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# State-constrained optimal control applied to cell-cycle-specific cancer chemotherapy

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## SUMMARY

In this paper, the optimal drug injection problem arising in cancer treatment by cell-cycle-specific chemotherapy is investigated. The optimal control problem is state constrained in which the stage cost reflects the concern of maximal drug injection, while the state constraint imposes a lower bound on the total number of cells in the bone marrow. 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 state constraint is fulfilled for any member of the family. The existence of solutions is proved and the resulting approximation is characterized by appropriate two-sided inequalities. Simulations are provided to show the efficiency and relevance of the proposed formulation. Copyright © 2007 John Wiley & Sons, Ltd.

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KEY WORDS: optimal control; state constraints; cancer chemotherapy; cell-cycle-specific drugs

## 1. INTRODUCTION

The optimal way to administer drugs in cancer treatment by chemotherapy remains an open issue. This is because drugs kill both healthy and cancer cells. Another source of difficulty lies in the lack of unified mathematical models for the underlying dynamics [1–5]. 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. These drugs act on cells that are in a specific phase of the cell cycle. They are commonly used in treating cancers [6, 7]. For more details and a survey of the area, see [8, 9].

The fact that interest is focused on cell-cycle-specific chemotherapy is crucial when appreciating the relevance of the present paper. Indeed, in the case of non-cell-cycle-specific

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drugs, the recent paper by Matveev and Savkin [10] gives excellent answers to the problem in a quite general framework. Indeed, in [10], it has been proved that the optimal strategy is what is called the '*intensive chemotherapy*'. This strategy begins by injecting the maximal rate of drug until the variable $P+Q$ hits the constraint surface ($P+Q=$ the lowest admissible value, where $P$ is the number of proliferating cells while $Q$ is the number of healthy cells), then feedback control has to be applied that regulate $P+Q$ at its lowest allowable value.

Unfortunately, for cell-cycle-specific drugs, these results may not necessarily hold because their derivation in [10] heavily depends on the system model that is quite different in our case. However, the numerical results of Section 6 hereafter may strongly suggest that the '*intensive chemotherapy*' strategy seems to prevail also in the case of cell-cycle-specific drug. The rigorous proof of this fact may be a natural continuation of this work.

Figure 1 shows the cell-cycle diagram describing the bone-marrow cells transition between the proliferating phase and the rest phase as proposed in [1,2,11]. Denoting the number of cells in these two phases, respectively, by $P$ and $Q$, the system equations may be written as follows:

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

$$\dot{Q} = \alpha P - (\lambda + \beta)Q \tag{2}$$

where $\gamma$ is the cyclic cell growth rate, $\alpha$ is the transition rate from proliferating to resting, $\delta$ is the proliferating cells natural death rate, $\beta$ is the transition rate from resting to proliferating, $\lambda$ 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 system equations (1)–(2) may be written in a more compact form as follows:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} P \\ Q \end{pmatrix} = A(f)\begin{pmatrix} P \\ Q \end{pmatrix} =: (A_0 + fA_1)\begin{pmatrix} P \\ Q \end{pmatrix} \tag{3}$$

with a straightforward definition of $A(f)$, $A_0$ and $A_1 \in \mathbb{R}^{2\times 2}$. The control input $f$ is assumed to meet the following requirement:

$$f(t) \in [0,1] \quad \forall t \in [0,T]$$

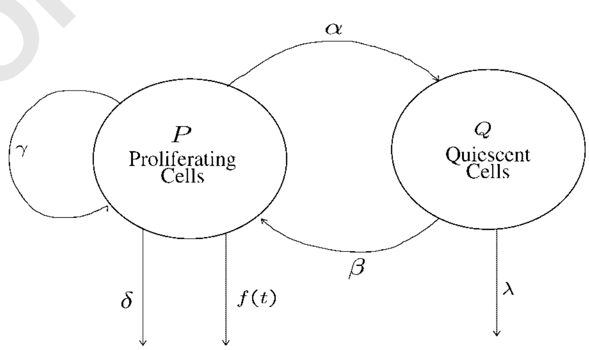


Figure 1. Schematic view of the cell cycle.





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where $T$ is the treatment duration. Note that $f(t) = 0$ means no drug is injected at time $t$ while $f(t) = 1$ means maximal rate is used.

The basic problem in cancer treatment by chemotherapy is to find a good strategy for drug injection over the treatment period. This is because drugs kill both cancer and healthy cells. To handle these contradictory effects of the drugs, the following objective functional proposed by Fister and Panetta [11] has to be maximized by suitably choosing the control profile $f(\cdot)$:

$$J(f) = \int_0^T \left[ a(P+Q) - \frac{1}{2}(1-f(t))^2 \right] \mathrm{d}t \tag{4}$$

The key idea in [11] is to update the coefficient $a$ in the objective functional (4) at the beginning of each treatment period in order to maintain the total final number of bone-marrow cells $(P+Q)(T)$ greater than some lower bound. In [11], it has also been suggested that an interesting control objective may be to maximize the quantity of injected drugs over the treatment interval $[0, T]$ while continuously respecting the following inequality constraint on the state trajectory, namely:

$$P(t) + Q(t) \geqslant \rho \quad \forall t \in [0, T] \tag{5}$$

However, the way in which the coefficient $a$ is updated to meet requirement (5) is not clearly given. In other words, the link between the optimal drug injection strategy in the sense of (4) and the exact optimal strategy in the sense of drug injected quantity under the state constraint (5) is not clear.

In [12], a similar two-compartment bilinear model is used to model cell dynamics and the optimal control problem is defined using the following cost function to be minimized:

$$J(f) = ||X(T)||_R^2 + \int_0^T (1-f(t))\, \mathrm{d}t \tag{6}$$

where $X := (P, Q)$ and $R \in \mathbb{R}^{2\times 2}$ are some positive-definite weighting matrix. Note that the stage cost in (6) is affine in control. Existence of optimal control of the above problem is studied in [12] where it has been shown that singular arcs are not optimal and that optimality is obtained *via* bang-bang control. Similar results have been also obtained for three-compartment models in [13]. However, constraints on the state have not been considered in this framework.

The reason for which several authors try to use stage or final penalty on the state in order to enhance constraint fulfillment comes from the fact that tackling the '*all time state constraint like the one in* (5)' is numerically involved in general despite the existence of general purpose solvers [14, 15]. Indeed, when tackling such constraints, two options are possible:

- Either the constraint (for all $t$, $h(x(t)) \leqslant 0$) is changed into

$$\int_0^T \max\{h(x(t)), 0\}\, \mathrm{d}t = 0$$

  which makes the constraint always active when viewed by the solver and hence make the solution *via* Lagrange multipliers rather heavy to tackle.
- Or a penalty is added as in [11, 12] using a weighting parameter that has to be '*tuned until the constraint is satisfied*.' In this case, there is generally no explicit value of the weighting parameter for which the solution of the unconstrained problem is guaranteed to be





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admissible in the sense of the original problem. Moreover, when a value of the weighting parameter is obtained that makes the corresponding solution admissible, there is generally no way to know how far one is from the exact solution of the original problem.

The aim of this paper is to design a family of unconstrained optimal control problems that approximate the original constrained optimal control problem given by

$$P_\rho(P_0, Q_0) : \min_{f(\cdot)} [J(f)] = \frac{1}{T}\int_0^T (1 - f(t))^2 \, dt$$

$$\text{under } f(t) \in [0,1] \quad \text{and} \quad P(t) + Q(t) \geqslant \rho \quad \forall t \in [0, T] \tag{7}$$

where $(P(t), Q(t))$ denotes the solution of (1)–(2) under the control profile $f(\cdot)$ starting from the initial condition $(P_0, Q_0)$. However, contrary to the general purpose transformation from constrained to unconstrained problems, the particular structure of the system under study, namely (1)–(2) is used here to prove some nice properties of the family of unconstrained approximating problems (see Section 2 hereafter).

The paper is organized as follows: first, a brief presentation of the results is given in Section 2. The mathematical background is recalled in Section 3. Some technical preliminary results are proposed in Section 4 to be used in the proof of the main results that are given in Section 5. Finally, Section 6 gives numerical experiments illustrating and assessing the theoretical results. To simplify reading, all proofs are reported in the Appendix.

## 2. BRIEF LOOK AT THE PAPER'S RESULTS

A family of state-unconstrained optimal control problems is defined that approximate the original problem (7) with any desired precision. For each value of the indexing set, the existence of solutions to the approximate problem is shown (Proposition 3) based on recent results on the existence of solutions for the non-convex optimal control problems [16]. Then, it is shown that the optimal injection strategy for the state-unconstrained approximating problem is (1) admissible in the sense of state constraint fulfillment for each value of the family index and (2) can approach the maximal injectable drug under exact state constraint with any desired precision (Proposition 4).

More precisely, if $\hat{J}_\rho^{\text{unconstr},\eta}$ denotes the solution of the state-unconstrained problem associated with the family index $\eta$ (to be defined later) while $\hat{J}_\rho^{\text{constr}}$ denotes the solution of the exact state-constrained optimal control problem (7), then one has (Proposition 4)

$$\hat{J}_{\rho-\eta}^{\text{unconstr},\eta} \leqslant \hat{J}_\rho^{\text{constr}} \leqslant \hat{J}_\rho^{\text{unconstr},\eta} \tag{8}$$

This provides a computable estimation of the approximation error using only state-unconstrained problems. Moreover, since $\hat{J}_\rho^{\text{unconstr},\eta}$ is continuous in $\rho$ and $\eta$, one can asymptotically retrieve the optimal cost of the original problem, thanks to Property (8), by taking

$$\hat{J}_\rho^{\text{constr}} = \lim_{\eta \to 0} \hat{J}_\rho^{\text{unconstr},\eta}$$



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## 3. THEORETICAL BACKGROUND

Consider the Bolza problem consisting of minimizing the following cost function:

$$\min_{u \in K^{[0,T]}} I(u) = G(x(T)) + \int_0^T F(x(t), u(t))\,\mathrm{d}t, \quad K \text{ compact} \tag{9}$$

$$\text{under } \dot{x}(t) = f(x(t), u(t)), \quad x(0) = x_0 \in \mathbb{R}^n \tag{10}$$

The following assumptions are needed to prove the existence of solutions to the above optimal control problem (9)–(10).

*Assumption 1*

1. The stage cost $F : \mathbb{R}^n \times \mathbb{R}^m$ is continuous and satisfies the following coercivity requirement for some $p > 1$ and $c > 0$

$$F(x, u) \geqslant c(|u|^p - 1) \tag{11}$$

2. The functions $G$, $F$ and $f$ are continuously differentiable in $x$.
3. For all $x \in \mathbb{R}^n$, the set $\mathscr{A}(x)$ defined by

$$\mathscr{A}(x) := \{(\sigma, f(x, u)) : F(x, u) \leqslant \sigma \quad u \in K\} \subset \mathbb{R}^{n+1} \tag{12}$$

is convex in $\mathbb{R}^{n+1}$.

Under the above assumption, the following result holds.

*Proposition 1 (See [16], Corollary 1.4)*
Under Assumption 1, the optimal control problem defined by (9)–(10) admits a solution.

## 4. 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 $P(t) + Q(t) \geqslant \rho$ 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 (7).

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

*Proposition 2*
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

$$\rho \leqslant \rho_{\min}(P_0, Q_0, T) := \min_{t \in [0,T]} \left[ C e^{A_0 t} \begin{pmatrix} P_0 \\ Q_0 \end{pmatrix} \right] \tag{13}$$

where $C := (1 \;\; 1)$.



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*Proof*
See the Appendix.

In the following section, an indexed family of state-unconstrained optimal control problems is defined to approximate the solution of the original optimal control problem (7) with any desired precision. This is achieved by using the following extended dynamical system denoted hereafter by $\sum_{r_0}$:

$$\dot{P} = (\gamma - \delta - \alpha - f(t))P + \beta Q \tag{14}$$

$$\sum_{r_0} \quad \dot{Q} = \alpha P - (\lambda + \beta)Q \tag{15}$$

$$\dot{R} = \varphi(r_0 - (P + Q)), \quad R(0) = 0 \tag{16}$$

where $\varphi : \mathbb{R} \to \mathbb{R}_+$ is given by

$$\varphi(r) = \max(0, r)\frac{a}{b + r}, \quad a > 0, \ \ b > 0 \tag{17}$$

To understand the relevance of the extended system (14)–(16), the following lemmas are needed:

*Lemma 1 (see Figure 2)*
For any $r_0 > 0$, any $\varepsilon \leqslant r_0/2$ 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

$$r_0 - (P(\tau) + Q(\tau)) \geqslant \varepsilon \quad \forall \tau \in [t, t + \delta t(r_0, \varepsilon)] \tag{18}$$

where $\delta t(r_0, \varepsilon) = (1/\gamma)\ln((r_0 - \varepsilon)/(r_0 - 2\varepsilon))$.

*Proof*
See the Appendix.

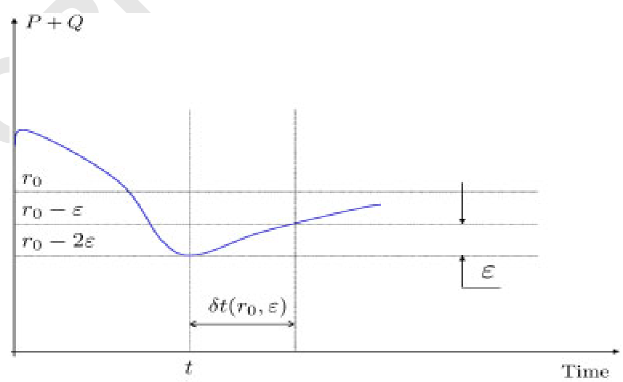


Figure 2. Illustration of Lemma 1. If at some instant $t$, $P(t) + Q(t) \leqslant r_0 - 2\varepsilon$, then there is a computable duration $\delta(r_0, \varepsilon)$ during which $P + Q$ is lower than $r_0 - \varepsilon$.







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*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 (14)–(16). Let $\mu$ be given by

$$\mu := \min_{t\in[0,T]} [P(t)+Q(t)] \tag{19}$$

then the following inequality holds

$$R(T) \geqslant G(r_0,\mu) := \frac{1}{\gamma}\ln\left(\frac{r_0+\mu}{2\mu}\right)\varphi\left(\frac{r_0-\mu}{2}\right) \tag{20}$$

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

*Proof*
See the Appendix.

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.

## 5. BASIC RESULTS

Recall that our aim is to find approximate solutions of the state-constrained optimization problem

$$P_\rho(P_0,Q_0): \min_f [J(f)] = \frac{1}{T}\int_0^T (1-f(t))^2\,\mathrm{d}t$$
$$\text{under } f(t)\in[0,1] \quad \text{and} \quad P(t)+Q(t)\geqslant\rho \quad \forall t\in[0,T] \tag{21}$$

in which $\rho$ satisfies the feasibility condition

$$\rho = \rho_{\min}(P_0,Q_0,T)-\eta_0, \quad \eta_0>0 \tag{22}$$

This is due to Proposition 2 establishing that for $\rho>\rho_{\min}(P_0,Q_0,T)$, there are no admissible profiles for (21). Recall also that $\rho_{\min}(P_0,Q_0,T)$ is explicitly computable using (13) so that for any given $\rho$, $\eta_0$ is also computable. Given $\eta_0$, 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:

$$P_\rho^\eta(P_0,Q_0): \min_{f(\cdot)\in[0,1]^{[0,T]}} \frac{R(T)}{G(\rho+\eta,\rho)} + \frac{1}{T}\int_0^T (1-f(t))^2\,\mathrm{d}t$$
$$\text{with } r_0=\rho+\eta \text{ in } (16) \tag{23}$$

where $R(T)$ is the solution at $t=T$ of the extended system (14)–(16) 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 (20).

The following proposition states that for any $\eta\in]0,\eta_0]$, the optimal control problem $P_\rho^\eta(P_0,Q_0)$ admits a solution.

*Proposition 3*
For all $\eta\in(0,\eta_0]$, the problem $P_\rho^\eta(P_0,Q_0)$ admits a solution.





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*Proof*
See the Appendix.

The following proposition states that for any $\eta \in (0, \eta_0]$, an optimal solution of $P^{\eta}_{\rho}(P_0, Q_0)$ is an admissible profile for the original problem $P_{\rho}(P_0, Q_0)$. Furthermore, the optimal solution of $P^{\eta}_{\rho}(P_0, Q_0)$ in terms of the injected quantity-related cost is surrounded by the optimal value of the original constrained problem on one hand and a slightly modified version of it on the other hand.

*Proposition 4*

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

$$\hat{J}_{\rho} \leqslant \frac{1}{T}\int_0^T (1 - \hat{f}^{\eta}_{\rho}(t))^2 \, \mathrm{d}t \leqslant \hat{J}_{\rho+\eta} \tag{24}$$

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

$$\frac{1}{T}\int_0^T (1 - \hat{f}^{\eta}_{\rho-\eta}(t))^2 \, \mathrm{d}t \leqslant \hat{J}_{\rho} \leqslant \frac{1}{T}\int_0^T (1 - \hat{f}^{\eta}_{\rho}(t))^2 \, \mathrm{d}t \tag{25}$$

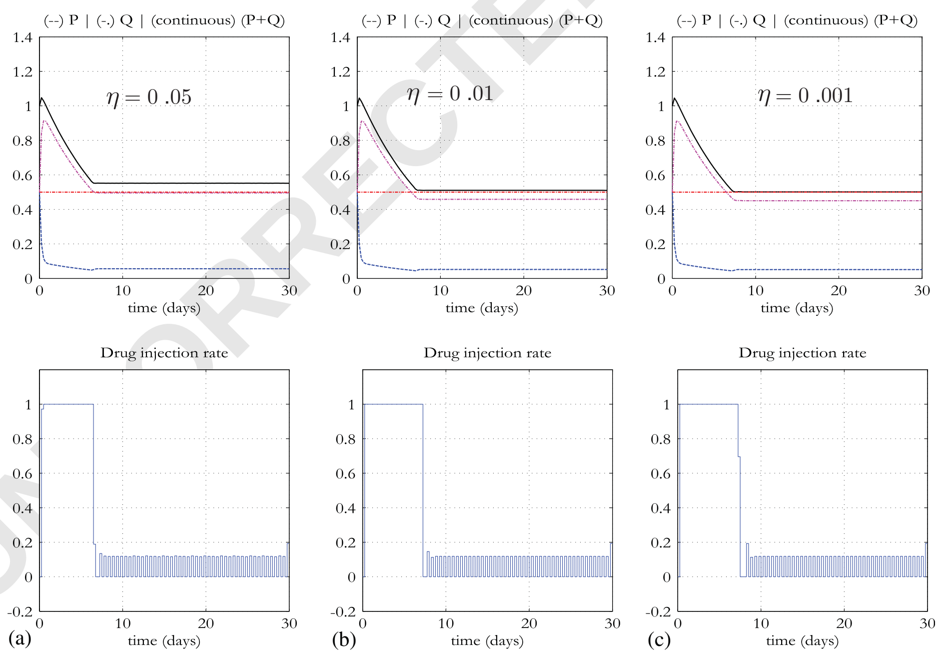


Figure 3. Solutions of the unconstrained optimal control problems $P^{\eta}_{\rho}(0.5, 0.5)$ for different values of the parameter $\eta$ and using the initialization $f(\cdot) \equiv 0$: (a) $\eta = 0.05$; (b) $\eta = 0.01$; and (c) $\eta = 0.001$.







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*Proof*
See the Appendix.

*Remark 1*
It is important to note that point 1 of Proposition 4 states that FOR ANY VALUE of $\eta$, a solution of the unconstrained problem is admissible for the constrained one. In this respect, the result is not classical in the sense that $\eta$ is not a weighting coefficient that transforms the exact constraint on terminal cost and for which there is some '*sufficiently high*' value for the solution to be admissible.

## 6. NUMERICAL EXPERIMENTS

In this section, the numerical values of the system's parameters given in [17] are used, namely

$$\gamma = 1.47, \quad \alpha = 5.64, \quad \lambda = 0.16, \quad \delta = 0$$

$$\beta = 0.48, \quad P_0 = Q_0 = 0.5, \quad \rho = 0.5, \quad T = 30 \text{ days}$$

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 has been used).

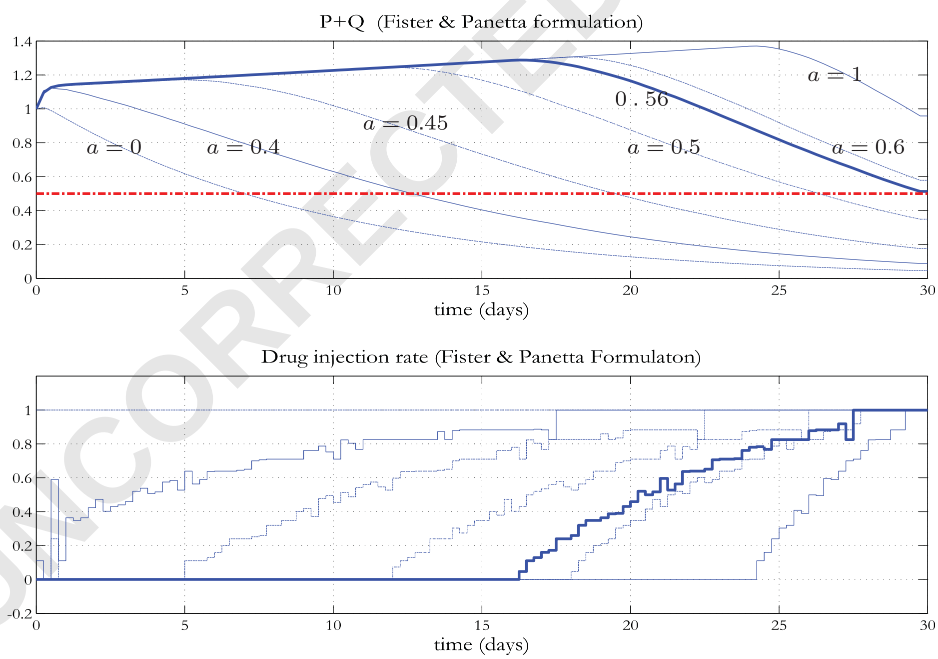


Figure 4. Solution of the optimal control problem (4) used in the formulation of [11] for different values of the weighting parameter $a$. Note that the value $a \approx 0.56$ is the minimum value that enables the all-time state constraint (5) to be satisfied. Initial conditions $(P(0), Q(0)) = (0.5, 0.5)$.







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The aim of the proposed set of simulations is to strengthen the following features:

- *One trial handling of the state constraint to any desired precision*: This feature can be viewed on Figure 3. Indeed, this figure shows the solutions of the unconstrained problems $P^{\eta}_{0.5}(0.5, 0.5)$ for different values of the parameter $\eta \in \{0.05, 0.01, 0.001\}$ and when the initial guess

$$\forall t \geqslant 0, \quad f(t) = 0$$

is used. Note how the constraint is tightly respected for smaller values of $\eta$ and that the quantity of the drug injected is greater when $\eta$ is smaller.

Note that the constraint fulfillment is obtained for any positive value of $\eta$ while if the formulation of [11] is used, several trials would have been necessary to find the value of the weighting parameter $a$ used in (4). This is shown in Figure 4 where the plots of $P + Q$ are given for different values of the weighting parameter $a$.

- *The intensive chemotherapy seems to be optimal*: In all the simulations of Figure 3, the strategy of intensive chemotherapy in the sense of [10] 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 [10] that are obtained for non-cell-cycle-specific chemotherapy probably

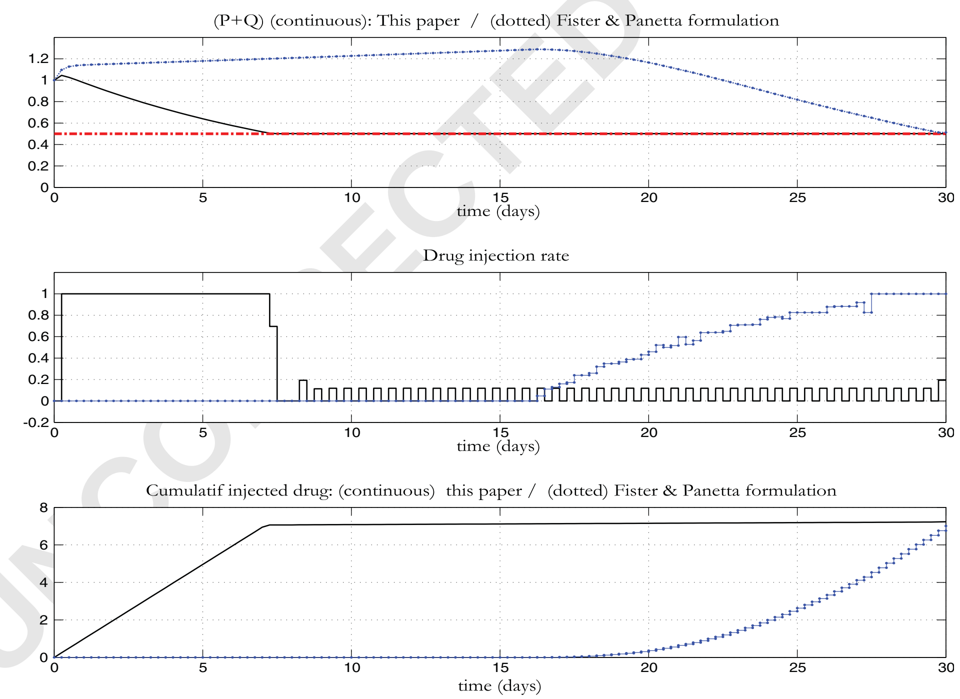


Figure 5. Comparison between the solutions of the unconstrained problem $P^{\eta}_{\rho}(0.5, 0.5)$ formulated in this paper ($\rho = 0.5$ and $\eta = 0.001$) and the solution of the optimal control problem (4) used in the formulation of [11] with the lowest admissible weighting parameter $a = 0.56$. The initial guess is taken equal to $f \equiv 0$.







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hold for the cell-cycle-specific drugs case. Further theoretical investigation in this direction might be of interest.

- *Surrounding the exact solution to the original problem*: Recall that according to Proposition 4, it is possible to compute a surrounding interval that contains the optimal value $\hat{J}_\rho^{\text{constr}}$ of the original constrained problem using the optimal values of two unconstrained problem $P_\rho^\eta$ and $P_{\rho-\eta}^\eta$ [see (8)] (Figure 5). The solutions of $P_{0.499}^{0.001}$ and $P_{0.5}^{0.001}$ have been computed and the results enable to write according to (8)

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

- *Existence of multiple solutions*: In many situations, numerical experiments suggest that there can be more than one solution to the constrained optimization problem. This makes the solution sensitive to the initial guess. Figure 6 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 guess $f(\cdot) \equiv 0$ and $f(\cdot) \equiv 1$, two different solutions are obtained that correspond to roughly the same drug injection-related cost, namely

$$\frac{1}{T}\int_0^T [1 - f(\tau)]^2 \, d\tau$$

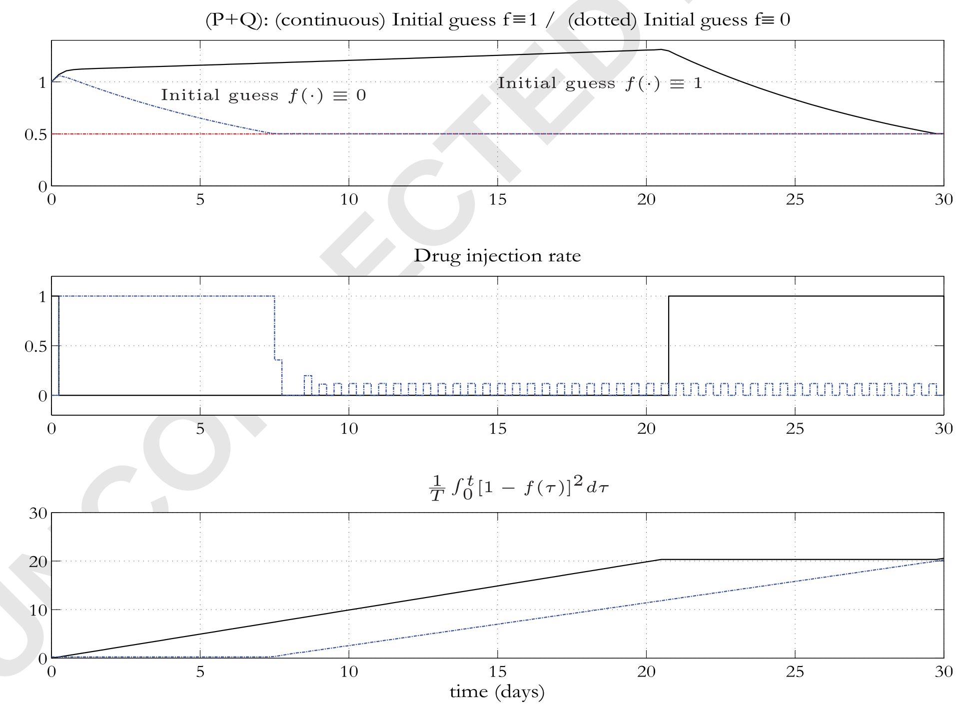


Figure 6. Comparison between two different solutions of the unconstrained problem $P_{0.5}^{0.001}(0.6, 0.4)$ resulting from two different initial guess $f \equiv 0$ (dotted line) and $f \equiv 1$ (continuous line). Note that these different solutions correspond to roughly the same cost values.







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Note, however, that this sensitivity to initial guess does not appear with the formulation of [11] since the intensive chemotherapy profile would be clearly *abusively* penalized by the cost $a(P+Q)$ in (4).

## 7. CONCLUSION

In this paper, it has been shown that by considering appropriate state-unconstrained optimal control problems (23), the solution of the state-constrained problem (21) occurring 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 (25).

It goes without saying that realistic control schemes have to deal with parametric uncertainties and/or measurement errors. The framework of the present paper has to be seen as an element in a more sophisticated control loop (predictive or adaptive) in which the estimated values of the system's parameters have to be systematically updated based on appropriate assumptions.

## APPENDIX

*Proof of Proposition 2*

Sufficiency is straightforward since (13) exactly means that $f\equiv 0$ is an admissible profile for $P_\rho(P_0,Q_0)$ since under $f\equiv 0$, one clearly has

$$\begin{pmatrix} P(t)\\ Q(t)\end{pmatrix} = \mathrm{e}^{A_0 t}\begin{pmatrix} P_0\\ Q_0\end{pmatrix}$$

To prove that (13) is necessary, we shall prove that for all non-identically vanishing $f^*\in[0,1]^{[0,T]}$, one has

$$\forall t\in[0,T],\quad (P(t)+Q(t))|_{f\equiv 0}\geqslant (P(t)+Q(t))|_{f=f^*} \tag{A1}$$

Indeed, this would imply that if $f^*$ is admissible then $f\equiv 0$ is admissible too. Now, proving (A1) amounts to prove that

$$\forall t\in[0,T],\quad Ce(t)\geqslant 0 \tag{A2}$$

with $e=X^0-X^*$ where $X^0(\cdot)$ and $X^*(\cdot)$ are solutions of

$$\dot{X}^0(t)=A_0X^0(t),\quad \dot{X}^*(t)=(A_0+f^*(t)A_1)X^*(t)$$

with the initial conditions $X^0(0)=X^*(0)=\binom{P_0}{Q_0}$. By definition of $e(t)$, straightforward computation with the fact that $e(0)=0$ leads to

$$e(t)=\int_0^t \mathrm{e}^{A_0\tau}\begin{pmatrix} f^*(\tau)X_1^*(\tau)\\ 0\end{pmatrix}\mathrm{d}\tau$$

therefore, in order to prove (A2), all we have to show is that

$$C\int_0^t \mathrm{e}^{A_0\tau}\begin{pmatrix} f^*(\tau)X_1^*(\tau)\\ 0\end{pmatrix}\mathrm{d}\tau\geqslant 0,\quad C=(1\ \ 1) \tag{A3}$$

but l.h.s. of (A3) is nothing but the total number of cells $P'(t)+Q'(t)$ at time $t$ of the fictitious population-like system of Figure 7 starting from the initial condition $P'(0)=Q'(0)=0$ when

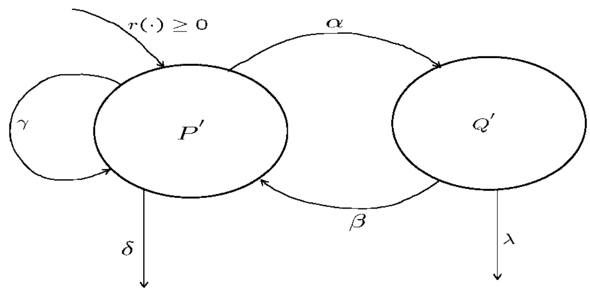


Figure 7. Fictitious population model used in the proof of Proposition 2.

injecting the positive input $r(\tau) = f^*(\tau)X_1^0(\tau)$. This clearly shows that (A3) holds, since clearly the fictitious system of Figure 7 can never admit negative total mass $P' + Q'$. □

*Proof of Lemma 1*

Let us compute the time derivative of $P + Q$

$$\frac{\mathrm{d}}{\mathrm{d}t}(P + Q) = (\gamma - \delta - f)P - \lambda Q$$

since $P$ and $Q$ remain clearly positive for any admissible control profile, the increasing rate of $P + Q$ is bounded. More precisely, one can write

$$\frac{\mathrm{d}}{\mathrm{d}t}(P + Q) \leqslant \gamma(P + Q) \tag{A4}$$

therefore

$$(P + Q)(t + \tau) \leqslant \mathrm{e}^{\gamma\tau}(P + Q)(t)$$

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

$$r_0 - (P(\tau) + Q(\tau)) \geqslant \frac{r_0 - \mu}{2} \quad \forall \tau \in \left[t^*, t^* + \delta t\left(r_0, \frac{r_0 - \mu}{2}\right)\right]$$

and since the r.h.s. of (16) is always positive and $\varphi$ is non-decreasing, one has

$$\begin{aligned} R(T) &\geqslant \int_{t^*}^{t^*+\delta t(r_0,(r_0-\mu)/2)} \varphi(r_0 - (P(\tau) + Q(\tau)))\,\mathrm{d}\tau \\ &\geqslant \int_{t^*}^{t^*+\delta t(r_0,(r_0-\mu)/2)} \varphi\left(\frac{r_0 - \mu}{2}\right)\mathrm{d}\tau = \delta t\left(r_0, \frac{r_0 - \mu}{2}\right)\varphi\left(\frac{r_0 - \mu}{2}\right) \end{aligned} \tag{A5}$$

which clearly gives (20) 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 (16) is identically 0 over $[0, T]$ and hence, by definition of $\varphi$, $r_0 - (P(\tau) + Q(\tau)) \leqslant 0$ and therefore $\mu \geqslant r_0$. The inverse implication is straightforward. □



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*Proof of Proposition 3*
We shall prove that Assumption 1 holds for the problem in question. The notations $u = f$ and $x = (P, Q, R)$ used are compatible with the generic notations of Section 3.

1. *Proof of point 1 of Assumption 1*. Note first that existence is not affected by scaling the cost function or adding constant. Therefore, the following $F(x, u)$ may be used in the proof:
$$\bar{F}(x,u) = (1-u)^2 + c_0 = \tfrac{1}{2}(u^2-1) + \tfrac{1}{2}u^2 - 2u + \tfrac{3}{2} + c_0$$
$$= \tfrac{1}{2}(u^2-1) + \tfrac{1}{2}(u-2)^2 \geqslant \tfrac{1}{2}(u^2-1)$$
by choosing $c_0 = \frac{1}{2}$. This proves that $\bar{F}(x,u)$ satisfies the coercivity condition (11) with $c = \frac{1}{2}$ and $p = 2$.
2. *Proof of point 2 of Assumption 1*. Straightforward.
3. *Proof of point 3 of Assumption 1*. Let $x = (P, Q, R) \in \mathbb{R}^3_+$ be given. Recall that in the new notations, one has (see the proof of point 1)
$$f(x,u) = A_0'(x) + uA_1'(x), \quad \bar{F}(x,u) = (1-u)^2 + c_0$$
Let $(\sigma_1, f_1) \in \mathbb{R}^4$ and $(\sigma_2, f_2) \in \mathbb{R}^4$ be two points in $\mathscr{A}(x)$, namely
$$f_i = A_0'(x) + u_iA_1'(x), \quad F(x,u_i) \leqslant \sigma_i, \quad i \in \{1,2\} \tag{A6}$$
one has to prove that for all $\epsilon \in [0,1]$, $\epsilon(\sigma_1, f_1) + (1-\epsilon)(\sigma_2, f_2) \in \mathscr{A}(x)$. For this, the following two facts must be proved:

(a) there is some $u$ such that $\epsilon f(x,u_1) + (1-\epsilon)f(x,u_2) = f(x,u)$. This is clearly the case with $u = \epsilon u_1 + (1-\epsilon)u_2$.
(b) For the above $u$, one must have $F(x,u) \leqslant \epsilon\sigma_1 + (1-\epsilon)\sigma_2$. This is only a direct consequence of the convexity of $F(x,u)$ w.r.t. $u$. □

*Proof of Proposition 4*

*Proof of 1*
In the proof we shall use the following notations:

- $\hat{P}^\eta_\rho(\cdot)$, $\hat{Q}^\eta_\rho(\cdot)$ and $\hat{R}^\eta_\rho(\cdot)$ are the optimal trajectories corresponding to the optimal control profile $\hat{f}^\eta_\rho(\cdot)$.
- $\hat{\mu}^\eta_\rho$ denotes the corresponding minimal value of $P + Q$, that is
$$\hat{\mu}^\eta_\rho := \min_{t\in[0,T]} \hat{P}^\eta_\rho(t) + \hat{Q}^\eta_\rho(t)$$
- The trajectories of the extended system under $f \equiv 0$ are denoted by $P_{f\equiv 0}(\cdot)$, $Q_{f\equiv}(\cdot)$ and $R_{f\equiv}(\cdot)$.

With the above notations, it is clear that proving point 1 amounts to establish the following inequality:
$$\hat{\mu}^\eta_\rho \geqslant \rho \tag{A7}$$

The optimality of $\hat{f}_\rho^\eta$ implies

$$\frac{\hat{R}_\rho^\eta(T)}{G(\rho+\eta,\rho)}+\frac{1}{T}\int_0^T (1-\hat{f}_\rho^\eta(t))^2\,\mathrm{d}t \leqslant \frac{R_{f\equiv 0}(T)}{G(\rho+\eta,\rho)}+1 \tag{A8}$$

but since $\eta \leqslant \eta_0$, one has (by definition (22) of $\eta_0$) $\rho+\eta \leqslant \rho_{\min}(P_0, Q_0, T)$ and therefore one has by Lemma 2 applied to the profile $f \equiv 0$ and $r_0 = \rho + \eta$

$$R_{f\equiv 0}(T) = 0 \tag{A9}$$

Furthermore, applying Lemma 2 with the optimal profile $\hat{f}_\rho^\eta(\cdot)$ enables to write

$$\hat{R}_\rho^\eta(T) \geqslant G(\rho+\eta, \hat{\mu}_\rho^\eta) \tag{A10}$$

using (A9)–(A10) in (A8) gives

$$\frac{G(\rho+\eta,\hat{\mu}_\rho^\eta)}{G(\rho+\eta,\rho)} \leqslant 1 \tag{A11}$$

and since $G(\rho+\eta,\cdot)$ is a decreasing function, Equation (A11) clearly gives (A7). □

*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 $(1/T)\int_0^T (1-f(t))^2\,\mathrm{d}t$. Therefore, by the optimality of $\hat{f}_\rho^\eta$, one necessarily has

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

which clearly gives the second inequality in (24). As for the first inequality, this directly stems from the fact that $\hat{f}_\rho^\eta$ 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

$$\hat{J}_\rho \leqslant \frac{1}{T}\int_0^T (1-\hat{f}_\rho^\eta(t))^2\,\mathrm{d}t$$

which clearly ends the proof of 2. As for (24), it is a direct consequence of (25) in which $\rho-\eta$ replaces $\rho$. □

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