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State-Constrained Optimal Control Applied to Cell-Cycle-Specific Cancer Chemotherapy

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Abstract. In this paper, the optimal drug injection problem arising in cancer treatment by cell-cycle-specific chemotherapy is investigated. It is shown that this problem can be approximately solved up to any desired precision by using an indexed family of state-unconstrained optimal control problems. The existence of solutions is proved and the resulting approximation is characterized by appropriate two-sides inequalities. Simulations are provided to show the efficiency and relevance of the proposed formulation.

1 Introduction

The optimal way to administer drugs in cancer treatment by chemotherapy remains an open issue. This is because there exists a lack of unified mathematical models for the underlying dynamics [7, 10, 8]. Indeed, models vary depending on the type of cancer and the family of drugs being used. In this paper, interest is focused on cell-cycle-specific chemotherapeutic drugs that act as killing agent. These drugs kill cells that are in a specific phase of the cell cycle (as for example Taxol or Cyclophosphamide [1]). They are commonly used in treating cancers [1, 11]. For more details and a survey of the area, see [4, 9]. The following set of equations describes the cell-cycle of the bone-marrow cell transition between the proliferating phase and the rest phase as proposed in [7, 1]

$$\dot{P} = (\gamma - \delta - \alpha - f(t))P + \beta Q \quad ; \quad \dot{Q} = \alpha P - (\lambda + \beta)Q, \tag{1}$$

where P and Q denote the number of cells in these two phases respectively, γ is the cyclic cell growth rate, α is the transition rate from proliferating to resting, δ is the proliferating cells' natural death rate, β is the transition rate from resting to proliferating, λ is the cell differentiation rate (mature bone-marrow cells leaving the bone marrow to enter blood stream as various types of blood cells) while f is the control describing the effect of the chemotherapeutic treatment that acts only on the proliferating cells. The control input f meets the following requirement : $f(t) \in [0, 1] \quad \forall t \in [0, T]$, where T is the

treatment duration. Note that $f(t) = 0$ means that no drug is injected at time t while $f(t) = 1$ means that maximal rate is used.
The basic problem in cancer treatment by chemotherapy is to find a good strategy for drug injection over a standard treatment period $[0, T]$. This is because drugs kill both cancer and healthy cells. The idea proposed in [1] is to use optimal control to maximize the quantity of drug injected over the treatment period while continuously respecting the following inequality constraint on the state trajectory

$$P(t) + Q(t) \geq \rho, \qquad \forall\ t \in [0, T]. \tag{2}$$

In [1], the state constraints are taken into account in the optimal control problem through the use of a weighting parameter a, but the way this coefficient is updated to meet the requirement (2) is not clearly given. A similar weighting technique is used in [2].
The aim of this paper is to design a family of unconstrained optimal control problems that approximate with any desired precision the original constrained optimal control problem given by :

$$\begin{aligned} P_\rho(P_0, Q_0) \quad &: \quad \min_{f(\cdot)} \Big[J(f)\Big] = \frac{1}{T}\int_0^T (1 - f(t))^2 dt \\ \text{under } f(t) \in [0,1] \quad &\text{and} \quad P(t) + Q(t) \geq \rho \quad \forall t \in [0, T], \end{aligned} \tag{3}$$

where $(P(t), Q(t))$ denotes the solution of (1) under the control profile $f(\cdot)$ starting from the initial condition (P_0, Q_0).

2 Preliminary results

Definition 1.
Given some initial conditions (P_0, Q_0), a control profile $f(\cdot) \in [0,1]^{[0,T]}$ leading to a state trajectory that meets the state constraint $P(t) + Q(t) \geq \rho$ on $[0, T]$ (for all t) is said to be an admissible profile for the optimal control problem $P_\rho(P_0, Q_0)$ defined by (3) . ♡

It is clear that $P_\rho(P_0, Q_0)$ may not have a non empty set of admissible profiles for any pair (T, ρ). The following proposition characterizes such pairs (T, ρ) for which $P_\rho(P_0, Q_0)$ admits a non empty set of admissible profiles.

Proposition 1.
A necessary and sufficient condition for $P_\rho(P_0, Q_0)$ to admit a non empty set of admissible profiles is that $f \equiv 0$ is an admissible profile for the optimal control problem $P_\rho(P_0, Q_0)$, namely

$$\rho \leq \rho_{min}(P_0, Q_0, T) := \min_{t \in [0,T]} \Big[C e^{A_0 t} \begin{pmatrix} P_0 \\ Q_0 \end{pmatrix} \Big], \quad \textit{where } C := \begin{pmatrix} 1 & 1 \end{pmatrix}. \tag{4}$$

Consider the following extended dynamical system denoted hereafter by $\sum_{r_0}$

$$\dot{P} = (\gamma - \delta - \alpha - f(t))P + \beta Q \tag{5}$$

$$\sum_{r_0} \qquad \dot{Q} = \alpha P - (\lambda + \beta)Q \tag{6}$$

$$\dot{R} = \varphi\Big(r_0 - (P+Q)\Big) \quad ; \quad R(0) = 0 \tag{7}$$

where $\varphi : \mathbb{R} \to \mathbb{R}_+$ is given by : $\varphi(r) = \max(0, r)\dfrac{a}{b+r}$, with $a > 0 \quad b > 0$.
To understand the relevance of the extended system (5)-(7), the following lemmas are needed (see the appendix for the proofs) :

Lemma 1.
For any $r_0 > 0$, any $\varepsilon \leq r_0/2$ and any control profile $f(\cdot) \in [0,1]^{[0,T]}$, if at some time t, the system trajectory satisfies $r_0 - (P(t) + Q(t)) = 2\varepsilon$, then one has

$$r_0 - (P(\tau) + Q(\tau)) \geq \varepsilon, \quad \forall \tau \in [t, t + \delta t(r_0, \varepsilon)], \tag{8}$$

where $\delta t(r_0, \varepsilon) = \frac{1}{\gamma} \ln\Big(\frac{r_0 - \varepsilon}{r_0 - 2\varepsilon}\Big)$.

Lemma 2.
Let $f \in [0,1]^{[0,T]}$ be any control profile. Denote by $P(\cdot)$, $Q(\cdot)$ and $R(\cdot)$ the corresponding state trajectories of the extended system (5)-(7). Let μ be given by

$$\mu := \min_{t \in [0,T]} \big[P(t) + Q(t)\big], \tag{9}$$

then the following inequality holds

$$R(T) \geq G(r_0, \mu) := \frac{1}{\gamma} \ln\Big(\frac{r_0 + \mu}{2\mu}\Big)\varphi\Big(\frac{r_0 - \mu}{2}\Big). \tag{10}$$

Moreover, $R(T) = 0$ if and only if $\mu \geq r_0$.

The two lemmas above show that the extended system is defined such that the final value of the state $R(T)$ may be used as a relevant indicator on the state constraint violation over the treatment period $[0, T]$. This is a key property that is extensively used in the following section.

3 Main results

Recall that our aim is to find approximate solutions of the state-constrained optimization problem (3) in which ρ satisfies the feasibility condition given in proposition 1

$$\rho = \rho_{min}(P_0, Q_0, T) - \eta_0 \quad ; \quad \eta_0 > 0. \tag{11}$$

Recall also that $\rho_{min}(P_0, Q_0, T)$ is explicitly computable using (4) so that for any given ρ, η_0 is also computable. Given η_0, the following family of state-unconstrained optimal control problems is defined for $\eta \in (0, \eta_0)$ on the extended system $\sum_{\rho+\eta}$ as follows

$$P_\rho^\eta(P_0,Q_0) \quad : \quad \min_{f(\cdot)\in[0,1]^{[0,T]}} \quad \frac{R(T)}{G(\rho+\eta,\rho)} + \frac{1}{T}\int_0^T \Big(1-f(t)\Big)^2 dt, \\ \text{with } r_0=\rho+\eta \text{ in (7)} \tag{12}$$

where $R(T)$ is the solution at $t=T$ of the extended system (5)-(7) starting from the initial condition $(P_0,Q_0,0)$ at $t=0$ under the control profile $f(\cdot)$ where $G(\cdot,\cdot)$ is defined by (10).
The following proposition, based on corollary 1.4 of [6], states that for any $\eta\in]0,\eta_0]$, the optimal control problem $P_\rho^\eta(P_0,Q_0)$ admits a solution.

Proposition 2. *For all $\eta\in(0,\eta_0]$, the problem $P_\rho^\eta(P_0,Q_0)$ admits a solution.*

The following proposition states the main result of this paper:

Proposition 3.

1. *For all $\eta\in(0,\eta_0]$, an optimal solution of the state-unconstrained problem $P_\rho^\eta(P_0,Q_0)$ is an admissible profile for the original state-constrained problem $P_\rho(P_0,Q_0)$.*
2. *If $\hat{J}_\rho$ [resp $\hat{f}_\rho^\eta$] denotes the minimal cost of the state-constrained problem $P_\rho(P_0,Q_0)$ [resp. the state-unconstrained problem $P_\rho^\eta(P_0,Q_0)$], then*

$$\hat{J}_\rho \quad \leq \quad \frac{1}{T}\int_0^T \Big(1-\hat{f}_\rho^\eta(t)\Big)^2 dt \quad \leq \quad \hat{J}_{\rho+\eta}. \tag{13}$$

3. *In particular, a lower and an upper bound on the exact solution of the constrained problem may be obtained by solving only unconstrained problems, namely*

$$\frac{1}{T}\int_0^T \Big(1-\hat{f}_{\rho-\eta}^\eta(t)\Big)^2 dt \leq \quad \hat{J}_\rho \quad \leq \quad \frac{1}{T}\int_0^T \Big(1-\hat{f}_\rho^\eta(t)\Big)^2 dt. \tag{14}$$

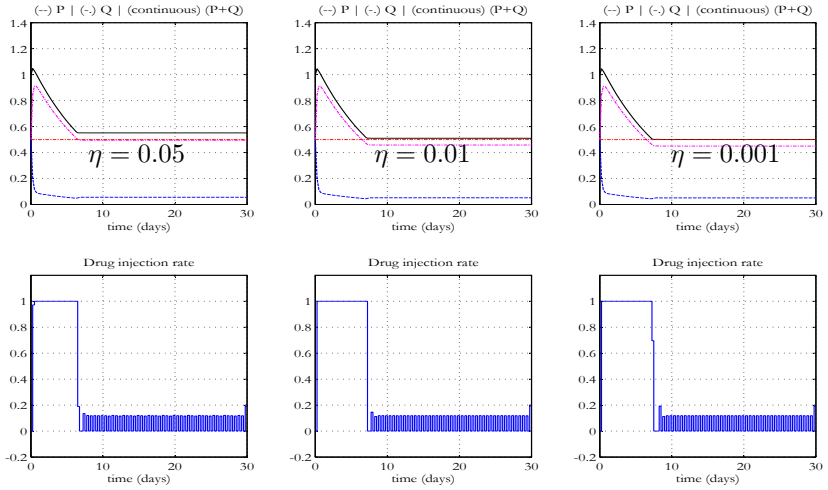
4 Numerical experiments

In this section, the numerical values of the system's parameters given in [3] are used, namely $\gamma=1.47$; $\alpha=5.64$; $\lambda=0.16$; $\delta=0$; $\beta=0.48$; $P_0=Q_0=0.5$; $\rho=0.5$; $T=30$days. The optimization horizon of 30 days has been divided into 120 decision intervals. A direct optimization method has been used (the subroutine DBCPOL of the FORTRAN IMSL scientific library). As illustrated by figure 1, the solutions of the unconstrained problems (12) can approximate the state constraint problem (3) to any desired precision. Indeed, this figure shows the solutions of the unconstrained problems $P_{0.5}^\eta(0.5,0.5)$ for different values of the parameter $\eta\in\{0.05,0.01,0.001\}$ and when the initial guess : $\forall t\geq 0 \quad f(t)=0$ is used. Note that the constraint fulfillment is obtained for any positive value of η while if the formulation of [1] is used, several trials would have been necessary to find the value of the weighting parameter a. Recall that according to proposition 3, it is possible to compute

a surrounding interval that contains the optimal value $\hat{J}_{\rho}^{constr}$ of the original constrained problem using the optimal values of two unconstrained problem P_{ρ}^{η} and $P_{\rho-\eta}^{\eta}$. The solutions of $P_{0.499}^{0.001}$ and $P_{0.5}^{0.001}$ have been computed and the results enables to write according to (13)

$$\hat{J}_{0.5}^{0.001} = 20.42 < \hat{J}_{0.5}^{constr} < 20.49 = \hat{J}_{0.499}^{0.001}$$

One can also note that in all the simulations of figure 1, the strategy of intensive chemotherapy in the sense of [5] seems to prevail. Indeed, the maximal drug injection rate is applied until the constrained quantity reaches its lower limit ($P + Q \approx 0.5$), then the quantity $P + Q$ is "*regulated around its limit value*". This suggests that the results of [5] that is obtained for non cell-cycle specific chemotherapy probably holds for the cell-cycle specific drugs case. Further theoretical investigation in this direction might be of interest.
Finally let us mention the existence of multiple solutions: In many situations, numerical experiments suggests that there can be more than one solution to the constrained optimization problem. This makes the solution sensitive to the initial guess. Figure 2 shows an example of such a situation for the initial state $(P(0), Q(0)) = (0.6, 0.4)$. Indeed, when using two different initial guesses $f(\cdot) \equiv 0$ and $f(\cdot) \equiv 1$, two different solutions are obtained. Note that this sensitivity to initial guess does not appear with the formulation of [1] since the intensive chemotherapy profile would be clearly *abusively* penalized by the cost $a(P + Q)$.



(a) (b) (c)

Fig. 1. Solutions of the unconstrained optimal control problems $P_{\rho}^{\eta}(0.5, 0.5)$ for different values of the parameter η and using the initialization $f(\cdot) \equiv 0$: (a) $\eta = 0.05$ (b) $\eta = 0.01$ (c) $\eta = 0.001$

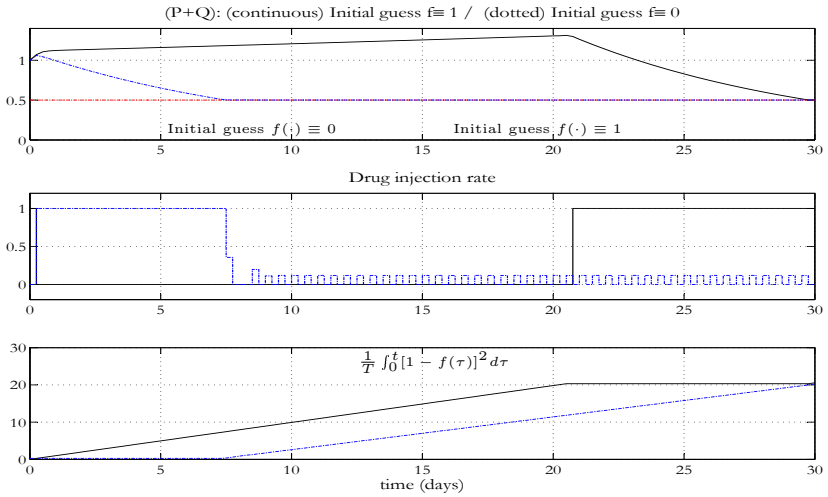


Fig. 2. Comparison between two different solutions of the unconstrained problem $P_{0.5}^{0.001}(0.6, 0.4)$ resulting from two different initial guess $f \equiv 0$ (dotted line) and $f \equiv 1$ (continuous line). Note that these different solutions correspond to roughly the same cost values.

5 Conclusion

In this paper, it has been shown that by considering appropriate state-unconstrained optimal control problems (12), the solution of the state-constrained problem (3) occuring in cancer cell-cycle specific chemotherapy can be approximated up to any desired precision. The resulting approximation error can be explicitly computed via the appropriate two-sided inequalities (14).

A Appendix

Proof of proposition 1. Sufficiency is straightforward since (4) exactly means that $f \equiv 0$ is an admissible profile for $P_\rho(P_0, Q_0)$. To prove that (4) is necessary, we shall prove that for all non identically vanishing $f^* \in [0,1]^{[0,T]}$, one has

$$\forall t \in [0,T] \quad , \quad (P(t) + Q(t))|_{f\equiv 0} \geq (P(t) + Q(t))|_{f=f^*}. \tag{15}$$

Indeed, this would imply that if f^* is admissible then $f \equiv 0$ is admissible too. Now, proving (15) amounts to prove that $\forall t \in [0,T]$ $Ce(t) \geq 0$, with $e = X^0 - X^*$ where $X^0(\cdot)$ and $X^*(\cdot)$ are solutions of $\dot{X}^0(t) = A_0 X^0(t)$; $\dot{X}^*(t) = (A_0 + f^*(t)A_1)X^*(t)$, with the initial conditions $X^0(0) = X^*(0) = \begin{pmatrix} P_0 \\ Q_0 \end{pmatrix}$. By

definition of $e(t)$, straightforward computation with the fact that $e(0) = 0$ leads to $e(t) = \int_0^t e^{A_0\tau}\begin{pmatrix} f^*(\tau)X_1^*(\tau) \\ 0 \end{pmatrix} d\tau$, therefore, in order to prove that $\forall t \in [0,T]\ Ce(t) \geq 0$, all we have to show is that

$$C\int_0^t e^{A_0\tau}\begin{pmatrix} f^*(\tau)X_1^*(\tau) \\ 0 \end{pmatrix} d\tau \geq 0 \quad ; \quad C = \begin{pmatrix} 1 & 1 \end{pmatrix}, \tag{16}$$

but l.h.s of (16) is nothing but the total number of cells $P^{'}(t) + Q^{'}(t)$ at time t of the fictitious population-like system starting from the initial condition $P^{'}(0) = Q^{'}(0) = 0$ when injecting the positive input $r(\tau) = f^*(\tau)X_1^0(\tau)$. This clearly shows that (16) holds, since clearly this fictitious system can never admit negative total mass $P^{'} + Q^{'}$. ♢

Proof of lemma 1. Based on the computation of the time derivative of $P+Q$ and noticing that P and Q remain clearly positive for any admissible control profile, the increasing rate of $P+Q$ is bounded. More precisely, one can write

$$\frac{d}{dt}(P+Q) \leq \gamma(P+Q), \tag{17}$$

therefore $(P+Q)(t+\tau) \leq e^{\gamma\tau}(P+Q)(t)$, now using $(P+Q)(t) = r_0 - 2\varepsilon$ and $(P+Q)(t+\tau) = r_0 - \varepsilon$ clearly gives the result. ♢

Proof of lemma 2. Let t^* be the time for which $\mu = P(t^*)+Q(t^*)$. Applying lemma 1 for $t = t^*$ and $2\varepsilon = r_0 - \mu$ results in $r_0 - (P(\tau)+Q(\tau)) \geq \frac{r_0-\mu}{2}, \quad \forall\tau \in [t^*, t^* + \delta t(r_0, \frac{r_0-\mu}{2})]$, and since the r.h.s of (7) is always positive and φ is non decreasing, one has

$$R(T) \geq \int_{t^*}^{t^*+\delta t(r_0,\frac{r_0-\mu}{2})} \varphi\Big(\frac{r_0-\mu}{2}\Big)d\tau = \delta t\Big(r_0, \frac{r_0-\mu}{2}\Big)\varphi\Big(\frac{r_0-\mu}{2}\Big), \tag{18}$$

which clearly gives (10) when using the expression of $\delta t(r_0, \varepsilon)$ (see lemma 1). As for the last feature, assume that $R(T) = 0$, the positiveness of $\varphi(\cdot)$ implies that the r.h.s of (7) is identically 0 over $[0,T]$ and hence, by definition of φ, $r_0 - (P(\tau) + Q(\tau)) \leq 0$ and therefore $\mu \geq r_0$. The inverse implication is straightforward. ♢

Proof of proposition 2. The proof is based on corollary 1.4 of [6].

Proof of proposition 3.

Proof of 1. In the proof we shall use the following notations : $\hat{P}_\rho^\eta(\cdot)$, $\hat{Q}_\rho^\eta(\cdot)$ and $\hat{R}_\rho^\eta(\cdot)$ are the optimal trajectories corresponding to the optimal control profile $\hat{f}_\rho^\eta(\cdot)$, $\hat{\mu}_\rho^\eta$ denote the minimal value of $P+Q$, that is $\hat{\mu}_\rho^\eta := \min_{t\in[0,T]} \quad \hat{P}_\rho^\eta(t) + \hat{Q}_\rho^\eta(t)$, and the trajectories of the extended system under $f \equiv 0$ are denoted by $P_{f\equiv 0}(\cdot)$, $Q_{f\equiv 0}(\cdot)$ and $R_{f\equiv 0}(\cdot)$. Thus, proving point 1. amounts to establish that $\hat{\mu}_\rho^\eta \geq \rho$. The optimality of $\hat{f}_\rho^\eta$ implies

$$\frac{\hat{R}_\rho^\eta(T)}{G(\rho+\eta,\rho)} + \frac{1}{T}\int_0^T (1 - \hat{f}_\rho^\eta(t))^2 dt \quad \leq \quad \frac{R_{f\equiv 0}(T)}{G(\rho+\eta,\rho)} + 1$$

but since $\eta \leq \eta_0$, one has (by the definition (11) of η_0) $\rho+\eta \leq \rho_{min}(P_0, Q_0, T)$ and therefore one has by lemma 2 applied to the profile $f \equiv 0$ and $r_0 = \rho+\eta$, $R_{f\equiv 0}(T) = 0$. Furthermore, applying lemma 2 with the optimal profile $\hat{f}^{\eta}_{\rho}(\cdot)$ enables to write $\hat{R}^{\eta}_{\rho}(T) \geq G(\rho+\eta, \hat{\mu}^{\eta}_{\rho})$, which gives $\dfrac{G(\rho+\eta, \hat{\mu}^{\eta}_{\rho})}{G(\rho+\eta, \rho)} \leq 1$, and since $G(\rho+\eta, \cdot)$ is a decreasing function, it clearly gives $\hat{\mu}^{\eta}_{\rho} \geq \rho$.

Proof of 2. Since any admissible profile $f(\cdot)$ for $P_{\rho}(P_0, Q_0)$ is a candidate solution for $P^{\eta}(\rho, P_0, Q_0)$ with terminal cost $R(T) = 0$, its corresponding cost w.r.t $P^{\eta}(\rho, P_0, Q_0)$ is simply $\frac{1}{T}\int_0^T (1-f(t))^2 dt$. Therefore by the optimality of $\hat{f}^{\eta}_{\rho}$, one necessarily has

$$\frac{\hat{R}^{\eta}_{\rho}(T)}{G(\rho+\eta, \rho)} + \frac{1}{T}\int_0^T (1-\hat{f}^{\eta}_{\rho}(t))^2 dt \leq \hat{J}_{\rho+\eta},$$

which clearly gives the second inequality in (13). As for the first inequality, this directly stems from the fact that $\hat{f}^{\eta}_{\rho}$ is an admissible profile for $P_{\rho}(P_0, Q_0)$ (point 1.) and therefore, by the optimality of $\hat{J}_{\rho}$, it results that $\hat{J}_{\rho} \leq \frac{1}{T}\int_0^T (1-\hat{f}^{\eta}_{\rho}(t))^2 dt$, which clearly ends the proof of 2. As for (13), it is a direct consequence of (14) in which $\rho - \eta$ replaces ρ. $\diamondsuit$

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