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Optimal discrete time control of antiangiogenic tumor therapy ⋆

Dániel András Drexler * **Johanna Sápi** * **Levente Kovács** *

* *Physiological Controls Research Center, Research and Innovation Center of Óbuda University, Óbuda University, Hungary (e-mails: {drexler.daniel,sapi.johanna,levente.kovacs}@nik.uni-obuda.hu).*

Abstract: The efficiency of therapeutic cancer treatment protocols can be increased by incorporating knowledge about the underlying physiological processes into the design of the protocol. The aim of this work is to find the optimal protocol resulting in minimal drug usage for fixed resting time between measurements and treatments (the sampling time) and predefined tumor volumes for the inspections. The minimal amount of drug is calculated by a binary search algorithm using the model of tumor growth. The monotonicity of the tumor growth model is proved providing that the search algorithm finds the optimal solution. The optimal therapeutic protocol is calculated for different sampling times, and we find that relatively small sampling times are desirable in many aspects.

Keywords: Physiological models, Optimal control, Nonlinear systems, Tumor therapy, Biomedical control.

1. INTRODUCTION

Antiangiogenic therapy is a targeted molecular therapy (TMT) that does not target the tumor cells directly, but acts by inhibiting angiogenesis, the formation of new blood vessels required to nourish the tumor cells when they grow beyond a certain size (see e.g. Kubota (2012)). Angiogenic inhibition is mostly used in combination with chemotherapy or radiotherapy, however application as monotherapy is also being considered recently. We consider the application of angiogenic inhibition as a monotherapy, and seek for optimal therapeutic protocols.

There are three major ways of drug administration in protocols in clinical practice: a) bolus doses (BDs), b) low-dose metronomic (LDM) regimen, and c) continuous infusion therapy. In the case of administration of intermittent bolus doses, the patient receives drug on given days and the therapy has rest periods between the injections. The injected amount of boluses can be the maximum tolerated dose (MTD) or a lower dose. The length of the rest periods depends on the amount of boluses, e.g. after MTD a longer rest period is required. The disadvantage of this method is that it involves regrowth of tumor cells, and in several cases the growth of selected clones will be resistant to the therapy, see e.g. Scharovsky et al. (2009). In order to avoid this adverse event, the anti-cancer drug can be administered in low doses over prolonged periods without extended rest periods which is called low-dose metronomic therapy, see e.g. Browder et al. (2000). Advantages of LDM are its antitumor efficacy and reduced acute toxicity; however its major disadvantage is the empiricism associated with determining the optimal biologic dose (OBD) as pointed out in Kerbel (2007). This is the most important problem oncologists are faced with when they are trying to translate LDM into the clinical application; however, according to our investigations, this can be solved by a closed-loop control, see e.g. Sápi et al. (2015b). The third way of drug administration is the continuous infusion therapy which is applicable within clinical environment, but not yet as a portable device, that has been investigated using closed-loop control in e.g. Sápi et al. (2015a) or Sápi et al. (2013). We investigate protocols of the first (BD) and second (LDM) type in this article focusing on the question whether more frequent, low-dose injections, or relatively rare, but large-dose injections are more desirable from the point of view of clinical applications.

In clinical practice, attaining the optimal dose requires a lot of empiricism. However, if we have a reliable model of the tumor growth and the parameters characterizing the tumor and the patient, we can use that model with those parameters to calculate the optimal dosage of the drug. In this article, we calculate the optimal dosages for different rest periods (or sampling time in engineering terminology) based on the tumor growth model proposed by Hahnfeldt et al. (1999) presented in Section 2.

In the light of the dosage problem, there are several articles in the literature which discuss controller managed antiangiogenic therapy. Nath et al. (2010) developed a nonlinear control using a new technique where an optimal desired trajectory was designed to minimize a performance index. They considered parametric uncertainties in the system model and an adaptive controller solved the tracking problem. Ledzewicz and Schättler (2008) constructed a synthesis of optimal controlled trajectories employing geometric methods based on the necessary conditions for

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optimality of the Maximum Principle from Krener (1977), and developed the structure of this optimal synthesis near the saturation point in Ledzewicz and Schättler (2009). Ledzewicz et al. (2009) considered the combination of antiangiogenic and chemotherapeutic agents as a multiple input optimal control problem and designed bang-bang and singular controls. Swierniak et al. (2003) analyzed two- and three-compartment models and found that singular controls are not optimal for this model class and provided necessary and sufficient conditions for optimality of bang-bang controls. However, all of these works suppose that continuous-time infusion therapy is applicable.

Here we consider that the therapy is realized by giving injections, with fixed rest period between the injections, as presented in Section 3. The doctor specifies the desired tumor volume for the next injection, and the minimal amount of injection is calculated that is required to reach the desired tumor volume. The algorithm to find this optimal drug dosage is explained in Section 3, along with the proof of the monotonicity of the tumor growth model as the function of the input, which is required for the convergence of the algorithm. The optimization algorithm can be used to find the optimal drug dosage in order to attain the desired tumor volume for a fixed rest period (sampling time).

Using the optimization algorithm defined in Section 3, we run simulations for different sampling times (rest periods) and compare the results in Section 4. We find that high sampling time results in a BD therapy, while low sampling time results in LDM therapy. We analyze the effect of sampling time on the amount of the required drug, and find that low sampling time is desirable.

The results show that LDM therapy is desirable, and can help clinicians to calculate the optimal dosage if the model of tumor growth and the value of the parameters in the model are known and the states of the model can be measured. We discuss further applications of the results in Section 5.

2. A MODEL OF TUMOR GROWTH UNDER ANGIOGENIC INHIBITION

A model of tumor growth under angiogenic inhibition was proposed by Hahnfeldt et al. (1999), and it describes the tumor growth dynamics in time t with the equations

$$\dot{x}_1(t) = -\lambda_1 x_1(t) \log\left(\frac{x_1(t)}{x_2(t)}\right) \tag{1}$$

$$\dot{x}_2(t) = b x_1(t) - d x_1^{2/3}(t) x_2(t) - \eta x_2(t) g(t), \tag{2}$$

with $x_1(t)$ being the tumor volume in time instant t given in mm^3, $x_2(t)$ is the volume of the supporting vasculature in time instant t given in mm^3, and $g(t)$ being the inhibitor serum level in time instant t given in mg/kg. The parameters acquired in Hahnfeldt et al. (1999) from mice experiments with Lewis lung carcinoma used as tumor and endostatin as the inhibitor are $\lambda_1 = 0.192\,1/\mathrm{day}$, $b = 5.85\,1/\mathrm{day}$, $d = 0.0087\,1/(\mathrm{mm}^2 \cdot \mathrm{day})$ and $\eta = 0.66\,\mathrm{kg}/(\mathrm{mg} \cdot \mathrm{day})$.

The inhibitor serum level is decreasing with the clearance rate of $\lambda_3 = 1.3\,1/\mathrm{day}$ which process is governed by the differential equation

$$\dot{g}(t) = -\lambda_3 g(t) + v(t) \tag{3}$$

with $v(t)$ being the rate of the extraneous drug delivery in time instant t given in $\mathrm{mg}/(\mathrm{kg} \cdot \mathrm{day})$. Since we want to model injections, we will consider impulse-like inputs. As a result, we will consider (3) with $v \equiv 0$, and model giving an injection at time τ by adding the amount of injection $u(\tau)$ to the value of $g(\tau)$, i.e. redefine $g(\tau) := g(\tau) + u(\tau)$. In our applications, this will be realized as modification of initial conditions only, so this does not complicate computations. Note that the unit of the new input u is mg/kg.

The nontrivial equilibrium of the system defined by (1) and (2) with constant inhibitor serum level $g(t) \equiv g_\infty$ is

$$x_{1,\infty} = x_{2,\infty} = \left(\frac{b - \eta g_\infty}{d}\right)^{3/2}, \tag{4}$$

see e.g. in Sápi et al. (2015a). This function being strictly monotonously decreasing in g_∞, takes its maximum when no inhibitor is present, i.e. $g_\infty = 0\,\mathrm{mg/kg}$, and it takes the value

$$x_{1,\max} = x_{2,\max} = \left(\frac{b}{d}\right)^{3/2}. \tag{5}$$

Note that the equilibrium $x_1 = 0\,\mathrm{mm}^3$ results if and only if $x_2 = 0\,\mathrm{mm}^3$, and the system can not be moved from that state, so we suppose that initially $x_1(0) > 0$ and $x_2(0) > 0$. The model is positive as it was shown in Sápi et al. (2015a), i.e. if $x_1(0) > 0$ and $x_2(0) > 0$, then $x_1(t) > 0$ and $x_2(t) > 0$ for all $t \geq 0$. From the positivity and (5) it follows that the functions x_1 and x_2 can have values in the interval $(0, (b/d)^{(3/2)}]$, i.e. the domain of the system defined by (1) and (2) is

$$\mathcal{D} = \left(0, \left(\frac{b}{d}\right)^{3/2}\right] \times \left(0, \left(\frac{b}{d}\right)^{3/2}\right]. \tag{6}$$

Note that this is a theoretical domain defined by the differential equations of the tumor growth model. In practice, angiogenesis takes place in tumors whose volume is big enough (above a few mm^3), below that volume the tumor can use the blood vessels of the host, and does not need to induce angiogenesis. However this limit is not known exactly, and may be different for each situation (depending on the type of tumor and the patient), therefore we will suppose later without the restriction of generality that the tumor volume is above $1\,\mathrm{mm}^3$, since it simplifies the proof of Theorem 1 in Subsection 3.2.

3. CALCULATION OF THE OPTIMAL DRUG AMOUNT

We consider the following theoretical scenario:

(S1) The patient visits the doctor in fixed intervals. We will call this interval the sampling time, denote it by T_s and measure it in days.
(S2) At each visit, the doctor investigates the patient, and we suppose that as a result all internal states (tumor volume, endothelial volume, inhibitor serum level) become available.
(S3) The doctor defines the desired tumor volume for the next investigation. The minimal amount of drug injection that is required to reach the desired tumor volume is calculated using the tumor growth model and the information acquired from the measurements in the previous step using an optimization algorithm.

Here we suppose that the conditions in the points (S1) and (S2) of this scenario are satisfied (the patient visits the doctor regularly, the measurements are available at each visit), and we give a solution for the optimization problem in point (S3). We will formalize the optimal control problem for this scenario in Subsection 3.1. We prove the monotonicity of tumor volume with respect to the drug input in Subsection 3.2, i.e. we show that for all positive initial system states it is true that increasing the amount of injected drug results in lower (or the same) tumor volume after the injection. Finally, we propose a binary search algorithm to find the minimal drug injection for point (S3) in Subsection 3.3.

3.1 The optimal control problem

At the kth investigation (kth step) we know the internal states of the system $x_1[k] := x_1(kT_s)$, $x_2[k] := x_2(kT_s)$, and $g[k] := g(kT_s)$. The desired tumor volume for the next step is denoted by $x_{1,d}[k+1]$. We are looking for the minimal amount of injection $u[k]$ such that the tumor volume in the next step is less than or equal to the desired tumor volume, i.e. $x_1[k+1] \leq x_{1,d}[k+1]$.

From the mathematical point of view, we consider the initial value problem defined by the differential equations (1), (2), and (3) on the time interval $[kT_s, (k+1)T_s]$ with initial conditions $x_1[k]$, $x_2[k]$ and $g[k] + u[k]$, and are looking for the minimal initial value $g[k] + u[k]$ such that $x_1[k+1] \leq x_{1,d}[k+1]$. Due to the nonlinear nature of the differential equation (2), we are not seeking for a symbolic solution, but solve the problem numerically in Subsection 3.3.

3.2 Monotonicity of the tumor growth model

In this subsection we show that the tumor growth model is monotonous in the sense that increasing the drug injection results in decreasing tumor volume. The inhibitor serum level function $g(t)$ in the time $t \in [kT_s, (k+1)T_s]$ is

$$g(t) = (u[k] + g[k]) \exp\left(-\lambda_3 (t - kT_s)\right) \tag{7}$$

with the amount of injection $u[k]$ given in the time instant kT_s. This function is strictly monotonous in $u[k]$, i.e. if $u[k]$ increases, then $g(t)$ also increases for $t \in [kT_s, (k+1)T_s]$. Next we show that the tumor volume as the solution of (1)–(3) with initial conditions $x_1[k], x_2[k], g[k]+u[k]$ is also monotonous in $u[k]$ on the time interval $[kT_s, (k+1)T_s]$.

Theorem 1. Consider the initial value problem on the interval $[kT_s, (k+1)T_s]$ defined by (1)–(3) with initial values $x_1[k] > 0$, $x_2[k] > 0$, and $g[k] + u[k] > 0$. Denote the solutions with input $u[k] := u^{(1)}$ by $x_1^{(1)}$, $x_2^{(1)}$, and $g^{(1)}$, while the solutions with input $u[k] := u^{(2)}$ by $x_1^{(2)}$, $x_2^{(2)}$, and $g^{(2)}$. The solutions exist, and $u^{(2)} > u^{(1)}$ yields that $x_1^{(2)} \leq x_1^{(1)}$ if the parameters of the model are positive, $b > d$, and $x_1(t) \geq 1\,\mathrm{mm}^3$ for $t \in [kT_s, (k+1)T_s]$.

Proof. Since the initial values are positive, the solutions of the differential equations are positive due to the positivity of the model. First, we start to prove the monotonicity of the system, then we prove the existence of the solutions and finish the proof of monotonicity after proving the existence. Since the functions x_1 and x_2 are positive, we can introduce the new functions y_1 and y_2 defined on the interval $[kT_s, (k+1)T_s]$ as

$$y_1 = \log x_1 \tag{8}$$

$$y_2 = \log x_2. \tag{9}$$

The time derivatives of these functions are

$$\dot{y}_1 = \frac{1}{x_1}\dot{x}_1 = -\lambda_1(\log(x_1) - \log(x_2)) \tag{10}$$

$$\dot{y}_2 = \frac{1}{x_2}\dot{x}_2 = b\frac{x_1}{x_2} - d x_1^{2/3} - \eta g. \tag{11}$$

so the transformed system dynamics is governed by the differential equations

$$\dot{y}_1 = -\lambda_1 y_1 + \lambda_1 y_2 \tag{12}$$

$$\dot{y}_2 = b e^{y_1 - y_2} - d e^{2y_1/3} - \eta g. \tag{13}$$

The second equation can be written in the form of

$$\dot{y}_2 = e^{2/3 y_1}\left(b e^{1/3 y_1 - y_2} - d\right) - \eta g. \tag{14}$$

We have already seen that $u^{(2)} > u^{(1)}$ yields $g^{(2)} > g^{(1)}$. Denote the transformed solutions with input $u^{(1)}$ by $y_1^{(1)}$ and $y_2^{(1)}$, while those with input $u^{(2)}$ by $y_1^{(2)}$ and $y_2^{(2)}$, respectively.

Equation (14) clearly shows that $g^{(2)} > g^{(1)}$ results in $\dot{y}_2^{(2)} < \dot{y}_2^{(1)}$, since the derivative of the function y_2 is a strictly monotonously decreasing function of g. Moreover, $\dot{y}_2^{(2)} < \dot{y}_2^{(1)}$ results in $y_2^{(2)} \leq y_2^{(1)}$, taking into consideration the initial conditions as well. Since $\dot{y}_1$ is a strictly monotonously increasing function of y_2, $y_2^{(2)} \leq y_2^{(1)}$ yields $\dot{y}_1^{(2)} \leq \dot{y}_1^{(1)}$ that results in $y_1^{(2)} \leq y_1^{(1)}$. If the right-hand side of (14) is a strictly monotonously increasing function of y_1, so $y_1^{(2)} \leq y_1^{(1)}$ implies that $\dot{y}_2^{(2)} \leq \dot{y}_2^{(1)}$, then we can conclude that $u^{(2)} > u^{(1)}$ results in $y_1^{(2)} \leq y_1^{(1)}$. Due to the monotonicity of the logarithm function, this also means that $u^{(2)} > u^{(1)}$ implies $x_1^{(2)} \leq x_1^{(1)}$. Thus, the proof of monotonicity is finished with the proof of the monotonicity of $\dot{y}_2$ in terms of y_1. We will prove that along with the existence of the solutions.

First consider the case $x_1 \geq 1\,\mathrm{mm}^3$ and $x_2 \geq 1\,\mathrm{mm}^3$. Then $y_1 \geq 0$ and $y_2 \geq 0$ (for the sake of simplicity, we omit the dimensions of the transformed variables), thus the second differential equation (14) can be majored by

$$\dot{y}_2 = b e^{y_1 - y_2} - d e^{2y_1/3} - \eta g \leq b e^{y_1 - y_2} \leq b e^{y_{1\,\max}}. \tag{15}$$

Since $y_{1,\max} = \log(x_{1,max}) = 2/3 \log(b/d)$, the derivative of y_2 is less than or equal to the constant $b(b/d)^{2/3}$, so the system dynamics can be majored by the linear system

$$\dot{z}_1 = -\lambda_1 z_1 + \lambda_1 z_2 \tag{16}$$

$$\dot{z}_2 = b(b/d)^{2/3}. \tag{17}$$

Since the solution to these linear differential equations exist, and they are greater than or equal to the solution to the differential equation they major, we know that $0 \leq y_1 \leq z_1$ and $0 \leq y_2 \leq z_2$. As it was shown for similar problems in Farkas (2001), this implies that the solutions are bounded and exist if $y_1 \geq 0$ and $y_2 \geq 0$.

Now we show the monotonicity of $\dot{y}_2$ in y_1 if $y_1 \geq 0$ and $y_2 \geq 0$. Examine the sign of the term $be^{1/3y_1-y_2} - d$ in (14). This term has its minimum at the point $y_1 = 0$, $y_2 = y_{2,\max}$, i.e.

$$\min_{y_1,y_2\geq 0} be^{1/3y_1-y_2} - d = be^{-2/3\log(b/d)} - d = d^{2/3}\left(b^{1/3} - d^{1/3}\right) \quad (18)$$

that is positive since $b > d$. The positivity of the term $be^{1/3y_1-y_2} - d$ (and its monotonicity in y_1) yields that $\dot{y}_2$ is a monotonously increasing function of y_1 if $y_1 \geq 0$ and $y_2 \geq 0$.

Now consider the situation $x_1 \geq 1\,\mathrm{mm}^3$ but $x_2 \leq 1\,\mathrm{mm}^3$. In this case $x_1/x_2 > 1$, thus the original differential equation can be majored by

$$\dot{x}_1 = -\lambda_1 x_1 \underbrace{\log(x_1/x_2)}_{>0} < \lambda_1 x_1 \quad (19)$$

$$\dot{x}_2 = bx_1 - dx_1^{2/3}x_2 - \eta x_2 g < bx_1 - dx_1 - \eta g \quad (20)$$

so a majorant linear system for the original differential equations is given by

$$\dot{z}_1 = \lambda_1 z_1 \quad (21)$$

$$\dot{z}_2 = bz_1 - dz_1 - \eta g. \quad (22)$$

Since the solution of this system exists, and $1 \leq x_1 \leq z_1$ and $0 \leq x_2 \leq z_2$, this yields that the solution to the original differential equations exist if $x_1 \geq 1\,\mathrm{mm}^3$ and $x_2 < 1\,\mathrm{mm}^3$.

Since (2) can be written as

$$\dot{x}_2 = x_1^{2/3}(bx_1^{1/3} - dx_2) - \eta x_2 g \quad (23)$$

and $bx_1^{1/3} - dx_2 > 0$ if $b > d$ and $x_1 \geq 1\,\mathrm{mm}^3$, $x_2 < 1\,\mathrm{mm}^3$, the function $\dot{x}_2$ is a strictly monotonously increasing function of x_1, that yields that $\dot{y}_2$ is a strictly monotonously increasing function of y_1 due to the monotonicity of the logarithm function and the positivity of x_2, so the monotonicity is proved for the case $x_1 \geq 1\,\mathrm{mm}^3$, $x_2 < 1\,\mathrm{mm}^3$ that concludes the proof.

The parameters of the tumor model are always positive, and experiments in Hahnfeldt et al. (1999) showed that $b > d$ holds as well. Due to the physiology of angiogenesis, we can further suppose without the loss of generality that $x_1 \geq 1\,\mathrm{mm}^3$ holds as well, so the conditions of the theorem are true, and the monotonicity holds. As a result of this monotonicity, the algorithm described in the following subsection finds the minimal input that is required to achieve the desired tumor volume.

3.3 The search algorithm

Increasing the amount of drug in the injection leads to lower (or at least not greater) tumor volumes according to the tumor growth model as it was proved in Theorem 1. Thus we can find the minimal amount of injection required to reach a tumor volume at the next step that is not greater than the desired tumor volume using a binary search algorithm as follows.

Let $u_{\max}$ be the maximal amount of drug and let $u_{\min}$ be the minimal amount of the drug, and suppose that they are chosen so that the solution is in the interval $[u_{\min}, u_{\max}]$. E.g., we can use $u_{\min} = 0\,\mathrm{mg/kg}$, and an arbitrary initial guess for $u_{\max}$ that can be increased if the algorithm does not find a solution in that interval.

Data: The initial values $x_1[k]$, $x_2[k]$ and $g[k]$. The TOL accuracy of the solution. The desired tumor volume $x_{1,d}[k+1]$. The maximal drug injection $UMAX$.
Result: The minimal drug dosage $u[k]$ that is required to reach the desired tumor volume in the next step.

```
Let u_max = UMAX and u_min = 0 ;
while u_max − u_min > TOL do
    u = (u_max − u_min)/2;
    Calculate the tumor volume in the next time instant
    (k + 1)T_s by solving the initial value problem on time
    interval [kT_s, (k + 1)T_s] defined by (1)–(3) with initial
    values x_1[k], x_2[k], g[k] + u, denote it by x_1[k + 1];
    if x_1[k + 1] > x_{1,d}[k + 1] then
        u_min := u;
    else
        u_max := u;
    end
end
```

Algorithm 1: The search algorithm to find the minimal drug delivery

At each step of the iteration, choose the injection to be in the middle of the search interval, i.e. let $u[k] := (u_{\min} + u_{\max})/2$. Solve the initial value problem on the time interval $[kT_s, (k+1)T_s]$ defined by (1)–(3) with initial conditions $x_1[k]$, $x_2[k]$ and $g[k]+u[k]$. If the solution $x_1[k+1]$ is greater than the desired tumor volume $x_{1,d}[k+1]$, then we need to inject more drugs than $u[k]$, so we modify the lower bound of the search interval to $u_{\min} := u[k]$ and repeat the iteration step. If the solution $x_1[k+1]$ is less than or equal to the desired tumor volume, then we need less than or equal amount of injected drug, so we modify the upper bound as $u_{\max} := u[k]$ and repeat the iteration step. We continue this iteration until the search interval is narrow enough, i.e. $u_{\max} - u_{\min} < TOL$ becomes true where TOL is a small positive number defining the accuracy of the solution. The pseudocode of the algorithm is given in Algorithm 1.

4. APPLICATIONS OF THE OPTIMIZATION ALGORITHM

In this section we give some results using the optimization algorithm and the theoretical scenario. The initial tumor volume and endothelial volume will be the maximal values given by (4) for all the simulations in this section. The physiology of the tumor and the patient is modeled by the tumor growth model with the parameters given in Section 2. The optimization algorithm throughout the simulations will use the same tumor growth model with the same parameters.

First, we show a simulation for a theoretical scenario with $T_s = 1\,\mathrm{day}$ of resting time and 20 days of treatment. The desired tumor volume for each time step is calculated according to the expression

$$x_{1,d}[k] = x_1(0)\exp(-kT_s/T_d) \quad (24)$$

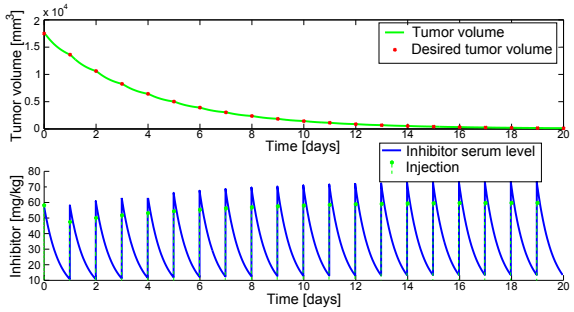

Fig. 1. The evolution of the tumor volume (green curve) and the desired tumor volume (red x mark) (upper figure) and the inhibitor serum level (blue curve) and the injected drug (green dot) (lower figure), with $T_s = 1\,\text{day}$, $T_d = 10\,\text{days}$

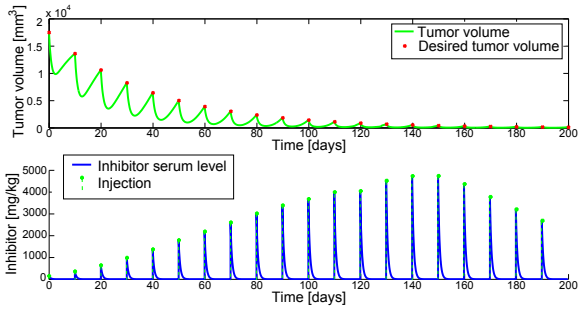

Fig. 2. The evolution of the tumor volume (green curve) and the desired tumor volume (red x mark) (upper figure) and the inhibitor serum level (blue curve) and the injected drug (green dot) (lower figure), with $T_s = 10\,\text{days}$, $T_d = 40\,\text{days}$

with $T_d = 10\,\text{days}$ and $k = 0, 1, 2, \ldots, 20$. The measurements for each inspection are acquired by simulations based on the tumor model and parameters defined in Section 2.

The result of the simulation is in Fig. 1. The desired tumor volumes are denoted by red x marks, while the current tumor volume function is shown by the green curve in the upper figure. The tumor volume function is very close to the desired exponential function, and it is equal to the desired tumor volumes defined by (24) in the times when measurement takes place.

The inhibitor serum level is in the lower figure of Fig. 1. The serum level function is the blue curve, while the injections are denoted by the green dots. The amount of injected drug is relatively high (but tolerable) at each occasion from physiological point of view, however the drug almost depleted from the patient before each investigation.

Second, we show a simulation for a theoretical scenario with $T_s = 10\,\text{days}$ (sampling time or rest period) and 200 days of treatment. The desired tumor volume for each time step is calculated by the expression (24) with $T_d = 40\,\text{days}$ (the time constant of the desired tumor regression). The measurements for each inspection are acquired by simulations based on the tumor model and parameters defined in Section 2. The results are in Fig. 2. The sampling time is much larger than the clearance of the inhibitor ($1/\lambda_3 = 0.76\,\text{day}$), so the injected drug is already depleted a long time ago when the patient goes to the next investigation, as it can be examined in the lower figure of Fig. 2. Since the inhibitor gets depleted, and there is no inhibitor present in the patient for a long period of time between the injections, the tumor grows back, so the tumor volume decreases right after the injection, but soon after that it starts to increase, resulting in valleys between the injections as it can be seen in the upper figure of Fig. 2. The high sampling time thus implies intolerably high injection values, as it is shown by the lower figure. This is caused because of the dynamics of the underlying physiological process, the desired tumor volume can only be reached if we give high input, since the inhibitor depletes too soon from the patient and the tumor grows back.

Due to the phenomena examined in Fig. 2, we analyzed the effect of the sampling time on the average tumor volume and the amount of inhibitor used during the therapy. We have run the simulations with sampling times $T_s = 1, 2, \ldots, 14\,\text{days}$. In order to get comparable results, we chose the T_d value for the function (24) giving the desired tumor volume as $T_d = 4T_s$, so (24) will be independent of the sampling time. This yields that at the kth investigation the desired tumor volume will be the same ($x_1(0)\exp(k/4)$) independent of the sampling time.

The results of the simulation are shown in Table 1. For each sampling time, the table shows the maximal amount of drug that is injected at a single investigation, the total amount of injected drug during the whole therapy, and the tumor volume integral, i.e. the average of the tumor volume multiplied by the total time of the therapy.

The maximal amount of injected drug at each investigation and the total amount of injected drug during the whole therapy increases as the sampling time is increasing, just like it was observed in the comparison of the previous simulation results in Figs. 1 and 2. Moreover, as the sampling time increases, the amount of required inhibitor gets too high in physiological and economical points of view as well. So the situations suitable for clinical application are the simulation results with low sampling time.

On the other hand, the average tumor volume during the whole therapy becomes lower as the sampling time increases, due to the valleys observed in Fig. 2. However, since these valleys are the results of intolerably high inhibitor inputs, these results are not valid. As a conclusion, the theoretical scenario of Section 3 should be applied with low sampling times.

5. CONCLUSION

The theoretical scenario discussed here can be applied in practice if all inner states of the system can be measured, the model of the tumor growth is accurate, and the parameters of the model are known exactly. In this situation, the doctor can define the desired evolution of the tumor volume keeping in mind that greater decrease in the tumor volume requires greater inputs, or one can use for example the inputs generated offline like the ones in the simulation. Thus, if every state and parameter is known exactly, then Algorithm 1 yields the optimal solution.

However, in practice these conditions may not be true, i.e. the measurements are burdened with noise, we can

Table 1. Comparison of the results with different sampling times; the maximal amount of injected drug at one occasion in mg/kg, the total amount of injected drug in mg/kg, and the average of the tumor volume multiplied by the total time of the therapy in $mm^3 \cdot$ days

Sampling time (days)	Maximal injected drug (mg/kg)	Total drug (mg/kg)	Tumor volume integral ($mm^3 \cdot$ day)
1	59.76	1133.2	68357
2	77.16	1316.1	65564
3	128.47	2034.6	61986
4	225.95	3357.6	58219
5	399.86	5618.3	54559
6	698.08	9358.1	51115
7	1195.29	15404	47906
8	1971.20	25032	44915
9	3099.06	37844	42097
10	4752.49	56442	39591
11	7031.45	73972	37045
12	9849.99	101279	34921
13	13341.13	123496	32636
14	17630.78	140201	30268

not measure all the internal states, or the parameters of the model are not known exactly, we only have an approximation. The internal states can be estimated and the effect of measurement noise can be decreased if we develop sufficiently efficient state estimators. The perturbation in the model parameters can be handled e.g. with the application of controllers that have sufficient robustness. Even if the problem is solved using state estimators and robust controllers, the algorithm in this paper can be used to generate the optimal solution (since in the simulation we know the perturbed values of the parameters and all the internal states) that can serve as the benchmark solution for the evaluation process of robust controllers.

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