Optimal Control for Cancer Therapy Design

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Abstract

Receding horizon control (RH) is a powerful and well known technique used to embed feedback in the solution of a dynamic optimization problem. In most published approaches, RH control is associated to model predictive control and amounts to minimize a cost defined over an horizon that slides in time. The optimization is done with respect to a sequence of candidate values for the manipulated variable, of which only the first is used. When considering nonlinear control problems, if the candidate sequence of the manipulated variables is left free of any constraint related to the plant dynamics (apart from operational constraints), there is the danger that the numerical method used converges to a local minimum. In this study, instead, the minimization is performed using a relaxation algorithm that approximates the solution of Pontryagin’s optimality conditions. This approach has the advantage of shaping the solution using the state and adjoint equations and, in addition, provides a natural approach to continuous RH problems. This algorithm is applied here to design therapies for tumor growth, modeled by the Gompertz model. A comparison of quadratic costs with costs that lead to sparse control signals, i.e. that are zero instead of assuming a small value, is also done.

Introduction

The possibility of modeling live phenomena by dynamic systems naturally leads to the consideration of dynamic optimization problems associated to them [1], where a time function that represents the manipulated variable along a time horizon is chosen so as to optimize a performance measure. This is true in particular in relation to cancer, where the design of therapies for tumor reduction motivated many studies, of which [2–7] are significant examples. Indeed, optimal control provides a natural mean to formulate the multiobjective problem of reducing the size of a tumor while minimizing the accumulated toxic effect of the drug, or drugs, being administered. Most studies rely on the necessary optimal conditions of Pontryagin [1,8] that are solved using a suitable numerical method [8–10]. The availability of increasing computing power, as well as progress on software, with packages like cvx [11] allowing to solve convex optimization problems by programming their definition almost as in mathematical language, brings a renewed interest on the topic.

The micro-structure and evolution of the bone tissue depends of a complex process in which different cells interact through biochemical signaling substances [12]. The bone is continuously being degraded (resorption) and rebuilt, in a process called remodeling. In a healthy young human adult, bone formation and resorption are equilibrated along time.

The cells that are responsible for these two processes are osteoclasts and osteoblasts. Osteoblasts produce new bone by collagen synthesis and making it calcify. Opposite, osteoclasts are responsible for bone degradation. In the healthy body the number of both types of these cells must be properly coordinated. For that sake, an important inducer of osteoclast differentiation is RANKL ( [13], pp.706). When an osteoclast precursor comes in contact with RANKL molecules, this results in the maturation of an osteoclast. On the other way, osteoblasts produce also OPG that inhibits RANKL and prevents osteoclast maturation. The balance between RANKL and OPG signaling determines the degree of activation of osteoclasts and settles bone remodeling.

Cancer disrupts this balance and causes both bone disturbances and the emission of substances that favor the occurrence of metastases ( [13], pp. 703-709). In particular,
multiple myeloma is an hematological disease characterized by the unrelenting prolif-
eration of plasma cells that causes destructive osteolytic lesions associated with severe
pain and pathological fractures due to decreased osteoblastic and increased osteoclastic
activity [14, 15].

The above process of bone remodeling can be represented by mathematical models that
address both physiological and pathological situations. While many articles have been
published addressing a variety of situations, we only cite here [16]. In this work, a lumped
nonlinear state-space model, with state variables given by the number of osteoclasts and
osteoblasts, has been developed, being able to predict a number of behaviors actually
observed in patients, including nonlinear oscillations.

The above model has been extended in [17] for the myeloma bone disease, including the
tumor size in the state and therapeutic drug administration as manipulated variables.

Although optimal control provides a powerful tool to link clinical requirements to mathe-
matical objectives, the resulting control law is open-loop, with all the inherent drawbacks.
Since, in addition, some optimal drug administration profiles are such that, for a long
period, the drug dose is kept at a minimum level, being only increased close to the end of
the optimization interval, this means that the patient will remain with little or no treat-
ment at all for a significant period of time. To circumvent this problem, [6] proposes to
split the optimization interval in two parts.

To tackle the above problems, we examine in the possibility of using a receding horizon
(RH) strategy [18], in which, at a given time $t$, an optimal control problem is solved in the
time horizon between $t$ and $t + T$, called the prediction horizon. Of the resulting control
function only the part between $t$ and $t + \delta$ is actually used, with the whole procedure
being repeated at $t + \delta$. This procedure has the advantage of making a feedback every
$\delta$ units of time. Usually, RH control is considered in the framework of discrete-time
predictive control [19], and the samples of the manipulated variable along the prediction
horizon are left free and, in nonlinear problems, can be stuck by local minima. In this
study, instead, we use Pontryagin’s minimum principle to select them. Although the
idea of using Pontryagin’s principle together with RH control is not new [20, 21], this has
not been considered for tumor growth control.

The report is organized in two parts: A first part were two models for the tumor growth
are presented, along with two possible cost functional for the optimal control law. A
second part describes the bone remodeling model incorporating the tumor growth dy-
namics and a study on the Gompertz model with different parameters in order to meet
the bone remodeling model parameters. The first part is organized as follows: The two
tumor growth models and the therapies considered are described in section 1. In section
2 is performed a study of optimal control design for the two models of tumor growth
considered. Pontryagin’s minimum principle (PMP) is also reviewed in section 2, to-
gether with a numerical solution algorithm for optimal control problems and application
examples. Section 3 formulates the RH algorithm based on PMP and shows results
on tumor growth for both models. The second part is organized as follows: The bone
remodeling dynamics is presented in section 4 and study on the Gompertz model with
different parameters is presented in section 5 for optimal control and in section 6 for
receding horizon strategy. In section 7 is presented the PI controller designed for bone
mass recovery acceleration. Finally, section 7 draws conclusions.
PART I

1 Tumor growth dynamics and therapies

Let $X \in \mathbb{R}$ be a function of time that reflects the size of a tumor. The most simple model for the evolution of $X$ is

$$\dot{X}(t) = a X(t) - b u(t),$$  \hspace{1cm} (1)

where $a$ and $b$ are positive parameters and $u$ is a time function that reflects the drug administered to the patient by unit of time.

In the absence of treatment, model (1) leads to and exponential growth of $X$. The treatment corresponds to a positive function $u$ and reduces the growth rate of $X$. If $u$ is large enough, $X$ may decrease and even become negative, which is a non-realistic assumption, and limits the range of values for which the model is valid.

A more realistic model is the Gompertz model that is widely used in the literature

$$\dot{X}(t) = \gamma X(t) \log\left(\frac{L}{X(t)}\right) - \epsilon_1 X(t) u(t),$$  \hspace{1cm} (2)

where, again, $\gamma$, $\epsilon_1$ and $L$ are positive parameters.

In the absence of treatment, model (2) leads now to an S-shaped growth, with $x$ tending to $M$ when time increases.

The manipulated variable $u$, assumed to be positive, also causes a decrease on the rate of growth of $X$. However, when $X$ becomes small, the effect of $u$ also decreases and there is no danger that $X$ is driven to negative values.

Two therapies are considered. One has the function of killing the tumor cells that corresponds to the manipulated variable $u(t)$ in (2) being obtained with an optimal control law.

A second therapy is considered where bisphosphonates are administered to suppress the production of osteoclasts. This therapy is associated to the variable $v(t)$. Therefore, (32) becomes

$$\dot{C}(t) = \alpha_1 C(t)^{g_{11}} \left(1+r_{11} \frac{X(t)}{L}\right) B(t)^{g_{21}} \left(1+r_{21} \frac{X(t)}{L}\right) - \left(\beta_1 + \epsilon_2 v(t)\right) C(t),$$  \hspace{1cm} (3)

where $\epsilon_2$ is a nonnegative parameter. The design of this therapy is formulated as a regulation problem that is to be solved with a proportional-integral (PI) controller that drives the bone mass to a prescribed value that is close to the healthy situation.

1.1 Associated control problems

Assume that there is a period of time $t$, between $t = 0$ and $t = T$, in which a therapy is to be specified, in the form of a function $u : [0, T] \to \mathbb{R}$. When designing such a function, two conflicting objectives have to be considered. First, the tumor size $X$ is to be driven to a small value, an objective which demands high values of $u$. Second, the toxicity, which is a function of the cumulative drug dose applied is to be minimized, an objective that calls for small values of $u$. Both these objectives are expressed in mathematical terms in a cost functional to be minimized. Two possibilities explored in this article are:
- **Quadratic cost**

\[ J_1 = \eta X(T) + \int_0^T \left[ \xi X^2(t) + \rho u^2(t) \right] dt. \]  

The quadratic cost assumes that the toxic effects of the therapy are proportional to \( u^2 \). In (4) \( \eta, \xi, \) and \( \rho \) are parameters.

- **Minimum therapy cost**

\[ J_2 = x(T) + \rho \int_0^T u(t) dt. \]  

The minimum therapy tries to balance the tumor sized at the end of the optimization interval, \( X(T) \), and the total amount of drug administered.

For the problem to be well posed, for \( J_2 \) it is assumed that, for any \( t \in [0, T] \), \( u \) verifies

\[ 0 \leq u \leq u_{\text{max}}, \]  

where \( u_{\text{max}} \) is a parameter.

In both cases, \( \rho > 0 \) is a parameter that defines the balance between both objectives. Smaller values of \( \rho \) lead to larger values of \( u \) and smaller values of \( X(T) \), and conversely.
2 Optimal control

2.1 Pontryagin’s minimum principle

Consider the following optimal control problem:

**Problem 1**

Let
\[ \dot{X} = f(X, u), \quad X(t_0) = X_0, \]  
(7)
with \( X \in \mathbb{R}^n, t \in [0, T] \) with, \( T \) constant and, for each \( t, u \in U \subset \mathbb{R} \), where \( U \) is a convex set of admissible control values. It is assumed that there is one and only one solution to (7).

Find \( u \) such as to minimize the cost
\[ J = \Psi(X(T)) + \rho \int_0^T L^*(X, u) \, dt. \]  
(8)
with \( \Psi \) and \( L^* \) given functions.

A set of necessary conditions satisfied by the solution of Problem 1 is given by

**Pontryagin’s minimum principle** [8]

Along an optimal trajectory for \( X, u \) and \( \lambda \), the following necessary conditions for the solution of Problem 1 are verified:

- The state \( X \) and \( u \) verify the state equation (7), with the prescribed initial condition.
- The co-state \( \lambda \) verifies the adjoint equation
\[ -\dot{\lambda} = \lambda^T f_X(X, u) + L^*_X(X, u), \]  
(9)
with the terminal condition
\[ \lambda(T) = \Psi_X(X)\big|_{X=X(T)}. \]  
(10)
- For each \( t \), the Hamiltonian function, defined by
\[ H(\lambda, X, t) = \lambda^T f(X, u) + L^*(X, u), \]  
(11)
is minimum with respect to \( u \).

In (9), the following notation is used with \( i \) the line index and \( j \) the columns index
\[ f_X(X, u) = \left[ \frac{\partial f_i}{\partial X_j} \right], \quad L_X = \left[ \frac{\partial L^*_i}{\partial X_j} \right], \quad \Psi_X = \left[ \frac{\partial \Psi}{\partial X_j} \right]. \]  
(12)
2.2 Exponential growth with quadratic cost

In relation to tumor growth, the problem with the linear model \( (1) \) and either \( J_1 \) or \( J_2 \) admits a closed form solution that is interesting because it provides some insight on what to expect in more complicated cases. Therefore, start by considering the linear model \( (1) \) with the quadratic cost \( J_1 \) given by \( (4) \). It is assumed that \( \eta = 1 \) and \( \xi = 0 \). For simplicity we consider the case \( a = 1 \).

The adjoint equation \( (9) \) with the co-state terminal condition \( (10) \) becomes

\[
\dot{\lambda} = -\lambda, \quad \lambda(T) = 1, \tag{13}
\]

that yields the explicit solution for the co-state

\[
\lambda(t) = e^{T-t}. \tag{14}
\]

The Hamiltonian function \( (11) \) is

\[
H = \lambda(X - bu) + \rho u^2. \tag{15}
\]

Since \( H \) is a quadratic function and there are no constraints, the minimum verifies

\[
\frac{\partial H}{\partial u} = 0. \tag{16}
\]

From \( (16) \) and \( (14) \), it follows that the optimal control law is

\[
u^*(t) = \frac{b}{\rho} e^{T-t}. \tag{17}\]

2.3 Exponential growth with sparsity cost

Consider again the exponential growth model \( (1) \), but now with the cost \( J_2 \) given by \( (5) \). The adjoint equation is again given by \( (13) \), with the same terminal condition. The co-state is therefore given by \( (14) \).

However, the Hamiltonian is given by

\[
H = \lambda X + (\rho - b \lambda)u. \tag{18}
\]

Since the Hamiltonian has now a linear dependency on \( u \), its minimum value is obtained at the boundary of the set of the admissible values for \( u \), which is the interval \([0, u_{\text{max}}]\).

If \( \lambda < \rho/b \), \( H \) is an increasing function of \( u \), and the minimum is at the minimum possible for \( u \), given by \( u = 0 \). Conversely, if \( \lambda > \rho/b \), \( H \) is a decreasing function of \( u \), and the minimum is at \( u = u_{\text{max}} \). Therefore, from \( (14) \), it is concluded that there is an instant \( t_s \) in which the drug dose switches from \( u_{\text{max}} \) (for \( t < t_s \)) to 0 (for \( t > t_s \)). The switching time \( t_s \) can be computed from the condition

\[
\lambda(t_s) = \frac{\rho}{b}, \tag{19}
\]

yielding

\[
t_s = T - \log \left( \frac{\rho}{b} \right). \tag{20}\]

Comparing the control laws obtained by minimizing \( J_1 \) and \( J_2 \) it is concluded that \( J_2 \) yields a so-called sparse control law. While \( J_1 \) yields a control law that starts from its highest value and then progressively decreases, \( J_2 \) yields a control law that never attains small values, replacing them by zero. Sparse optimal control is a topic that is receiving an increased attention [22].
2.4 Gompertz model with sparsity cost

Consider the Gompertz model (2), with the minimum therapy cost \( J_2(5) \). For \( \eta = 0 \), the adjoint equation becomes

\[
\dot{\lambda} = \lambda \left( 1 + \epsilon_1 X - \gamma \log \left( \frac{L}{X} \right) \right) - \gamma
\]

(21)

with the terminal condition \( \lambda(T) = 1 \), and the Hamiltonian equation is

\[
H = \lambda \gamma X \log \left( \frac{L}{X} \right) - \epsilon_1 \lambda X u + \rho u.
\]

(22)

In the same way as (19), the Hamiltonian is linear on \( u \) and the control law is of bang-bang type.

2.5 Gompertz model with quadratic cost

Consider the Gompertz model (2) for the tumor growth, with the quadratic cost \( J_1(4) \). For \( \eta = 0 \), the adjoint equation becomes

\[
\dot{\lambda} = \lambda \left( 1 + \epsilon_1 X - \gamma \log \left( \frac{L}{X} \right) \right) - 2 X,
\]

(23)

with the terminal condition \( \lambda(T) = 0 \) The Hamiltonian equation is, in this case

\[
H = \lambda \gamma X \log \left( \frac{L}{X} \right) + X^2 - \epsilon_1 \lambda X u + \rho u^2.
\]

(24)

Since no restrictions are imposed, from (16), the optimal control law is given by

\[
u^*(t) = \frac{\epsilon_1}{2 \rho} \chi(t) x(t).
\]

(25)

2.6 Numerical solution

When considering the Gompertz, or other nonlinear models, it is not possible to obtain the optimal control law in an analytical way. A possibility is to use the following numerical relaxation algorithm

**Algorithm A1**

Divide the time interval between \( t = 0 \) and \( t = T \) into \( N \) subintervals of duration \( \Delta t = T/N \). Let \( t_i = (i-1)\Delta t \), \( i = 1, \ldots, N + 1 \). To each \( t_i \) associate a value \( u_i \) and let the linear interpolation of these values in each subinterval define the control function.

Recursively execute the following steps:

1. For \( i = 1, \ldots, N + 1 \) select an initial guess of the optimal control, \( u_i \). Set the iteration counter \( K = 0 \).
2. Solve forward (from \( t = 0 \) to \( t = T \) the state equation (7) with the initial condition \( X_0 \) and the control that results from the interpolation of the \( u_i^K \).
3. Solve backwards (\( t = T \) to \( t = 0 \)) the adjoint equation (9) with the terminal condition (10).
4. For $i = 1, \ldots, N + 1$

$$u_i^{K+1} = \arg \min_v \left( H \left( \lambda(t_i), x(t_i), v \right) \right)$$

subject to $u_i^{K+1} \in U, \forall i$.

5. Set $K = K + 1$ and go to step 2. until convergence is met.

Steps 2. and 3. are solved with an appropriate ordinary differential equation solver. In the examples reported in the next section, MATLAB `ode45` with variable step-size and precision of $10^{-6}$ has been used. For step 4. the `cvx` MATLAB interface has been used [11].
3 Receding horizon control

The numerical approximation of the optimal control obtained from Algorithm A1 can be recast in a RH framework as follows.

**Algorithm A2**

At time \( t \), recursively compute the following steps:

1. Solve the optimal control problem with \( X_0 = X(t) \) (the state at time \( t \)) as initial condition, from \( t \) to \( t + T \), using Algorithm A1.

2. Apply to the system the optimal control approximation obtained in step 1., from \( t \) to \( t + \delta \).

3. Make \( t \leftarrow t + \delta \) and go to step 1.

\[ \square \]

3.1 Gompertz model with quadratic cost

Figs. 1, 2 and 3 compare the optimal control with RH control for different values of \( \delta \) for a situation in which the Gompertz model (2) is used with \( \gamma = 0.3, \epsilon_1 = 0.45, L = 1 \), and \( X_0 = 0.975 \). The cost functional is quadratic (4), with \( \eta = 0, \xi = 1 \), and \( \rho = 0.3 \).

![Figure 1: RH control for different values of \( \delta \) and the optimal control (O.C.) for the same horizon \( T = 20 \) days.](image)

As it is apparent, smaller values of \( \delta \) lead to a bigger degradation with respect to the optimal control performance. However, a smaller \( \delta \) has the advantage of causing feedback more often, thereby rejecting unmeasurable disturbances when \( \delta \) increases, the performance approaches the optimal one (Fig. 2).

Another advantage of RH control is that (Fig. 1), close to \( t = T \), it does not drastically reduce the dose as happens with the optimal law (for \( \eta = 0 \)). For optimal control this drawback can be circumvented by using a nonzero value for \( \eta \) in order to adjust the terminal cost.
Figure 2: Quadratic cost of the RH control for different values of $\delta$, with an horizon of $T = 20$ days. The optimal control $J^*$ is indicated by the arrow.

Figure 3: Cumulative drug dose applied, $P(T)$, for different values of $\delta$, with an horizon of $T = 20$ days.
Fig. 4 illustrates the effect of parameter $\rho$. When $\rho$ increases, more importance is given to the toxicity term, associated to $u$, in (4). Hence, the cumulative drug dose applied during the whole horizon, $P(T)$, decreases when $\rho$ increases. The price to pay is that, consequently, the final tumor size $X(T)$ increases.

Fig. 5 illustrates the capacity of the RH control to reject a disturbance, in contrast with the optimal controller. In the simulation reported in Fig. 5, a stochastic disturbance has been added to the Gompertz model. This disturbance can be interpreted as a modeling error. When the optimal controller is used, no corrective actions are taken because the manipulated variable is computed off-line, a blind way. Instead, when using RH control there is a feedback associated to the measure of tumor size, that influences the initial condition of the computation every $\delta = 5$ days. As a consequence, RH control is able to counteract the disturbance and leads to a small tumor size.

Figure 4: Effect of the parameter $\rho$ of the cost functional on the RH controller action, for an horizon of $T = 20$ days, and with $\delta = 5$ days. The tumor reduction $X(t)$ and the controller action $u(t)$ are plotted on the first two plots. The final tumor size $X(T)$ for the different values of $\rho$ is plotted on the top right plot and the final cost functional $J(T)$ and the cumulative drug dose $P(T)$ are plotted on the bottom two plots.
Figure 5: RH closed-loop control performance for an horizon of $T = 20$ days and $\delta = 5$ days, in the presence of disturbances. The optimal control (O.C.) for the same horizon is also plotted.

3.2 Gompertz model with sparsity cost

When using the functional (5), the Hamiltonian function becomes a linear function of $u$, and the optimal control can only assume the extreme values of $u$, either $u = 0$ or $u = u_{\text{max}}$. Indeed, the Hamiltonian (22) a linear function of $u$.

Let

$$\theta = \rho - \lambda \epsilon_1 X$$

be the slope of the Hamiltonian with respect to $u$. From Fig. 6, it is apparent that, if $\theta > 0$ the optimal choice of $u$ is $u^* = 0$, while if $\theta < 0$ the optimal choice is $u^* = u_{\text{max}}$.

An example is provided if Figs. 7, 8 and 9 for $\rho = 0.03$ and $T = 20$. Fig. 8 shows the co-state and Fig. 7 shows the state along the optimal trajectories obtained with Algorithm A1. From these optimal trajectories it is possible to compute the slope $\theta$ and to compare it with zero. When $\theta$ crosses 0, there is a switching in the value of the manipulated variable form $u = 0$ (before the switching instant $t_s$) to $u_{\text{max}}$. The value of $t_s$ is marked by an arrow in Fig. 9 and coincides with the transition computed by Algorithm A1 and shown in Fig. 7.
Figure 7: Optimal control performance for an horizon of $T = 20$.

Figure 8: The co-state $\lambda$ computed for the optimal control plotted in Fig. 7.

Figure 9: The slope $\theta$ as a function of time, computed for the optimal control plotted in Fig. 7. The vertical arrow indicates the switching time $t_s$. 
Fig. 10 shows the switching time $t_s$, assuming that there is only one switch between $u = 0$ before $t_s$ and $u = u_{\text{max}}$ after $t_s$, for an horizon of $T = 20$. A similar dependence holds for $T = 5$. This plot clearly shows that there is a minimum of the cost.

Figure 10: The cost (5) as a function of the switching time $t_s$ when $u$ is only allowed to vary from 0 to $u_{\text{max}}$.

Fig. 11 provides an example in which the cost (5) is used with $\rho = 0.03$ and $T = 5$, both for optimal and RH control.
Figure 11: RH closed-loop control performance with the minimum therapy cost for an horizon of $T = 5$ days and $\delta = 2.5$ days. The optimal control (O.C.) for the same horizon is also plotted.
4 Bone remodeling dynamics

The model used in this study corresponds to the one described in [16, 17], with slight modifications. These modifications consist in the way that the drug affects the tumor growth equation, and also the way the drugs affect the remodeling part of the model.

4.1 Bone remodeling model

The bone remodeling process involves the activity of osteoclasts, which are cells that breakdown bone in a process called bone resorption, and osteoblasts, that are responsible for bone formation. The mathematical model that expresses the dynamic interaction between osteoclasts $C(t)$ and osteoblasts $B(t)$, described in [16], uses normalized variables and is

$$
\dot{C}(t) = \alpha_1 C(t)^{g_{11}} B(t)^{g_{21}} - \beta_1 C(t),
$$

$$
\dot{B}(t) = \alpha_2 C(t)^{g_{12}} B(t)^{g_{22}} - \beta_2 B(t),
$$

where $\dot{Y}$ is the derivative of the number of cells $Y$, parameters $\alpha_i$ and $\beta_i$, with $i = 1, 2$, represent the activity of cell production and removal, and parameters $g_{ij}$, with $i, j = 1, 2$ describe the net effect of all the factors that are involved in osteoclasts and osteoblasts formation. For instance, the effect of all the factors produced by osteoclasts that regulate its own production are expressed by parameter $g_{11}$, referred as autocrine regulation, while parameter $g_{12}$ express the regulation of osteoclasts in the production of osteoblasts, referred as paracrine regulation. Conversely, parameters $g_{21}$ and $g_{22}$ are the paracrine and autocrine regulation, respectively, of all the factors produced by osteoblasts. In this model, the parameter $g_{11}$ is responsible for the oscillatory mode of the bone remodeling process [16].

The bone mass $Z(t)$ is modeled by

$$
\dot{Z}(t) = -\kappa_1 C^*(t) + \kappa_2 B^*(t),
$$

where parameters $\kappa_i$, for $i = 1, 2$, are the normalized activity of bone resorption and bone formation constants. In (30), the number of cells $Y^*$ is given by

$$
Y^*(t) = \begin{cases} 
Y(t) - Y_e & \text{if } Y(t) > Y_e, \\
0 & \text{if } Y(t) \leq Y_e,
\end{cases}
$$

where $Y_e$ is the steady state of $\dot{Y}(t)$.

In the presence of bone pathologies, the bone remodeling dynamics is disrupted. In [17], the tumor dynamics $X(t)$ is incorporated in the bone remodeling process, describing the osteoclasts and osteoblasts dynamics by

$$
\dot{C}(t) = \alpha_1 C(t)^{g_{11}} \left(1 + r_{11} \frac{X(t)}{L}\right) B(t)^{g_{21}} \left(1 + r_{21} \frac{X(t)}{L}\right) - \beta_1 C(t),
$$

$$
\dot{B}(t) = \alpha_2 C(t)^{g_{12}} \left(1 + r_{11} \frac{X(t)}{L}\right) B(t)^{g_{22}} - \beta_2 B(t).
$$
where $r_{ij}$, with $i, j = 1, 2$, are nonnegative parameters. The steady state solution of (32) and (33) is

$$C_e = \left( \frac{\beta_1}{\alpha_1} \right) \frac{1 - (g_{22} - r_{22})}{\Delta} \left( \frac{\beta_2}{\alpha_2} \right) \frac{g_{21}(1 - r_{21})}{\Delta},$$  \hspace{1cm} (34)

$$B_e = \left( \frac{\beta_1}{\alpha_1} \right) \frac{g_{12}}{(1 + r_{12})\Delta} \left( \frac{\beta_2}{\alpha_2} \right) \frac{1 - g_{11}(1 + r_{11})}{\Delta},$$  \hspace{1cm} (35)

where

$$\Delta = \frac{g_{12}g_{21}(1 - r_{21})}{1 + r_{12}} - (1 - g_{11}(1 + r_{11}))(1 - g_{22} + r_{22}),$$  \hspace{1cm} (36)

and it is assumed that $X$ is also in its steady state.

Fig. 12 shows the tumor growth dynamics (2) and the bone remodeling dynamics. The bone remodeling model parameters chosen are in accordance with [16,17]. The bone cell formation constant rates assume values of $\alpha_1 = 3$ cells/day and $\alpha_2 = 4$ cells/day, and the bone cell removal constant rates take values of $\beta_1 = 0.2$ day$^{-1}$ and $\beta_2 = 0.02$ day$^{-1}$. The autocrine and paracrine parameters take values of $g_{11} = 1.1$, $g_{22} = 0$, $g_{12} = 1$ and $g_{21} = -0.5$. The parameters $r_{ij}$ take values of $r_{11} = 0.005$, $r_{22} = 0.2$, $r_{12} = 0$ and $r_{21} = 0$. The constants of the normalized activity of the bone formation and resorption assume values of $k_1 = 0.0748$ cell$^{-1}$ day$^{-1}$ and $k_2 = 3.22 \times 10^{-4}$ cell$^{-1}$ day$^{-1}$. The initial values are $C(0) = 15$, $B(0) = 316$ and $X(0) = 1$. Here, the tumor growth model assume values of $\gamma = 0.005$ and $L = 100$. 

![Figure 12: Bone remodeling dynamics in the presence of tumor growth.](image_url)
5 Optimal control of Gompertz model with different parameters

In this section the parameters considered for the Gompertz model of the tumor growth is the same parameters considered in the simulation of Fig. 12, and therefore, $\gamma = 0.005$ and $L = 100$.

Considering the Gompertz model (2) with the quadratic cost (4) ($\xi = 0$), the Hamiltonian function is (24) and, from (16), its minimum is

$$u^*(t) = \epsilon_1 \frac{\lambda(t) X(t)}{2 \rho},$$

which is the optimal control law. The computation of the minimum with respect to $u$ of the Hamiltonian function by (16) assumes that the minimum is an interior point of the set of admissible control values $U$. This assumption has to be checked a posteriori. If the minimum occurs at the boundary of $U$, one must resort to a minimization algorithm. The package cvx [11] can be used in this problem. The advantage of using the closed formula (37) is its faster computation speed.

Fig. 13 provides the optimal control law for an horizon of $T = 180$ days, for different values of $\rho$, showing that for smaller values of $\rho$, the drug dose increases, while the tumor size decreases. The final value of $u$ is always zero since, at every $t$, this variable is proportional to $\lambda$, and the final value of $\lambda$, $\lambda(T) = 0$. As a consequence, $X(t)$ increases when $t$ approaches $T$. This situation could be changed by modifying the cost imposing a penalty on the final tumor size $X(T)$. From (10) it is concluded that $\lambda(T)$ would no longer vanish, neither $u(t)$. Parameter $\epsilon_1$ has the value of 0.018 and $X(0) = 80$.

![Figure 13: Optimal control performance for an horizon of $T = 180$. Effect of the parameter $\rho$.](image)

Fig. 14 illustrates the effect of parameter $\rho$. When $\rho$ increases, more importance is given to the toxicity term, associated to $u$, in (4). Hence, the cumulative drug dose applied during the whole horizon, $P(T)$, decreases when $\rho$ increases. The price to pay is that, consequently, the final tumor size $X(T)$ increases.

Figs. 15, 16, 17 and 18 show a sensitivity study of the results obtained with optimal control when the parameters of the Gompertz model (2) have values that are different
Figure 14: Effect of the parameter $\rho$ of the cost functional on the O.C. law, for an horizon of $T = 180$ days. The final cost functional $J(T)$ and the cumulative drug dose $P(T)$ are plotted on the top two plots and the final tumor size $X(T)$ is plotted on the left bottom plot, as functions of the parameter $\rho$. The final tumor size is plotted as a function of the cumulative drug dose, for each $\rho$, on the right bottom plot.

from the ones assumed when performing control design. Fig. 15 shows the change $\Delta J$ in percentage of the cost $J$ when the optimal control computed with the nominal value of the parameters $\gamma$ and $L$ is applied to the Gompertz model with varied parameters $\gamma + \Delta \gamma$ and $L + \Delta L$. For $\Delta \gamma = 0$ and $\Delta L = 0$ is is $\Delta J = 0$. As is apparent from Fig. 15, the sensitivity of the cost with respect to perturbations on $\gamma$ and $L$ is approximately linear. Fig. 16 shows the time evolution of the tumor size $X$, where the optimal control $u$ computed with the nominal parameter is applied to the model with values of the parameters that vary with respect to the nominal ones, corresponding to the extremes of the variation range in Fig. 15. Figs. 17 and 13 show similar results for parameter $\epsilon_1$. Also here, the sensitivity of the cost with respect to $\Delta \epsilon_1$ is approximately linear, as shown in Fig. 17. Fig. 18 shows the time evolution of the tumor when $\epsilon_1$ assumes different values, but always using the nominal value in controller design.
Figure 15: Change of the cost as a function of changes of $\gamma$ and $L$ when the optimal control is designed for the nominal value of the parameters.

Figure 16: Tumor evolution of $X$ when the optimal control is designed for the nominal values of the parameters $\gamma$ and $L$. 
Figure 17: Change of the cost as a function of changes of $\epsilon_1$ when the optimal control is designed for the nominal value of the parameter.

Figure 18: Time evolution of $X$ for different values of parameter $\epsilon_1$, when the optimal control is designed for the nominal parameters.
6 RH for Gompertz model with different parameters

In this section the parameters considered for the Gompertz model of the tumor growth is the same parameters considered in the simulation of Fig. 12.

Figs. 19, 20 and 21 compare the optimal control with RH control for different values of $\delta$.

![Graph showing tumor size and control over time](image)

Figure 19: RH control for different values of $\delta$ and the optimal control (O.C.) for the same horizon $T = 180$ days.

![Graph showing quadratic cost over $\delta$](image)

Figure 20: Quadratic cost of the RH control for different values of $\delta$, with an horizon of $T = 180$ days. The optimal control $J^*$ is indicated by the arrow.

As shown in Fig. 19, close to $t = T$, RH control does not drastically reduce the dose as happens with the optimal law, and decreases the final tumor size. For optimal control this drawback can be circumvented by using a convenient terminal cost. However, the optimal control is designed for a horizon of fixed length. If the control action is to be kept for an indefinite period of time, it is better to use RH control. Another advantage is that RH control provides a feedback control, being able to update the state variables in order to reject disturbances. Fig. 20 and 21 show the decreasing cost and cumulative...
drug dose as $\delta$ increases. The highest lower bound of the cost is, of course, the one obtained for $\delta = T$.

Fig. 22 illustrates the capacity of the RH control to reject a disturbance, in contrast with the optimal controller. In the simulation reported in Fig. 20, a stochastic disturbance has been added to the Gompertz model. This disturbance may correspond to a modeling error, either due to a model/controller parameter mismatch, or associated with unmodeled dynamics. The disturbance model has been selected merely for exemplificative purposes, and corresponds to a sequence of independent random variables with a gaussian distribution, with zero mean and variance 2, with a sampling interval of 0.5 days, that is passed by a filter with transfer function

$$F_n(s) = \frac{0.5}{s + 0.5}. \quad (38)$$

When the optimal controller is used, no corrective actions to counteract the disturbance are taken because the manipulated variable is computed off-line, in a blind way. Instead, when using RH control there is a feedback associated to the measure of tumor size, that influences the initial condition of the computation every $\delta = 60$ days. As a consequence, RH control is able to counteract the disturbance and leads to a smaller tumor size.
Figure 22: RH closed-loop control performance for an horizon of $T = 180$ days and $\delta = 60$ days, in the presence of disturbances. The optimal control (O.C.) for the same horizon is also plotted.
7 PI control for bone mass regulation

If the tumor size is reduced due to the specific therapy that is dosed by the optimal controller, the bone mass will increase, but very slowly. In order to speed-up bone mass recovery, a PI controller for the bone mass regulation is presented in this section. In this case it is considered that the optimal control law for the tumor growth is applied to the system and a PI controller is used to suppress the osteoclast production by scheduling and adequate therapy. The PI controller is designed to track the error $e(t)$ between the desired value of the bone mass (100%) and the measured bone mass $Z(t)$, and to compute the appropriate drug dose $v(t)$ in order to prevent the bone mass resorption form the osteoclasts. The control signal is the drug dose $v(t)$, which is applied in (34), and is defined by

$$v(t) = K_p e(t) + K_i \int_0^T e(t) \, dt.$$  \hfill (39)

The parameters considered for the bone remodeling model are the same parameters considered in the simulation of Fig. 12, described in section 1. Fig. 23 shows the effect of a PI controller with $K_p = 0.01$ and $K_i = 0.02$, for $\epsilon_2 = 0.03$, applied to the system with the RH controller designed for $T = 180$ days and $\delta = 60$ days for the tumor growth control. The PI controller is able to increasingly drive the bone mass to the desired value faster than without PI control. The controller action $v(t)$ suppresses the osteoclasts production that leads to higher values of bone mass.
Figure 23: Bone remodeling and tumor growth dynamics with and without the PI controller for bone mass regulation.
Conclusions

The combination of optimal and receding horizon control provides a natural framework to obtain therapies for tumor growth, that was complemented with a PI controller for bone therapy. Optimizing the therapy can be readily formulated as an optimal control problem, whose solution yields a time profile for drug administration. This open-loop solution can be transformed into a feedback control law, with all the inherent advantages, by using the receding horizon strategy. In an example provided, RH improves control performance with respect to the open-loop optimal control in the presence of disturbances.

A number of important issues were not addressed in this report. The first one is drug resistance and multi-drug treatment.

Other aspects are related to improving the model in what concerns drug administration, and they comprise the inclusion of pharmacokinetic drug models, modeling the fact that drugs have no effect below some threshold, and the fact that drugs are not continuously perfused in the patient but instead are administered in concentrated time doses that are best represented as a sequence of impulses.

Although the above aspects are essential when modeling a realistic therapy of cancer, they exceed the objective of this study that was circumscribed to make a first illustration of how the receding horizon can be applied to cell-kill strategies to turn an optimal profile into a feedback control law and complement it with a PI controller to moderate osteoclast excessive action and speed-up bone mass recovery.
References


