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

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POSTA 06

Introduction

The optimal way to administer drugs in cancer treatment chemotherapy remains an open issue because of **a lack of unified models**. This is due to:

- the existence of many types of cancer
- the existence of many different families of drugs

Our focus : cell-cycle-specific chemotherapeutic drugs that act as killing agent

Outlines

- Part I: Model and problematic presentation
- Part II: Preliminary results
- Part III: Main results
- Part IV: Numerical experiments
- Part V: Conclusion

Part I

Model and problematic

Cell-cycle dynamics

Dynamics of the cell-cycle of the bone-marrow cell transition between the proliferating phase and the rest phase:

$$\dot{P} = (\gamma - \delta - \alpha - f(t))P + \beta Q \quad (1)$$
$$\dot{Q} = \alpha P - (\lambda + \beta)Q \quad (2)$$

with

- P number of cells in the proliferating phase
- Q number of cells in the resting phase

K. R. Fister and J. C. Panetta *Optimal Control Applied to Cell-Cycle-Specific Cancer Chemotherapy* . SIAM Journal on Applied Mathematics, 60(3):1059-1072, 2000.

f : **control action** describing the effects of the chemotherapeutic treatment with $f(t) \in [0,1]$

- $f(t) = 0$ no drug injected at time t
- $f(t) = 1$ maximal rate of drug is used

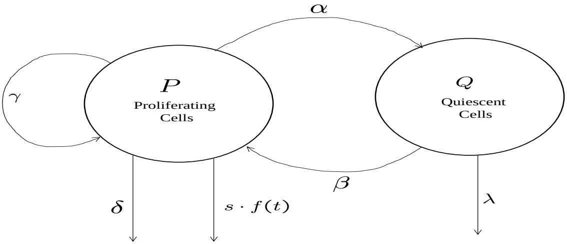

Figure: Schematic view of the cell cycle

Optimal treatment strategy

Design optimal control to maximize the quantity of drug injected over the treatment period T while continuously respecting the following inequality constraint on the state trajectory

$$P(t) + Q(t) \geq \rho \ \forall t \in [0, T]$$

Through the use of weighting parameters

K. R. Fister and J. C. Panetta *Optimal Control Applied to Cell-Cycle-Specific Cancer Chemotherapy* . SIAM Journal on Applied Mathematics, 60(3):1059-1072, 2000.

U. Ledzewicz and H. Schättler *Optimal Bang-Bang Controls for a Two-Compartment Model in Cancer Chemotherapy*, Journal of Optimization Theory and Applications, 114(3):609-637, 2002.

Unconstrained optimal control problems

We propose to design **a family of unconstrained optimal control problems** that approximate to any desired precision the original constrained optimal control problem given by :

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

$$\text{under } f(t) \in [0,1] \quad \text{and} \quad P(t)+Q(t) \geq \rho \quad \forall t \in [0,T] \tag{3}$$

where $(P(t), Q(t))$ solution of (1)-(2) under the control profile $f(\cdot)$ starting from the initial condition (P_0, Q_0)

Part II

Preliminary results

Admissible control profile

Definition

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)

But a solution of $P_\rho(P_0, Q_0)$ **may not exist for any pair** (T, ρ)

Existence of an admissible control profile

Proposition

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*

$$\rho \leq \rho_{min}(P_0, Q_0, T) := \min_{t \in [0,T]} \left[Ce^{A_0 t} \begin{pmatrix} P_0 \\ Q_0 \end{pmatrix} \right] \quad (4)$$

where $C := \begin{pmatrix} 1 & 1 \end{pmatrix}$.

Extended dynamical system $\sum_{r_0}$:

$$\sum_{r_0} \quad \begin{aligned} \dot{P} &= (\gamma - \delta - \alpha - f(t))P + \beta Q && (5) \\ \dot{Q} &= \alpha P - (\lambda + \beta)Q && (6) \\ \dot{R} &= \varphi\Big(r_0 - (P+Q)\Big) \quad ; \quad R(0) = 0 && (7) \end{aligned}$$

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

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

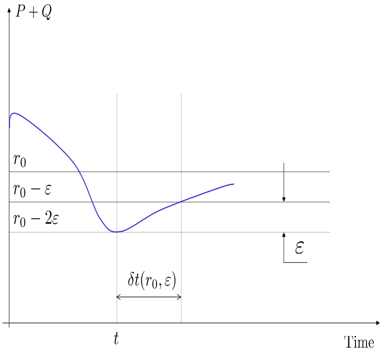

Figure: If at some instant t, $P(t)+Q(t) \le r_0 - 2\varepsilon$, then there is a computable duration $\delta(r_0,\varepsilon)$ during which $P+Q$ is lower than $r_0-\varepsilon$.

LEMMA

For any $r_0 > 0$, any $\varepsilon \le r_0/2$ 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

$$r_0 - (P(\tau)+Q(\tau)) \ge \varepsilon \quad (8)$$
$$\forall \tau \in [t, t+\delta t(r_0,\varepsilon)] \quad (9)$$

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

Indicator on the state constraint violation

LEMMA

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

$$\mu := \min_{t\in[0,T]} \Big[P(t) + Q(t)\Big] \tag{10}$$

then the following inequality holds

$$R(T) \geq G(r_0,\mu) := \frac{1}{\gamma}\ln\Big(\frac{r_0+\mu}{2\mu}\Big)\varphi\Big(\frac{r_0-\mu}{2}\Big) \tag{11}$$

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

Key property: **$R(T)$ a relevant indicator on the state constraint violation** over the treatment period [0,T]

Part III

Main results

Computable approximate solution

AIM: find approximate solutions of the state-constrained optimization problem

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

$$\text{under } f(t) \in [0, 1] \ \text{ and } P(t) + Q(t) \geq \rho \ \forall t \in [0, T] \ (12)$$

in which

$$\rho = \rho_{min}(P_0, Q_0, T) - \eta_0 \, ; \quad \eta_0 > 0. \quad (13)$$

$\rho_{min}(P_0, Q_0, T)$ **is explicitly computable using (4) so that for any given** ρ**,** η_0 **is also computable**

Family of state-unconstrained optimal control problem

For $\eta \in (0, \eta_0)$, the **family of state-unconstrained optimal control problem** is defined on the extended system $\sum_{\rho+\eta}$ as follows:

$$P_\rho^\eta(P_0, Q_0) \quad : \quad \min_{f(\cdot)\in[0,1]^{[0,T]}} \quad \frac{R(T)}{G(\rho+\eta,\rho)} + \frac{1}{T}\int_0^T \Big(1 - f(t)\Big)^2 dt$$
$$\text{with } r_0 = \rho + \eta \text{ in } (7) \tag{14}$$

where $R(T)$: 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 (11)

Properties of the state-unconstrained optimal control problem

For the optimal control problem $P_\rho^\eta(P_0, Q_0)$, we have:

- existence of a solution of $P_\rho^\eta(P_0, Q_0)$

Proposition

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

- an optimal solution of $P_\rho^\eta(P_0, Q_0)$ is an admissible profile for the original problem $P_\rho(P_0, Q_0)$ for any value of η, thus η **is not a weighting coefficient**
- a lower and an upper bound on the exact solution of the constrained problem may be obtained **by solving only unconstrained problems**

Properties of the state-unconstrained optimal control problem

Proposition

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*

$$\hat{J}_\rho \quad \leq \quad \frac{1}{T}\int_0^T \Big(1 - \hat{f}_\rho^\eta(t)\Big)^2 dt \;\leq\; \hat{J}_{\rho+\eta} \tag{15}$$

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*

$$\frac{1}{T}\int_0^T \Big(1 - \hat{f}_{\rho-\eta}^\eta(t)\Big)^2 dt \leq \hat{J}_\rho \leq \frac{1}{T}\int_0^T \Big(1 - \hat{f}_\rho^\eta(t)\Big)^2 dt \tag{16}$$

Part IV

Numerical experiments

Solutions of unconstrained optimal control problem

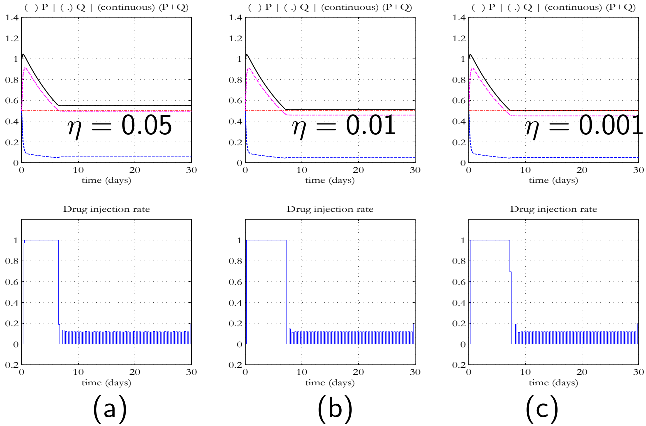

Figure: Solutions of the unconstrained optimal control problems $P_\rho^\eta(0.5, 0.5)$ for different values of the parameter η and using the initialization $f(\cdot) \equiv 0$

Numerical experiments

Those simulations illustrate the following:

- the solutions of the unconstrained problems can approximate the state constraint problem to **any desired precision**
- the constraint is **tightly respected** for smaller values of η and that the quantity of the drug injected is greater when η is smaller
- constraint fulfillment is obtained for **any** positive value of η
- the strategy of **intensive chemotherapy** seems to prevail

A. S. Matveev and A. V. Savkin *Application of optimal Control Theory to Analysis of Cancer Chemotherapy Regimens.*Systems & Control Letters, 46:311-321, 2002.

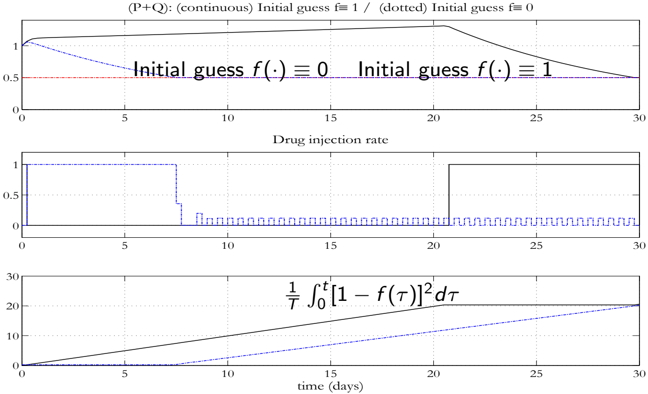

Figure: Comparison between two different solutions of the unconstrained problem $P_{0.5}^{0.001}(0.6, 0.4)$ resulting from two different initial guess $f \equiv 0$ (dotted line) and $f \equiv 1$ (continuous line)

Part V

Conclusion

Conclusions

By considering appropriate state-unconstrained optimal control problems

- the solution of the state-constrained problem 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

Perspectives

Perspectives :

Realistic control schemes have to deal with **parametric uncertainties and/or measurement errors**

$=>$ this work 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