p_{cc}x_c)x_c$, where $p_{hh}, p_{hc}, p_{ch}, p_{cc} \geq 0$.
- Sensitivity of the healthy and cancer cells to cytotoxic drugs is modelled by the parameters $s_h > 0$ and $s_c > 0$ respectively.

The fact that cancer cells proliferate more than healthy cells leads to $\mu_h < \mu_c$. Moreover, in the presence of targeted therapy, cancer cell proliferation must be slowed down. To have $\frac{\mu_h}{1+\kappa_h u_2} > \frac{\mu_c}{1+\kappa_c u_2}$ for some u_2, a necessary and sufficient condition is to assume $\frac{\mu_h}{\kappa_h} > \frac{\mu_c}{\kappa_c}$. Cancer cells are also expected to be more sensitive to cytotoxic drugs than healthy cells, and thus $s_c > s_h$.

***Assumptions** 1:* In the following, we consider the two hypotheses:

- $\mu_c > \mu_h$,
- $\frac{\mu_h}{\kappa_h} > \frac{\mu_c}{\kappa_c}$.

As a consequence of these assumptions, if we fix the value of u_1 and consider u_2 varying, we can observe that the presence of cytostatic drugs reduces the growth rate of cancer cells much more than that of healthy cells (Fig. 1).

TABLE I
DESCRIPTION OF THE MODEL PARAMETERS

Parameters	Descriptions
μ_h	Proliferation rate of healthy cells
μ_c	Proliferation rate of cancer cells
κ_h	Sensitivity of healthy cells to cytostatic drugs
κ_c	Sensitivity of cancer cells to cytostatic drugs
p_{hh}	Death rate of healthy cells due to the competition between healthy cells
p_{hc}	Death rate of healthy cells due to the competition between healthy cells and cancer cells
p_{ch}	Death rate of cancer cells due to the competition between healthy cells and cancer cells
p_{cc}	Death rate of cancer cells due to the competition between cancer cells
s_h	Sensitivity of healthy cells to cytotoxic drugs
s_c	Sensitivity of cancer cells to cytotoxic drugs

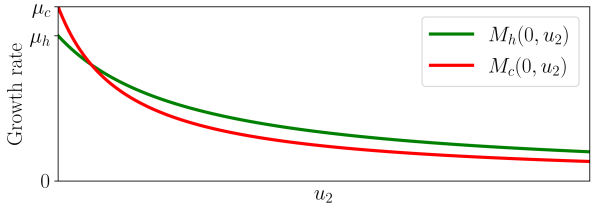

Fig. 1. Illustration of the growth rates without competition when $u_1 = 0$.

***Remark** 1:* The assumption $\frac{\mu_h}{\kappa_h} > \frac{\mu_c}{\kappa_c}$ gives us $\kappa_c > \kappa_h$, i.e., the cytostatic drug has a greater impact on cancer cells than on healthy cells.

B. Model investigation

A first interesting case is the one without competition. Indeed, in this system, cell populations are linked only via controls. By varying u_1 and u_2, we can make some noteworthy observations.

Without competition, i.e., $F_h = F_c = 0$, we are thus interested in studying the dynamics

$$\begin{cases} \dot{x}_h = M_h(u_1, u_2)x_h, \\ \dot{x}_c = M_c(u_1, u_2)x_c. \end{cases} \tag{3}$$

We define M for all $(u_1, u_2) \in [0, u_1^{\max}] \times [0, u_2^{\max}]$ the difference between the two growth rates M_h and M_c

$$\begin{aligned} M(u_1, u_2) =& M_h(u_1, u_2) - M_c(u_1, u_2) \\ =& \frac{\mu_h}{1 + \kappa_h u_2} - \frac{\mu_c}{1 + \kappa_c u_2} - (s_h - s_c)u_1. \end{aligned}$$

When considering the maximization of M through the simultaneous variation of u_1 and u_2, one can first remark that u_1 should be set at 0 or $u_1^{\max}$ if $s_h < s_c$ or $s_h > s_c$.

Indeed, differentiating M with respect to u_1 leads to

$$\frac{\partial M}{\partial u_1} = -(s_h - s_c).$$

Thus, when $s_h < s_c$, taking $u_1 = u_1^{\max}$ maximizes M. On the contrary, when $s_h > s_c$, taking $u_1 = 0$ maximizes M.

In the cases $s_h \neq s_c$, we are then interested in maximizing M with respect to u_2 in order to quantify what we illustrated in Fig. 2. To do this, we calculate

$$\frac{\partial M}{\partial u_2}(u_1, u_2) = -\frac{\kappa_h \mu_h}{(1+\kappa_h u_2)^2} + \frac{\kappa_c \mu_c}{(1+\kappa_c u_2)^2}.$$

We solve

$$\begin{aligned}
&\frac{\partial M}{\partial u_2}(u_1, u_2) = 0 \\
\iff & -\frac{\kappa_h \mu_h}{(1+\kappa_h u_2)^2} + \frac{\kappa_c \mu_c}{(1+\kappa_c u_2)^2} = 0 \\
\iff & u_2^2(-\mu_h \kappa_h \kappa_c^2 + \mu_c \kappa_h^2 \kappa_c) \\
& + u_2(-2\mu_h \kappa_h \kappa_c + 2\mu_c \kappa_h \kappa_c) \\
& - \mu_h \kappa_h + \mu_c \kappa_c = 0.
\end{aligned}$$

We obtain two solutions

$$u_2^{M\pm} = \frac{\kappa_h \kappa_c(\mu_h - \mu_c) \pm \sqrt{\mu_h \mu_c \kappa_h \kappa_c (\kappa_c - \kappa_h)^2}}{\kappa_h^2 \kappa_c^2 (-\frac{\mu_h}{\kappa_h} + \frac{\mu_c}{\kappa_c})}.$$

According to Assumptions 1, the denominator is negative as is the first term of the numerator, hence u_2^{M-} is positive. Also, since $\kappa_h \kappa_c(\mu_c - \mu_h) < \sqrt{\mu_h \mu_c \kappa_h \kappa_c (\kappa_c - \kappa_h)^2}$ is equivalent to $\left(\frac{\mu_h}{\kappa_h} - \frac{\mu_c}{\kappa_c}\right)\kappa_h \kappa_c(\mu_h \kappa_h - \mu_c \kappa_c) < 0$, the assumptions imply that u_2^{M+} is negative. Hence $\frac{\partial M}{\partial u_2}(u_1, u_2) = 0$ has a unique positive solution.

We denote this solution $\overline{u}_2$ in the following, and we assume $u_2^{\max}$ to be greater than this solution (see Fig. 2). The two cases $s_h < s_c$ and $s_h > s_c$ are then illustrated for the (u_1, u_2) maximization in Fig. 3.

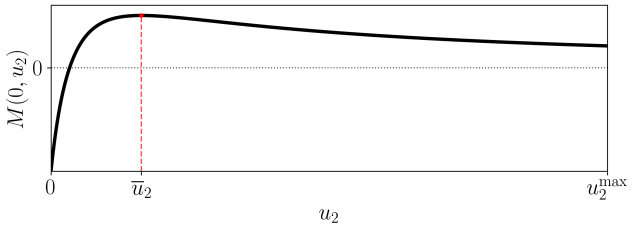

Fig. 2. Illustration of function M without competition when $u_1 = 0$.

III. Optimal control problem

A. Formulation of the optimal control problem

We want to maximize the proportion of healthy cells over a fixed therapy time, which we denote T_f.

To this end, we define

$$\mathcal{U}_{T_f} := \{(u_1, u_2) \in L^\infty([0, T_f])^2 \mid 0 \leq u_i \leq u_i^{\max}, i = 1, 2\}$$

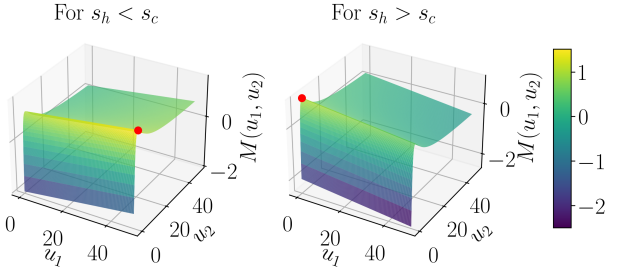

Fig. 3. Maximization of function M by varying u_1 and u_2, on the left, for $s_h < s_c$ and on the right, for $s_h > s_c$ (the red dot is the maximum).

the set of admissible controls. We are thus interested in finding the optimal controls u_1 and u_2 that satisfy

$$\max_{(u_1,u_2)\in\mathcal{U}_{T_f}} \int_0^{T_f} \frac{x_h}{x_h + x_c} \tag{OCP}$$

subject to the dynamics (1) and verifying the initial condition $(x_h(0), x_c(0)) = (x_{h_0}, x_{c_0}) \in {\mathbb{R}_+^*}^2$.

B. Application of the Pontryagin's Maximum Principle

Denote the state vector as $\boldsymbol{x} = (x_h, x_c)$ and the co-state vector as $\boldsymbol{\lambda} = (\lambda_h, \lambda_c)$. Let $\lambda_0 \in \mathbb{R}$.
We denote H the Pontryagin Hamiltonian function, given by:

$$\begin{aligned}
&H(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) \\
=&\lambda_0 \frac{x_h}{x_h + x_c} + \lambda_h R_h(\boldsymbol{x}, u_1, u_2) x_h + \lambda_c R_c(\boldsymbol{x}, u_1, u_2) x_c.
\end{aligned}$$

If the control $(u_1, u_2) \in \mathcal{U}_{T_f}$ associated to the trajectory (x_h, x_c) is optimal on $[0, T_f]$ then there exists two adjoint states $\lambda_h : [0, T_f] \longrightarrow \mathbb{R}$ and $\lambda_c : [0, T_f] \longrightarrow \mathbb{R}$ absolutely continuous and a real number $\lambda_0 \geq 0$ such that $(\lambda_0, \lambda_h, \lambda_c)$ is non-trivial and such that

$$\begin{cases}
\dot{\lambda}_h = -\dfrac{\partial H}{\partial x_h}(x_h, x_c, u_1, u_2, \lambda_h, \lambda_c), \\
\dot{\lambda}_c = -\dfrac{\partial H}{\partial x_c}(x_h, x_c, u_1, u_2, \lambda_h, \lambda_c).
\end{cases}$$

We have the condition of maximization

$$H(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) = \max_{(v_1,v_2)\in\mathcal{U}_{T_f}} H(\boldsymbol{x}, v_1, v_2, \boldsymbol{\lambda}).$$

The Pontryagin Hamiltonian function can be expressed as a sum of three terms as follows:

$$H(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) = h_0(\boldsymbol{x}, \boldsymbol{\lambda}) + h_1(\boldsymbol{x}, u_1, \boldsymbol{\lambda}) + h_2(\boldsymbol{x}, u_2, \boldsymbol{\lambda})$$

where

- $h_0(\boldsymbol{x}, \boldsymbol{\lambda}) = \lambda_0 \frac{x_h}{x_h + x_c} + \lambda_h(-p_{hh} x_h - p_{hc} x_c) x_h + \lambda_c(-p_{ch} x_h - p_{cc} x_c) x_c$,
- $h_1(\boldsymbol{x}, u_1, \boldsymbol{\lambda}) = -(\lambda_h s_h x_h + \lambda_c s_c x_c) u_1$,
- $h_2(\boldsymbol{x}, u_2, \boldsymbol{\lambda}) = \lambda_h(\frac{\mu_h}{1+\kappa_h u_2}) x_h + \lambda_c(\frac{\mu_c}{1+\kappa_c u_2}) x_c$.

Note that the Hamiltonian is affine in u_1.

The co-state equations are given by

$$\begin{cases} \dot{\lambda}_h = -\lambda_0 \dfrac{x_c}{(x_h+x_c)^2} + 2\lambda_h p_{hh} x_h + \lambda_h p_{hc} x_c \\ \qquad + \lambda_c p_{ch} x_c - \lambda_h \dfrac{\mu_h}{1+\kappa_h u_2} + \lambda_h s_h u_1, \\ \dot{\lambda}_c = \lambda_0 \dfrac{x_h}{(x_h+x_c)^2} + \lambda_h p_{hc} x_h + \lambda_c p_{ch} x_h \\ \qquad + 2\lambda_c p_{cc} x_c - \lambda_c \dfrac{\mu_c}{1+\kappa_c u_2} + \lambda_c s_c u_1. \end{cases} \tag{4}$$

Since the final point $(x_h(T_f), x_c(T_f))$ is free, the transversality conditions are

$$\lambda_h(T_f) = 0 \text{ and } \lambda_c(T_f) = 0. \tag{5}$$

If $\lambda_0 = 0$, then $\lambda_h = \lambda_c = 0$ for all times due to (4) and (5), and Pontryagin's Maximum Principle does not apply. Therefore, we consider normal extremals with $\lambda_0 = 1$.

For the following, we define the switching function Φ_1 by $\Phi_1 = \frac{\partial H}{\partial u_1} = \frac{\partial h_1}{\partial u_1}$ and we define also the function Φ_2 by $\Phi_2 = \frac{\partial H}{\partial u_2} = \frac{\partial h_2}{\partial u_2}$.

The optimal controls u_1^* and u_2^* then verify for $t \in [0, T_f]$:

$$u_1^*(t) = \begin{cases} 0 & \text{if } \Phi_1(t) < 0, \\ u_1^s(t) & \text{if } \Phi_1(t) = 0, \\ u_1^{\max} & \text{if } \Phi_1(t) > 0, \end{cases} \tag{6}$$

and

$$u_2^*(t) = \begin{cases} 0 & \text{if } \Phi_2(t) < 0, \\ u_2^s(t) & \text{if } \Phi_2(t) = 0, \\ u_2^{\max} & \text{if } \Phi_2(t) > 0. \end{cases} \tag{7}$$

where the expressions of u_1^s and u_2^s have to be determined.

IV. Analysis of the singular solutions

In order to fully-characterize the optimal solutions of (OCP), we will analyze our model in two different cases: with and without competition between cells. In the case without competition, the dynamics of healthy and cancer cells are however connected via the two control variables.

A. Study of the case without competition

Firstly, we consider the case without competition, when $F_h = F_c = 0$.

***Theorem** 1:* Assume $F_h = F_c = 0$.

(i) If $s_h \neq s_c$, there is no singular arc for u_1.

(ii) Over $[0, T_f]$, the optimal control in (7) is $u_2^* = u_2^s = \overline{u}_2$.

Proof:

(i) The switching function is in this case

$$\begin{aligned} \Phi_1(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) =& \frac{\partial h_1}{\partial u_1}(\boldsymbol{x}, u_1, \boldsymbol{\lambda}) \\ =& -(\lambda_h s_h x_h + \lambda_c s_c x_c) \end{aligned}$$

One can remark the presence of the terms $x_h\lambda_h$ and $x_c\lambda_c$ in the expression. We define for all $x_h, x_c, \lambda_h, \lambda_c \in \mathbb{R}$ the function $\Psi(\boldsymbol{x}, \boldsymbol{\lambda}) = \lambda_h x_h + \lambda_c x_c$. Differentiating Ψ with respect to time, we get $\dot{\Psi}(\boldsymbol{x}, \boldsymbol{\lambda}) = 0$, and thus Ψ is constant. The transversality conditions give $\Psi(x_h(T_f), x_c(T_f), \lambda_h(T_f), \lambda_c(T_f)) = 0$ and we conclude that $\Psi = 0$. This leads to $\Phi_1(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) = -\lambda_h x_h(s_h - s_c)$ which is non-zero assuming $s_h \neq s_c$.

(ii) We set for all $u_2 \in [0, u_2^{\max}]$

$$m_h(u_2) = \frac{\mu_h}{1+\kappa_h u_2} \quad \text{and} \quad m_c(u_2) = \frac{\mu_c}{1+\kappa_c u_2}$$

and we get

$$\begin{aligned} \Phi_2(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) =& \frac{\partial h_2}{\partial u_2}(\boldsymbol{x}, u_2, \boldsymbol{\lambda}) \\ =& \lambda_h m_h'(u_2) x_h + \lambda_c m_c'(u_2) x_c. \end{aligned}$$

Then, since (i) states that, $\lambda_h x_h + \lambda_c x_c = 0$, we end up with,

$$\begin{aligned} \Phi_2(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) =& \lambda_h m_h'(u_2) x_h + \lambda_c m_c'(u_2) x_c \\ =& \lambda_h x_h (m_h'(u_2) - m_c'(u_2)) \\ =& \lambda_h x_h \frac{\partial M}{\partial u_2}(u_1, u_2). \end{aligned}$$

Consequently, since $\lambda_h x_h \neq 0$, the previous equality leads to $\partial M(u_1, u_2)/\partial u_2 = 0$, and thus $u_2^* = u_2^s = \overline{u}_2$. ■

B. Study of the case with competition

With competition, it is interesting to note that certain subcases lead to results similar to those without competition. Therefore, before addressing the general case, let us first examine the scenario where the competition terms offset each other.

1) Competition of the form $F_h = F_c$: This is equivalent to consider that $p_{hh} = p_{ch}$ and $p_{hc} = p_{cc}$. In this particular scenario, we prove similar results as in Theorem 1.

***Theorem** 2:* Assume $F_h = F_c$.

(i) If $s_h \neq s_c$, there is no singular arc for u_1.

(ii) Over $[0, T_f]$, the optimal control in (7) is $u_2^* = u_2^s = \overline{u}_2$.

Proof:

(i) We define for all $x_h, x_c, \lambda_h, \lambda_c \in \mathbb{R}$ the function $\Psi(\boldsymbol{x}, \boldsymbol{\lambda}) = \lambda_h x_h + \lambda_c x_c$.
Differentiating with respect to time,

$$\dot{\Psi}(\boldsymbol{x}, \boldsymbol{\lambda}) = (p_{hh} x_h + p_{hc} x_c)(\lambda_h x_h + \lambda_c x_c),$$

that is

$$\dot{\Psi}(\boldsymbol{x}, \boldsymbol{\lambda}) = (p_{hh} x_h + p_{hc} x_c)\Psi(\boldsymbol{x}, \boldsymbol{\lambda}).$$

Since the null function is solution of the differential equation and the transversality conditions give $\Psi(x_h(T_f), x_c(T_f), \lambda_h(T_f), \lambda_c(T_f)) = 0$, we conclude that $\Psi = 0$. We can directly deduce from the relation $\Psi = 0$ and the expression of the switching function that

$$\Phi_1(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) = -\lambda_h x_h (s_h - s_c)$$

and conclude as in Theorem 1, that there is no singular arc for u_1 if $s_h \neq s_c$.

(ii) Similarly to Theorem 1 (ii), we obtain

$$\begin{aligned} \Phi_2(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) =& \lambda_h m_h'(u_2) x_h + \lambda_c m_c'(u_2) x_c \\ =& \lambda_h x_h (m_h'(u_2) - m_c'(u_2)) \\ =& \lambda_h x_h \frac{\partial M}{\partial u_2}(u_1, u_2), \end{aligned}$$

which leads to $u_2^* = u_2^s = \overline{u}_2$.

■

2) General competition (arbitrary F_h and F_c): We can generalize our calculations to the case with competition.

***Theorem** 3:* We set

$$\Delta := -\mu_h\mu_c\kappa_h\kappa_c\lambda_h x_h\lambda_c x_c(\kappa_c - \kappa_h)^2 \tag{8}$$

and assume $\Delta \geq 0$ and $\mu_h\kappa_c\lambda_h x_h + \mu_c\kappa_h\lambda_c x_c \neq 0$. In the case with competition, the expressions for u_2 provided by $\Phi_2 = 0$ are given by:

$$u_2^{s\pm} = \frac{-(\mu_h\kappa_h\kappa_c\lambda_h x_h + \mu_c\kappa_h\kappa_c\lambda_c x_c) \pm \sqrt{\Delta}}{(\mu_h\kappa_h\kappa_c^2\lambda_h x_h + \mu_c\kappa_h^2\kappa_c\lambda_c x_c)}. \tag{9}$$

Proof: We solve

$$\begin{aligned}
&\Phi_2(\boldsymbol{x}, u_1, u_2, \boldsymbol{\lambda}) = 0\\
\iff &-\lambda_h\frac{\kappa_h\mu_h}{(1+\kappa_h u_2)^2}x_h - \lambda_c\frac{\kappa_c\mu_c}{(1+\kappa_c u_2)^2}x_c = 0\\
\iff &u_2^2(\mu_h\kappa_h\kappa_c^2\lambda_h x_h + \mu_c\kappa_h^2\kappa_c\lambda_c x_c)\\
&+ u_2(2\mu_h\kappa_h\kappa_c\lambda_h x_h + 2\mu_c\kappa_h\kappa_c\lambda_c x_c)\\
&+ \mu_h\kappa_h\lambda_h x_h + \mu_c\kappa_c\lambda_c x_c = 0.
\end{aligned}$$

If $\mu_h\kappa_h\kappa_c^2\lambda_h x_h + \mu_c\kappa_h^2\kappa_c\lambda_c x_c \neq 0$, i.e., $\mu_h\kappa_c\lambda_h x_h + \mu_c\kappa_h\lambda_c x_c \neq 0$, we set Δ given in (8) from Theorem 3 which leads to the expressions of the two solutions in (9).

■

***Remark** 2:* At this stage, note that we cannot ensure that the control u_2^s is admissible, i.e., that $u_2^s(t) \in [0, u_2^{\max}]$ for all $t \in [0, T_f]$. However, in the next section, we show numerically that the singular arc is mostly admissible since it exhibits a turnpike-like behavior around an admissible control value.

V. Dynamics of the Solutions

A. Direct optimization

We illustrate our theoretical results using simulations to qualitatively observe the behavior of our populations and controls. To this end, we choose parameters that satisfy Assumptions 1, namely $\mu_c > \mu_h$ and $\frac{\mu_h}{\kappa_h} > \frac{\mu_c}{\kappa_c}$. Unless specified otherwise, the parameters used for the simulations are provided in Table II, and in that case we have $\overline{u}_2 \approx 2.4$. We can take $u_2^{\max} = 15$, greater than $\overline{u}_2$, as illustrated in Fig. 2 with our parameters. Additionally, we choose $u_1^{\max} = 15$ and the initial conditions are given in Table III. For the simulations of our optimal control problem (OCP), we employ a direct method and reconstruct our analysis from the states, co-states, and controls provided by the `Bocop` software [21], [22], whose settings are in Table IV.

TABLE II
The Model Parameters

	$\mu_\cdot$	$\kappa_\cdot$	$p_{\cdot h}$	$p_{\cdot c}$	$s_\cdot$
Healthy cells x_h	10	0.5	0.03	0.02	0.04
Cancerous cells x_c	12	1	0.02	0.01	0.05

As expected, without competition, the chemotherapy dose u_1 is at its maximum $u_1^{\max} = 15$ as we are in the case $s_h < s_c$ (Fig. 4). For the cytostatic dose u_2, we obtain a constant for u_2^s corresponding to the expression of $\overline{u}_2$ calculated previously (function Φ_2 null). The combination of targeted therapy and chemotherapy enabled us to restrict the cancer cell population compared to the healthy cell population, but without eliminating it.

TABLE III
Initial Conditions and Control Bounds

x_{h_0}	x_{c_0}	Control u_1	Control u_2
150	50	$[0, u_1^{\max} = 15]$	$[0, u_2^{\max} = 15]$

TABLE IV
`Bocop` Settings.

Discretization method	Time steps	NLP Tolerance
`Midpoint`	5000	$< 10^{-14}$

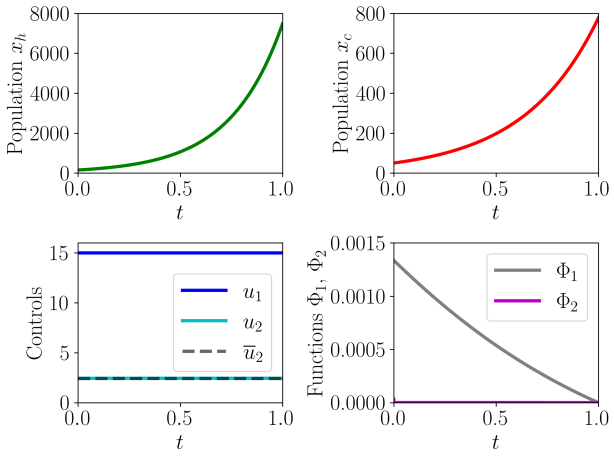

Fig. 4. Solutions of (OCP) without competition: parameters p_{hh} p_{hc}, p_{ch}, p_{cc} are zero and other parameters are given in Table II and initial conditions in Table III. At the top, trajectories of healthy population and cancerous population. At the bottom left, trajectories of optimal controls and comparison of u_2 with the expression found for $\overline{u}_2$. At the bottom right, the functions $\Phi_1 = \partial H/\partial u_1$ and $\Phi_2 = \partial H/\partial u_2$.

By introducing slight competition in the specific case $p_{hh} = p_{ch} = 0.03$ and $p_{hc} = p_{cc} = 0.02$, the trajectories of u_1 and u_2 are similar to those without competition as expected by Theorem 2. On the other hand, the behavior of the cellular populations changes, leading to the elimination of the cancerous cell population (Fig. 5). In this way, it is noteworthy that competition helps constrain the cellular populations.

By increasing the value of the final time T_f in the general case of competition (Fig. 6), we observe a solution u_2^* distant from the solution $\overline{u}_2$, before eventually converging to this value at the final time. In our scenario, the population of cancerous cells eventually goes extinct, as in the previous example.

B. Static OCP

Denote $\mathcal{X} = \mathbb{R}_+^2 \setminus \{(0,0)\}$ and $\mathcal{U} = [0, u_1^{\max}] \times [0, u_2^{\max}]$. The static optimal control problem [23] associated

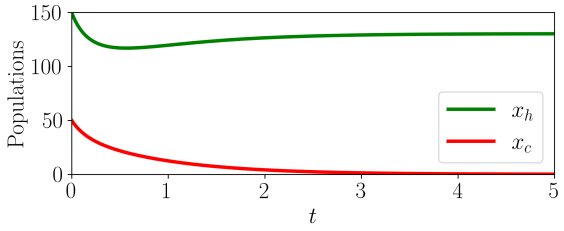

Fig. 5. Trajectories of healthy population and cancerous population for (OCP) when $F_h = F_c$: competition parameters are given by $p_{hh} = p_{ch} = 0.03$ and $p_{hc} = p_{cc} = 0.02$, other parameters are in Table II and initial conditions in Table III.

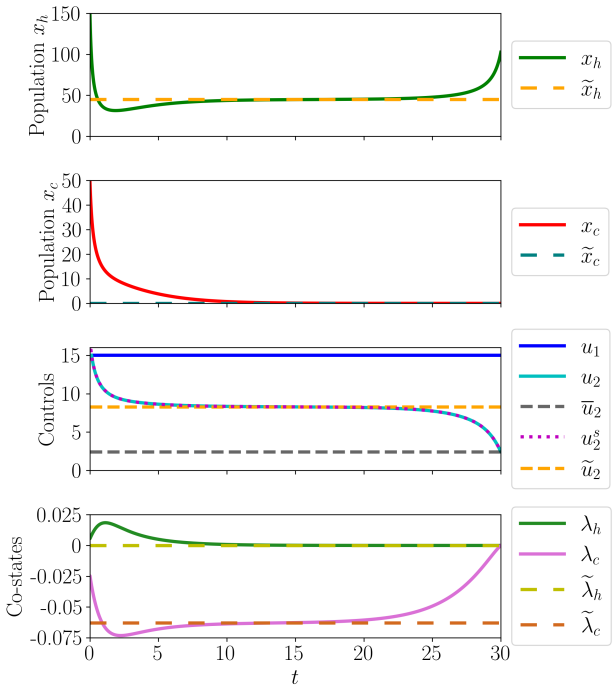

Fig. 6. Solutions of (OCP) with competition: parameters are given in Table II and initial conditions in Table III. Two first figures: trajectories of healthy population and cancerous population. Third figure: trajectories of optimal control u_1 and u_2 and comparison the expression of u_2^s and the one found for $\overline{u}_2$. At the bottom: trajectories of co-states. The static points have been added.

with (OCP) is

$$\max_{(x_h,x_c,u_1,u_2)\in\mathcal{X}\times\mathcal{U}} \frac{x_h}{x_h+x_c}$$

under the constraint

$$\begin{cases} R_h(x_h,x_c,u_1,u_2)x_h = 0, \\ R_c(x_h,x_c,u_1,u_2)x_c = 0. \end{cases}$$

We assume that this maximization problem has a solution $(\widetilde{\boldsymbol{x}},\widetilde{\boldsymbol{u}}) = (\widetilde{x}_h,\widetilde{x}_c,\widetilde{u}_1,\widetilde{u}_2)$. According to the Lagrange multipliers rule, there exists $\widetilde{\boldsymbol{\lambda}} = (\widetilde{\lambda}_h,\widetilde{\lambda}_c) \in \mathbb{R}^2$ such that

$$\begin{cases} \dfrac{\partial H}{\partial \boldsymbol{\lambda}}(\widetilde{\boldsymbol{x}},\widetilde{\boldsymbol{u}},\widetilde{\boldsymbol{\lambda}}) = 0, \\ -\dfrac{\partial H}{\partial \boldsymbol{x}}(\widetilde{\boldsymbol{x}},\widetilde{\boldsymbol{u}},\widetilde{\boldsymbol{\lambda}}) = 0, \\ \dfrac{\partial H}{\partial \boldsymbol{u}}(\widetilde{\boldsymbol{x}},\widetilde{\boldsymbol{u}},\widetilde{\boldsymbol{\lambda}}) = 0. \end{cases} \tag{10}$$

Solving this system leads us to four different cases upon whether $\widetilde{x}_h$ and $\widetilde{x}_c$ vanish or not. The best static solution is the one corresponding to $\widetilde{x}_c = 0$. Depending on the parameters, this solution may not be possible, and we end up with a strictly positive solution that satisfies the maximization objective.

Considering the case where $\widetilde{x}_c$ is null, we find after solving system (10)

$$\begin{cases} \widetilde{x}_h = \frac{1}{p_{hh}}\left(\frac{\mu_h}{1+\kappa_h\widetilde{u}_2} - s_h\widetilde{u}_1\right), \\ \widetilde{x}_c = 0, \\ \widetilde{\lambda}_h = 0, \\ \widetilde{\lambda}_c = -\frac{1}{p_{ch}\widetilde{x}_h^2 - x_h\frac{\mu_c}{1+\kappa_c\widetilde{u}_2} + x_h s_c\widetilde{u}_1}. \end{cases} \tag{11}$$

These solutions, dependent on $\widetilde{u}_1$ and $\widetilde{u}_2$, will consequently rely on the initial conditions.

When the final time T_f is large, the optimal solution $(\boldsymbol{x},\boldsymbol{u},\boldsymbol{\lambda})$ remains close to the static point $(\widetilde{\boldsymbol{x}},\widetilde{\boldsymbol{u}},\widetilde{\boldsymbol{\lambda}})$.

This is the turnpike phenomenon, more formally characterized by the following inequality [23]:

$$\begin{aligned} \|\boldsymbol{x}(t)-\widetilde{\boldsymbol{x}}\| + \|\boldsymbol{\lambda}(t)-\widetilde{\boldsymbol{\lambda}}\| + \|\boldsymbol{u}(t)-\widetilde{\boldsymbol{u}}\| \\ \leq C_1(e^{-C_2 t} + e^{-C_2(T_f-t)}) \end{aligned}$$

for all $t \in [0,T_f]$, where C_1 and C_2 are positive constants.

More precisely, this turnpike phenomenon is illustrated in Fig. 6 for the states, co-states and controls, when T_f is sufficiently large. Initially, during a short time interval, we observe that the solution moves from the initial condition towards the static point (11). Then, for a much longer period, the solution remains stationary at this static point (11) before finally transitioning from the stationary point to the final state that satisfies the transversality conditions. Direct optimization also shows that as T_f increases, the transient phases do not extend, and the solution spends more time on the turnpike arc (the static point).

C. Saturating control

In Fig. 6, note also that the obtained optimal control u_2 significantly exceeds $\overline{u}_2$. In this case, if we take a lower value for $u_2^{\max}$, such that $u_2^{\max}$ is lower than the value of $\widetilde{u}_2$ in Fig. 6, then a bang arc occurs instead of the singular one. This situation is illustrated in Fig. 7, where we set $u_2^{\max} = 7$. This bang inevitably leads to a lower cost than when there is no saturation. Furthermore, note that the value of x_h and x_c when $u_2^{\max} = 7$ is higher.

VI. Discussion and Conclusion

We studied an OCP based on a model describing the dynamics of healthy and cancer cell populations under the effect of cytotoxic and cytostatic drug concentrations. While this system is limited in capturing the high complexity of cell interactions, it provides a foundation for further improvements. It allowed us firstly to gain a better understanding of the cell dynamics in the absence of competition between cancer and healthy cells, focusing on maximizing the proportion of healthy cells. Applying the PMP allowed us to derive expressions for some singular solutions. When using

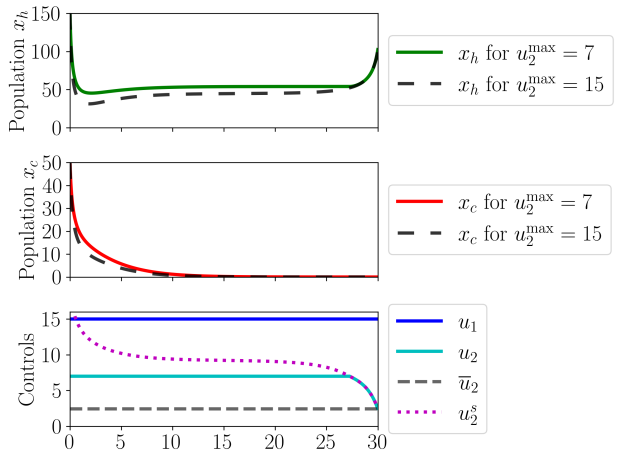

Fig. 7. Solutions of (OCP) with competition: parameters are given in Table II and initial conditions in Table III. At the top, trajectories of healthy and cancerous populations for $u_2^{\max} = 7$ and comparison with the trajectories when $u_2^{\max} = 15$. At the bottom, trajectories of optimal controls when $u_2^{\max} = 7$ and comparison of u_2 with the expression found for $\overline{u}_2$.

sufficiently high maximum tolerated doses in our numerical results (through direct methods), singular arcs emerged in the optimal solutions for cytostatic drugs.

This contribution focused on a simplified system involving only two cell populations: healthy and cancerous cells. However, cancer is more heterogeneous; cellular phenotypic composition evolves over time, in particular during treatment, due to genetic and epigenetic modifications [24], [25], [26], [27], [28]. Therefore, incorporating such phenomena, among others, into the ODE model will be the focus of future work.

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