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

Pauline Mazel<sup>1</sup>, Walid Djema<sup>2</sup>, Frédéric Grogard<sup>3</sup>

**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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sents a generalized Lotka-Volterra system with inputs,

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

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,

$$\begin{aligned} R_h(x_h, x_c, u_1, u_2) &= M_h(u_1, u_2) - F_h(x_h, x_c), \\ R_c(x_h, x_c, u_1, u_2) &= M_c(u_1, u_2) - F_c(x_h, x_c). \end{aligned}$$

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:

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

and

$$\begin{aligned} F_h(x_h, x_c) &= p_{hh}x_h + p_{hc}x_c, \\ F_c(x_h, x_c) &= p_{ch}x_h + p_{cc}x_c. \end{aligned}$$

which leads to the dynamic system,

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

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

TABLE I  
DESCRIPTION OF THE MODEL PARAMETERS

Parameters	Descriptions
$\mu_h$	Proliferation rate of healthy cells
$\mu_c$	Proliferation rate of cancer cells
$\kappa_h$	Sensitivity of healthy cells to cytostatic drugs
$\kappa_c$	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

the presence of cytostatic drugs reduces the growth rate of cancer cells much more than that of healthy cells (Fig. 1).

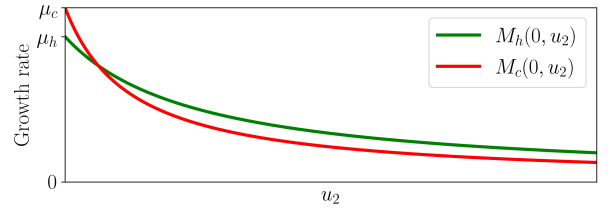


Fig. 1. Illustration of the growth rates without competition when  $u_1 = 0$ .

**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

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

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

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

We obtain two solutions

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

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  $(\frac{\mu_h}{\kappa_h} - \frac{\mu_c}{\kappa_c}) \kappa_h \kappa_c (\mu_h \kappa_h - \mu_c \kappa_c) < 0$ , 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  $\bar{u}_2$  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.

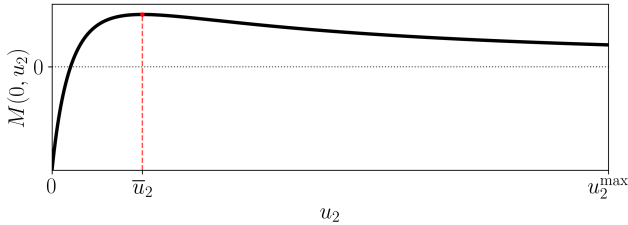


Fig. 2. Illustration of function  $M$  without competition when  $u_1 = 0$ .

### 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

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

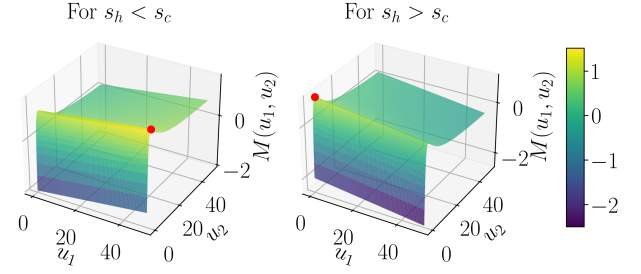


Fig. 3. Maximization of function  $M$  by varying  $u_1$  and  $u_2$ , on the left, for  $s_h < s_c$  and on the right, for  $s_h > s_c$  (the red dot is the maximum).

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

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

subject to the dynamics (1) and verifying the initial condition  $(x_h(0), x_c(0)) = (x_{h0}, x_{c0}) \in \mathbb{R}_+^2$ .

#### B. Application of the Pontryagin's Maximum Principle

Denote the state vector as  $\mathbf{x} = (x_h, x_c)$  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:

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

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  $\lambda_h : [0, T_f] \rightarrow \mathbb{R}$  and  $\lambda_c : [0, T_f] \rightarrow \mathbb{R}$  absolutely continuous and a real number  $\lambda_0 \geq 0$  such that  $(\lambda_0, \lambda_h, \lambda_c)$  is non-trivial and such that

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

We have the condition of maximization

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

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

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

where

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

Note that the Hamiltonian is affine in  $u_1$ .

The co-state equations are given by

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

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

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

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  $\Phi_1$  by  $\Phi_1 = \frac{\partial H}{\partial u_1} = \frac{\partial h_1}{\partial u_1}$  and we define also the function  $\Phi_2$  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  $t \in [0, T_f]$ :

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

and

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

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  $u_2^* = u_2^s = \bar{u}_2$ .

*Proof:*

- (i) The switching function is in this case

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

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  $\Psi(x, \lambda) = \lambda_h x_h + \lambda_c x_c$ . Differentiating  $\Psi$  with respect to time, we get  $\dot{\Psi}(x, \lambda) = 0$ , and thus  $\Psi$  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  $\Phi_1(x, u_1, u_2, \lambda) = -\lambda_h x_h (s_h - s_c)$  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

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

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

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

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  $u_2^* = u_2^s = \bar{u}_2$ . ■

##### 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  $u_2^* = u_2^s = \bar{u}_2$ .

*Proof:*

- (i) We define for all  $x_h, x_c, \lambda_h, \lambda_c \in \mathbb{R}$  the function  $\Psi(x, \lambda) = \lambda_h x_h + \lambda_c x_c$ .

Differentiating with respect to time,

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

that is

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

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

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

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

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

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

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

**Theorem 3:** We set

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

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:

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

*Proof:* We solve

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

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  $\Delta$  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  $\bar{u}_2 \approx 2.4$ . We can take  $u_2^{\max} = 15$ , greater than  $\bar{u}_2$ , 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

	$\mu$	$\kappa$	$p_h$	$p_c$	$s$
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

TABLE III  
INITIAL CONDITIONS AND CONTROL BOUNDS

$x_{h0}$	$x_{c0}$	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	$< 10^{-14}$

$s_h < s_c$  (Fig. 4). For the cytostatic dose  $u_2$ , we obtain a constant for  $u_2^s$  corresponding to the expression of  $\bar{u}_2$  calculated previously (function  $\Phi_2$  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.

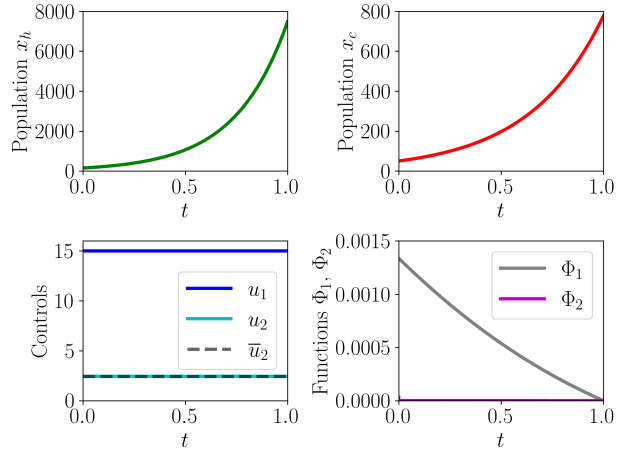


Fig. 4. Solutions of (OCP) without competition: parameters  $p_{hh}$ ,  $p_{ch}$ ,  $p_{cc}$  are zero and other parameters are given in Table II and initial conditions in Table III. At the top, trajectories of healthy population and cancerous population. At the bottom left, trajectories of optimal controls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

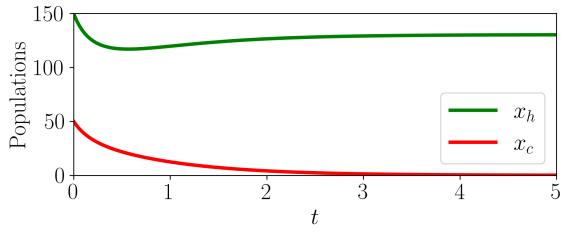


Fig. 5. Trajectories of healthy population and cancerous population for (OCP) when  $F_h = F_c$ : competition parameters are given by  $p_{hh} = p_{ch} = 0.03$  and  $p_{hc} = p_{cc} = 0.02$ , other parameters are in Table II and initial conditions in Table III.

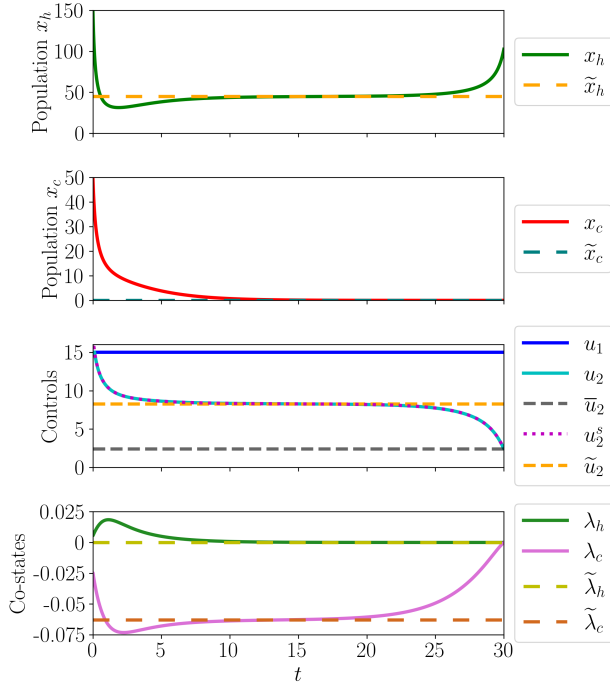


Fig. 6. Solutions of (OCP) with competition: parameters are given in Table II and initial conditions in Table III. Two first figures: trajectories of healthy population and cancerous population. Third figure: trajectories of optimal control  $u_1$  and  $u_2$  and comparison the expression of  $u_2^s$  and the one found for  $\tilde{u}_2$ . 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  $(\tilde{x}, \tilde{u}) = (\tilde{x}_h, \tilde{x}_c, \tilde{u}_1, \tilde{u}_2)$ . According to the Lagrange multipliers rule, there exists  $\tilde{\lambda} = (\tilde{\lambda}_h, \tilde{\lambda}_c) \in \mathbb{R}^2$  such that

$$\begin{cases} \frac{\partial H}{\partial \lambda}(\tilde{x}, \tilde{u}, \tilde{\lambda}) = 0, \\ -\frac{\partial H}{\partial x}(\tilde{x}, \tilde{u}, \tilde{\lambda}) = 0, \\ \frac{\partial H}{\partial u}(\tilde{x}, \tilde{u}, \tilde{\lambda}) = 0. \end{cases} \quad (10)$$

Solving this system leads us to four different cases upon whether  $\tilde{x}_h$  and  $\tilde{x}_c$  vanish or not. The best static solution is the one corresponding to  $\tilde{x}_c = 0$ . 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  $\tilde{x}_c$  is null, we find after solving system (10)

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

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

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

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

$$\|x(t) - \tilde{x}\| + \|\lambda(t) - \tilde{\lambda}\| + \|u(t) - \tilde{u}\| \leq C_1(e^{-C_2 t} + e^{-C_2(T_f - t)})$$

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  $\bar{u}_2$ . In this case, if we take a lower value for  $u_2^{\max}$ , such that  $u_2^{\max}$  is lower than the value of  $\tilde{u}_2$  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



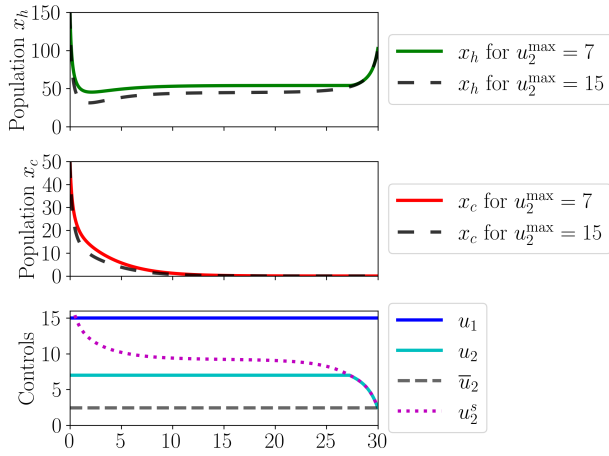


Fig. 7. Solutions of (OCP) with competition: parameters are given in Table II and initial conditions in Table III. At the top, trajectories of healthy and cancerous populations for  $u_2^{\max} = 7$  and comparison with the trajectories when  $u_2^{\max} = 15$ . At the bottom, trajectories of optimal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

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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