Discrete LQR strategy for Determining Optimal Inhibitor Dose Level Based on Mathematical Model of Tumor Growth Dynamics

Optimal Control - Project Report
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Abstract

Cancer treatment is one of the most difficult challenges dealt by researchers and doctors. Differently from the conventional radiotherapy and chemotherapy, anti-angiogenic therapy, although expensive, has many advantages for the patients. In this report an optimal control design for determining a minimum inhibitor dose level for cancer treatment is discussed. Starting from a nonlinear dynamical model for tumor growth dynamics under angiogenic inhibition, a linearizing feedback is applied and, after the discretization of the linearized model, a discrete linear quadratic regulator (LQR) for nonzero set point is presented. Simulations of the closed-loop system are provided, showing the effectiveness of the proposed approach.

1 Introduction

Cancer represents one of the most lethal diseases in the world, thus requiring researchers to develop more and more sophisticated therapies for saving people's life [1, 2].

The use of mathematical models in medicine often gives many advantages and a more clear picture of the observed phenomenon. In fact, thanks to the modeling of the dynamics of interest, one may have the possibility of looking at its behaviour under special and interesting conditions, and so providing better therapies and treatments based on obtained information [3–6]. Apart of conventional therapies as radiotherapy or chemotherapy, which have many side-effects for the patient, modern therapies, called targeted molecular therapies, influence the life cycle of the cancerous cells and have limited side-effects [6, 7]. In this work, anti-angiogenic therapy applied to a tumor growth dynamical model will be discussed and simulated.

Anti-angiogenic therapy has effects on the vascular growth of the tumor and angiogenic inhibitors prevent tumor cells from growing own blood vessels. The main advantages of this therapy is that, with the blocking of the nutrition for the tumor growth, it will degrade and decrease in size, so the tumor will have lower tendency in developing drug resistance.

The first in investigating the dynamics of tumor growth under angiogenic stimulator and inhibitor effects was Philip Hahnfeldt et al. [8], using a simplified model to design and compare different strategies. In the years, other similar works have been developed from this simplified model, such as a bang-singular-bang structure, an optimal linear control and some approaches based on feedback linearization of the original model [6, 9]. Since the cost of angiogenic inhibitor is expensive, the ideal situation is to have the least possible amount of total inhibitor dose. For this reason, an approach proposed by Dewangga et al. [6] was to employ an optimal control technique, namely a linear quadratic regulator (LQR) in discrete time, in order to give the best result in terms of the minimum amount of dose necessary to bring the tumor at a minimum and safe size.

In section 2 a brief introduction to the biomedical background, the mathematical model of tumor growth dynamics and its feedback-linearized equivalent model are presented. In section 3, the response of the system to constant levels of inhibitor dose is studied, while in section 4 an optimal control strategy based on discrete LQR is addressed. Then, section 5 is a discussion of the implementation details. In section 6 experimental setup and simulation results are discussed and, finally, in section 7 we draw the conclusions.

2 Mathematical Model of Tumor Growth Dynamics

2.1 Biomedical Background

Anti-angiogenic therapy influences the vascular growth of tumors. In fact, a growing tumor, after it reaches a diameter of few millimeters (about 1-2 mm^3), needs to develop its own vessels and capillaries for blood supply, since the ones of the host are not enough for its supply of nutrients anymore [10].

This process is called angiogenesis and is based on the stimulation of endothelial cells growth by tumor cells. In turn, the endothelial cells provide the lining for the newly forming blood vessels, which are able to sustain tumor growth. These cells have also receptors sensitive to inhibitors which try to prevent the birth of new blood vessels and capillaries.

So angiogenesis can be seen as a balance of stimulatory and inhibitory mechanisms regulated through micro-environmental factors [11].

2.2 Tumor Growth Dynamics Under Angiogenic Inhibition

In 1999 Hahnfeldt et al. [8] proposed a mathematical model in the form of a nonlinear system for tumor growth under angiogenic stimulator/inhibitor control.

They carried out experiments at the Harvard Medical University on mice injected with Lewis lung carcinoma cells. The original model is composed of three differential equations, however a simplified second-order model is considered. The dynamical system consists of two main variables: the primary tumor volume, x_1 (mm^3), and the carrying capacity of the vasculature, x_2 (mm^3). A growth function describes the size of the tumor dependent on the carrying capacity chosen as Gompertzian. So the rate of change in the primary tumor volume is modelled as:

$$\dot{x}_1 = -\lambda x_1 \ln \frac{x_1}{x_2} \tag{1}$$

where λ indicates the tumor growth parameter. The dynamics for the carrying capacity is a balance between stimulation and inhibition, so it can be modeled as:

$$\dot{x}_2 = -\mu x_2 + S(x_1, x_2) - I(x_1, x_2) - eux_2 \tag{2}$$

where μx_2 describes the loss of endothelial cells due to natural causes (often neglected), I and S denote endogenous inhibition and stimulation terms respectively and eux_2 is a loss due to external additional inhibition. The variable u is the control and represents the angiogenic dose rate (mg/kg/day), while e is the anti-angiogenic killing parameter. From the work by [8], it is shown that the inhibitor will impact on the target endothelial cells in a way that grows as the volume of cancer cells to the power of $\frac{2}{3}$, so the inhibitor term will have the form

$$I(x_1, x_2) = dx_1^{2/3} x_2 \tag{3}$$

with d death rate. Moreover, the inhibitor term will tend to grow at a rate of $x_2^{\tilde{\alpha}} x_1^{\tilde{\beta}}$ with $\tilde{\alpha} + \tilde{\beta} = \frac{2}{3}$, so by choosing appropriate values for $\tilde{\alpha}$ and $\tilde{\beta}$ the stimulation term will be

$$S(x_1, x_2) = bx_1. \tag{4}$$

So the overall final dynamical model is the following

$$\begin{aligned} \dot{x}_1 &= -\lambda x_1 \ln \frac{x_1}{x_2} \\ \dot{x}_2 &= bx_1 - dx_1^{2/3} x_2 - eux_2 \\ y &= x_1 \end{aligned} \tag{5}$$

The parameters chosen in the experiments are: $\lambda = 0.192$ day^{-1}, $b = 5.85$ day^{-1}, $d = 0.00873$ $day^{-1}mm^{-2}$ and $e = 0.66$ $day^{-1}(mg/kg)^{-1}$.

Variables and parameters	Meaning	Value and measure unit
x_1	primary tumor volume	mm^3
x_2	carrying capacity of the vasculature	mm^3
λ	tumor growth parameter	0.192 day^{-1}
u	control input, angiogenic dose rate	mg/kg
e	anti-angiogenic killing parameter	0.66 $\text{day}^{-1}(\text{mg/kg})^{-1}$
d	death rate/disaggregation of endothelial cells	0.00873 $\text{day}^{-1}\text{mm}^{-2}$
b	parameter of the stimulation term	5.85 day^{-1}
r	desired tumor volume	mm^3
z_1, z_2	new coordinates in the linearized system	
$v = \alpha + \beta$	linearizing feedback	
A, B, C	linear system matrices	
A_d, B_d, C_d	discrete time linear system matrices	
J	cost function	
H	matrix weighting the terminal deviation	
Q	matrix weighting the trajectory deviation	
R	scalar weighting the control effort	
K, G	optimal gain and control gain	

Table 1: Summary of the main variables and parameters of the model and simulations, together with the corresponding meaning, value and measure unit, where possible.

2.3 Feedback Linearization of Nonlinear Tumor Growth Model

As shown in [6,9] feedback linearization is chosen to linearize the nonlinear tumor growth model, since it will be useful in the following in order for the LQR strategy to be applied. A linearizing feedback can be computed based on the output and the transformed coordinates of the nonlinear system. If it exists, the linearized system between input v and output y is a series of integrators [12].

For this purpose, the computation of the relative degree of the measured output of the system must be carried out. It results to be $r = 2$, which is the order of the system, so exact linearization can be employed. So the first $r = 2$ elements of the coordinate transformations are defined as:

$$\begin{aligned} z_1 &= \phi_1(x) = h(x) = x_1 \\ z_2 &= \phi_2(x) = L_f h(x) = \frac{\partial h(x)}{\partial x} f = -\lambda x_1 \ln \frac{x_1}{x_2}. \end{aligned} \tag{6}$$

The new system of differential equations in these new coordinates is

$$\begin{aligned} \dot{z}_1 &= \frac{\partial \phi_1}{\partial x}\dot{x} = L_f h(x) = \phi_2(x) = z_2 \\ \dot{z}_2 &= \frac{\partial \phi_2}{\partial x}\dot{x} = L_f^2 h(x) + L_g L_f h(x) u \\ &:= \alpha(x) + \beta(x) u(t) \end{aligned} \tag{7}$$

where

$$\begin{aligned} \alpha(x) &= \left(\lambda \ln \frac{x_1}{x_2} + \lambda\right) \lambda x_1 \ln \frac{x_1}{x_2} + \lambda x_1 \frac{1}{x_2}\left(b x_1 - d x_1^{\frac{2}{3}} x_2\right) \\ \beta(x) &= -e\lambda x_1 \end{aligned} \tag{8}$$

Note that, in the article which inspired this project [6], there is a missing plus sign in the expression of $\alpha(x)$ in equation (8): probably a typo that could affect the reproducibility of the experiments (as can be seen in Appendix A in figures 6 and 5).

Finally, the linearizing feedback is

$$v = L_f^2(h(x)) + L_g L_f(h(x)) u = \alpha(x) + \beta(x) u \tag{9}$$

Therefore, one can easily obtain the following linearized model as

$$\begin{aligned} \dot{z}_1 &= z_2 \\ \dot{z}_2 &= v \\ y &= z_1 \end{aligned} \tag{10}$$

which can be rewritten in the matrix form

$$\begin{aligned} \dot{z} &= Az + Bv \\ y &= Cz \end{aligned} \tag{11}$$

with matrices

$$A = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}, B = \begin{bmatrix} 0 \\ 1 \end{bmatrix}, C = \begin{bmatrix} 1 & 0 \end{bmatrix}. \tag{12}$$

In order to go back to the original coordinates, the following mapping can be applied

$$\begin{aligned} x_1 &= z1 \\ x_2 &= z_1 exp\left(\frac{z_2}{\lambda z_1}\right) \\ u &= \frac{v - \alpha(x)}{\beta(x)}. \end{aligned} \tag{13}$$

3 Response of Tumor Growth Dynamics Under Different Constant Levels of Dose

In order to understand the profile of the tumor growth in the cases in which no therapy is taken and when, vice versa, different levels of inhibitor dose are applied, some simulations are shown. In particular, Runge-Kutta 45 with step size 0.1 is utilized and four constant levels of dose are employed.

It is known that the allowed inhibitor dose, which is represented by the control u of the system, is at maximum around $50 - 65$ mg/kg for physiological reasons, therefore the maximum dose is set to 50 mg/kg for safety [6, 9].

As can be seen in figure 1a, without any kind of therapy the tumor volume and the supporting vasculature volume increase. In fact, they rapidly reach a volume of 2000 mm^3 and 8000 mm^3 respectively, in about 20 days. Instead, when a constant inhibitor dose of 1 mg/kg is applied, we comprehend from figure 1b that there is a slower increase of the tumor volume with respect to the previous case, in fact it reaches 2000 mm^3 in about 26 days, proving that inhibitor therapy is able to affect the tumor growth. Increasing the constant dose to 20 mg/kg (figure 1c), we can finally see that the tumor volume decreases effectively, reaching a value of 0.2 mm^3 within 10 days, together with the supporting vasculature volume being always below the tumor volume.

Finally, the last figure shows the response of the tumor volume when the maximum allowed inhibitor dose is administrated. In this case, the volume decreases rapidly reaching 0.2 mm^3 in about 5 days and, also in this situation, the vasculature volume is always below the decreasing tumor volume.

Hence, the peculiarities of this scenario suggest that a necessary amount of inhibitor dose is required in order to decrease the tumor volumes. From the first equation of (5), supposing that there exists a level of inhibitor dose such that the supporting vasculature volume is less than tumor volume ($x_2 < x_1$), a condition can be stated as

$$\ln \frac{x_1}{x_2} > 0 \tag{14}$$

Therefore, since λ is positive, $\dot{x_1} < 0$. This means that the tumor may decrease if the inhibitor dose level u can maintain the supporting vasculature volumes x_2 below the tumor volumes x_1.

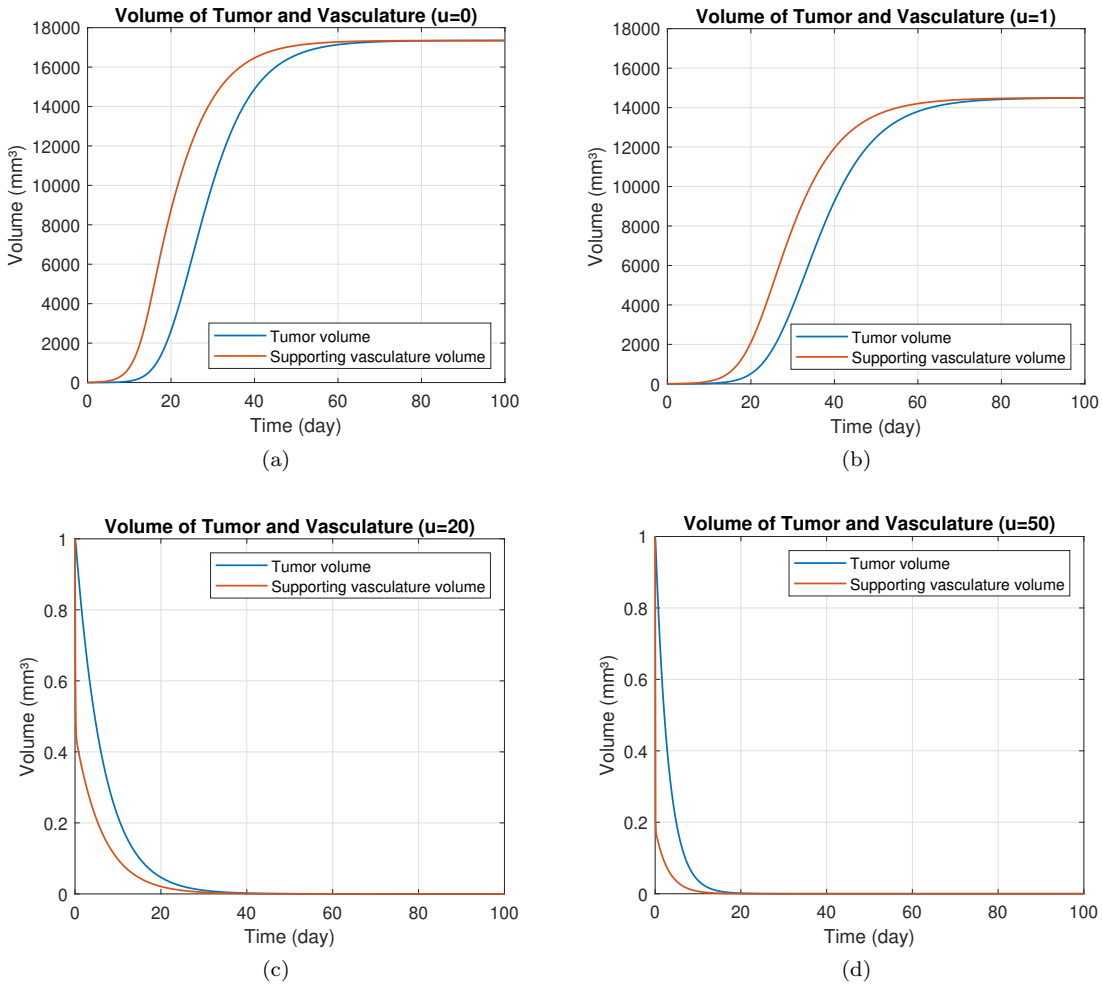

Figure 1: Response of tumor volume and supporting vasculature volume when (a) no therapy is conducted and with an administration of constant levels of inhibitor doses equal to (b) 1 mg/kg, (c) 20 mg/kg, (d) 50 mg/kg.

4 Optimal Inhibitor Dose Level

Having in mind all the previous analysis, a strategy to determine the optimal inhibitor dose level can be built by using the linearized mathematical model (7) and by employing an optimal control design.

4.1 Optimal Control Design: Discrete LQR

As we described in previous sections, the aim of this work is to find an optimal amount of inhibitor dose, the minimum one because of its expensive cost, to be employed in a anti-angiogenic therapy for decreasing the tumor volume at a safe size.

Since, with the current scientific knowledge, no medical device is able to handle continuous infusion cancer therapy, only a quasi-continuous infusion therapy can be achieved using discrete drug administration [13]. Therefore, there is a clear need for designing a discrete time control for a tumor growth model for real-life application. In order to do so, the first thing to do is to provide an equivalent discretized model of the chosen one of the form

$$z_k = A_d z_{k-1} + B_d v_{k-1} \tag{15}$$

obtained by using a sample time of 0.1s, with matrices

$$A_d = \begin{bmatrix} 1 & 0.1 \\ 0 & 1 \end{bmatrix}, \; B_d = \begin{bmatrix} 0.005 \\ 0.1 \end{bmatrix}, \; C_d = \begin{bmatrix} 1 & 0 \end{bmatrix}. \tag{16}$$

Algorithm 1: Recursive computation of the solution of the discrete Riccati Equation

Input: Input-weighting scalar R and time horizon N.
Output: State-feedback gain K and control gain G.
Processing:
1 Initiate $S_N = H$.
2 **for** $i = N-1:-1:0$ **do**
3 Compute

$$S_i = A_d^T \left[S_{i+1} - S_{i+1} B_d \left(R + B_d^T S_{i+1} B_d \right)^{-1} B_d^T S_{i+1} \right] A_d + Q$$
$$K_i = R^{-1} B_d^T A_d^{T\,-1} (S_i - Q)$$

4 **end for**
5 If the sequence K_i converges to a certain value at $i = 0$, set $K = K_0$. Otherwise, repeat from the beginning using larger input N.
6 Calculate $G = [C(I - A_d + B_d K)^{-1} B_d]^{-1}$

Algorithm 2: Determination of inhibitor dose level

Input: Current tumor volume value x_1, current tumor vasculature volume x_2 and desired tumor volume r.
Output: Current inhibitor dose level u.
Processing:
1 Perform coordinate transformation $x \to z$ using (6).
2 **for** $k = N-1:-1:0$ **do**
3 Calculate

$$\gamma = (I + B_d K)^{-1},\ \mathcal{A} = \gamma A_d,\ \mathcal{B} = \gamma B_d G$$

4 Calculate $z_{new} = \mathcal{A} z + \mathcal{B} r$
5 Calculate $v = -K z_{new} + G r$
6 Use (13) to compute u.

What can be done is to consider the discrete linear quadratic regulator (LQR) problem [14, 15], specifically considering (15) and the following performance index

$$J = \frac{1}{2} z_N^T H z_N + \frac{1}{2} \sum_{k=0}^{N-1} \left(z_k^T Q z_k + v_k^T R v_k \right) \tag{17}$$

in which z_k and v_k are the state variable and the input at time k, respectively, Q and H are positive semi-definite matrices weighting respectively the state trajectory deviation and the terminal deviation, while R is the positive definite input-weighting scalar. The objective is to minimize the tumor volume x_1, so it follows that the weight matrices are chosen as

$$H = Q = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}. \tag{18}$$

In this way, a state-feedback gain K is determined by using this discrete LQR, by minimizing the cost function J within finite time horizon N. The value of R, which is the input-weighting scalar which corresponds to the input v, is connected to the inhibitor dose level u with (9). Hence, its value is determined in order to have a minimum value for the total amount of inhibitor dose. The optimum values for K and control gain G are obtained in Algorithm 1, by solving recursively the Riccati equation in the backward direction [15]

$$S_i = A_d^T \left[S_{i+1} - S_{i+1} B_d \left(R + B_d^T S_{i+1} B_d \right)^{-1} B_d^T S_{i+1} \right] A_d + Q \tag{19}$$

for $i = N-1, ..., 0$.

Note that, also in this case, in the paper which inspired this work [6], there is a discrepancy in the G formula. In fact, the authors use a different expression of G with respect to the one described

in the references attached [14], that, if implemented as they describe, shows some strange behaviours in the simulations, leading to very different results with respect to the ones showed (as reported in Appendix A in figures 6 and 4). Instead, if implemented as we reported in Algorithm 1 [14], the results obtained are the same as the ones given in [6]. As described in Algorithm 2, since we are dealing with an LQR problem with nonzero setpoint, once computed K and G, it is possible to obtain the discrete state-feedback control law

$$v_k = -Kz_k + Gr \tag{20}$$

from which the inhibitor dose level u can be easily computed through (13).

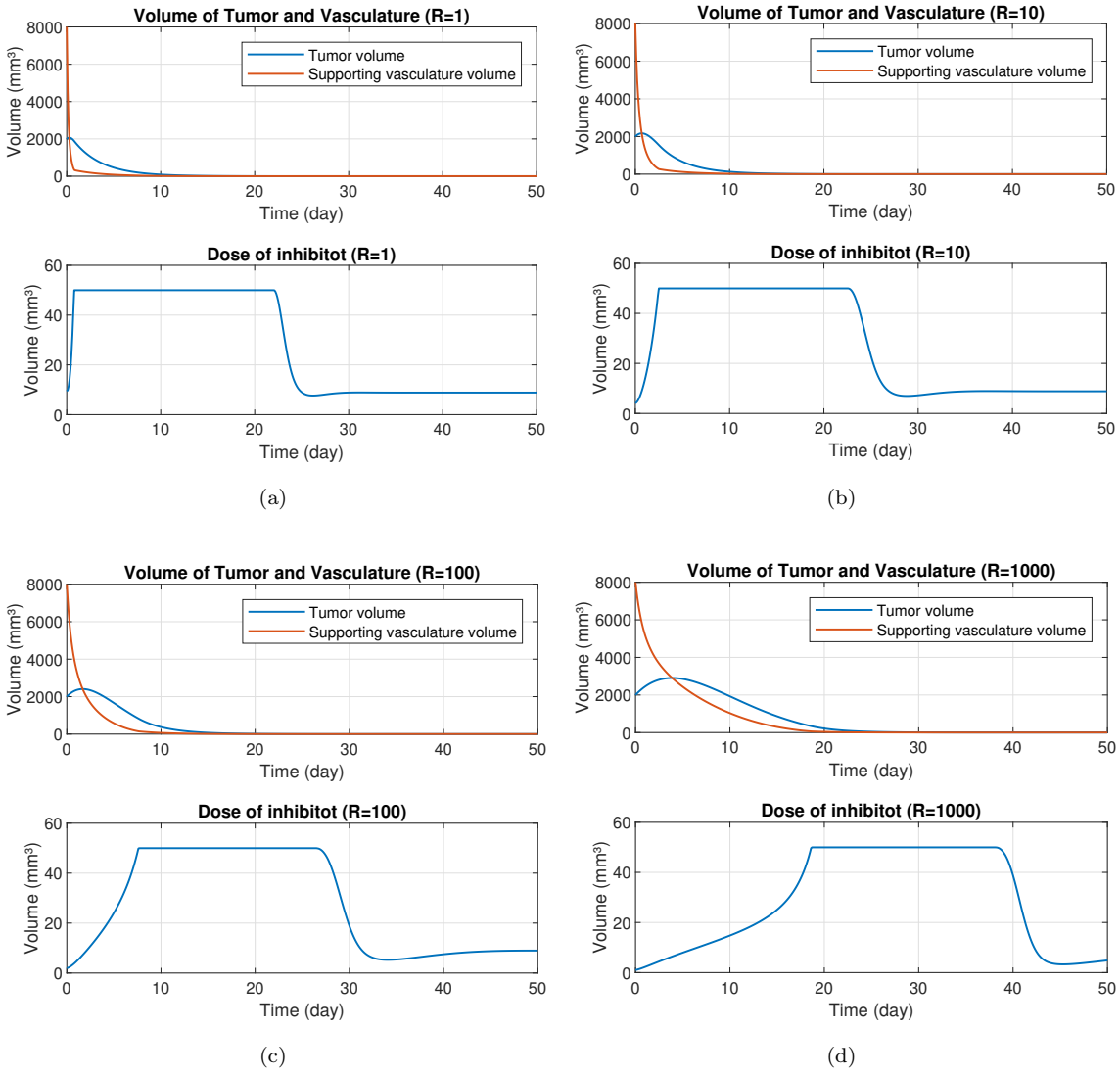

Figure 2: Response of tumor volume and supporting vasculature volume under the optimal level of inhibitor dose for different values of input-weighting scalar R: (a) $R = 1$, (b) $R = 10$, (c) $R = 100$, (d) $R = 1000$.

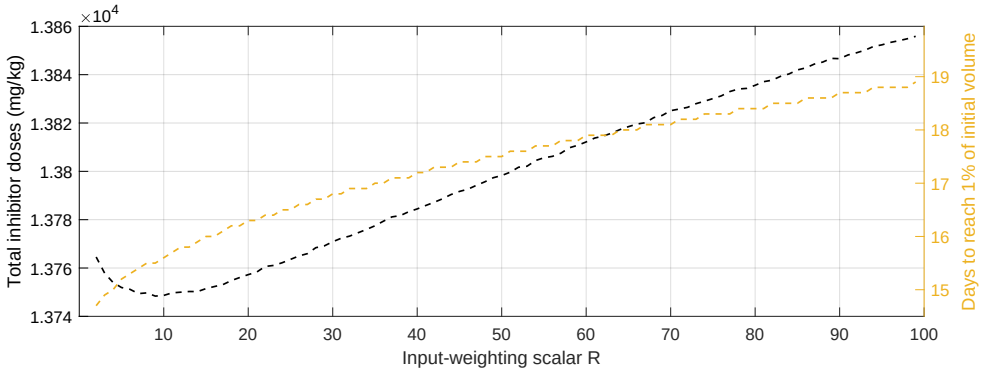

Figure 3: Investigation on input-weighting scalar R which gives the least amount of total inhibitor doses and least number of days to reach 1% of initial tumor volume.

5 Implementation details

In this section, the steps concerning the implementation of the optimal inhibitor dose level are addressed. First of all, Matlab version utilized in the simulation process is R2019b. The code, which can also be found in Appendix, is composed of four primary functions, namely `tumorModel()`, which provides the nonlinear dynamical model of the tumor growth dynamics, `dlqr_sp()`, that allows to obtain the optimal gain matrix K and the scalar gain G of the discrete time LQR with finite horizon and nonzero setpoint (Matlab implementation of Algorithm 1), `control_u()`, which computes the final optimal control u at each time step (Matlab implementation of Algorithm 2) saturated as required by the physiological reasons as explained in section 3 and, finally, `tumor_growth_simulation()`, in which, by using the above described functions, all the necessary quantities are computed and then the system is integrated over time by using `ode45()` Matlab function. Moreover, the `main()` function contains the problem statement, the model parameters and all the configurations tested during simulations presented in section 3 and 6.

6 Experimental Results and Discussion

6.1 Simulations

In this section the closed-loop evolution of the system is simulated with the obtained controller. Also in this case a Runge-Kutta 45 with step size 0.1 is utilized, the initial value of the state variables is set to $x_0 = [2000 \quad 8000]$, which corresponds to the initial tumor volume and initial supporting vasculature volume respectively. The choice of these values is due to the fact that most of mices are alive for a tumor volume range $0 - 2000$ mm^3 [9], hence, supposing that there is no therapy treatment, the worst case scenario is considered. As previously discussed, the tumor is not able to develop its supporting vasculature in a range of volumes of $1 - 2$ mm^3. Therefore, the set point value is set at a volume $r = 1$ mm^3.

We are looking for a value of R, the input-weighting scalar, such that it gives the least amount of total inhibitor doses within 50 days of treatment. During the simulation, different values of R are used, resulting in different behaviours for the tumor volumes as depicted in figure 2.

In figure 2a, it is possible to appreciate the tumor response and the level of inhibitor dose for $R = 1$. We have that the tumor reaches 1% of its initial value around 14.5 days, with the total amount of inhibitor dose of 1377.6 mg/kg. In the case of 2b, R was set to 10. Here, the total amount of inhibitor dose is 1374.9 mg/kg and the 1% of the tumor initial value is reached around 15.6 days. The third considered value for R is 100, as can be seen in figure 2c, where the tumor reaches its 1% within 18.9 days with a total inhibitor dose of 1385.7 mg/kg. Finally, in figure 2d the behaviour of the tumor volumes for $R = 1000$ is shown. In this case, the total amount of inhibitor dose is 1447.1 mg/kg, with 1% reached within approximately 27.2 days.

6.2 Discussion

From this analysis it seems that the days needed by tumor to reach the 1% of its initial value are more as R is larger. Moreover, the minimum amount of total inhibitor doses is reached for $R = 10$ and since the time length comparing $R = 1$ and $R = 10$ is not so different, it would be an advantage to have $R = 10$ since the aim of this study is to use the minimum amount of inhibitor dose as possible.

However, a better investigation is done by simulating the system for R in the range of $1 < R < 100$, with $R \in \mathbb{Z}$, which is shown in figure 3. From this we discover that a value for $R = 9$ is the best choice for giving the best optimal value of the total inhibitor dose. Therefore, during a treatment duration of 50 days, the least amount of total doses found by this procedure is 1374.8 mg/kg.

7 Conclusion

In this report we tackled the problem of the determination of the optimal inhibitor dose level for anti-angiogenic therapy in cancer treatment. The nonlinear model of a tumor growth dynamics has been considered and, on the discretization of its feedback-linearized equivalent model, a discrete linear quadratic regulator (LQR) with nonzero setpoint and finite length horizon has been applied. From the simulated responses of tumor volume and supporting vasculature volume, it has been shown that, utilizing the obtained control law with input-weighting scalar $R = 9$, a minimum total amount of inhibitor dose of 1374.8 mg/kg is found, which guarantees the decreasing of the tumor volume of 1% of its initial value within 15.5 days.

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A Appendix

In the following, the simulation results obtained with and without any modification of the formulas used in [6] are reported.

A.1 Differences on G

In figure 4 it is possible to see the results obtained without make the correction on the computation of the control gain G. It is clear that, in this case, the state does not converge at steady-state to the desired value r=1, instead it reaches, respectively for R from 1 to 100, the steady-state values $x_1 = x_2 = 186$, $x_1 = x_2 = 607$, $x_1 = x_2 = 1955$ and $x_1 = x_2 = 6242$.

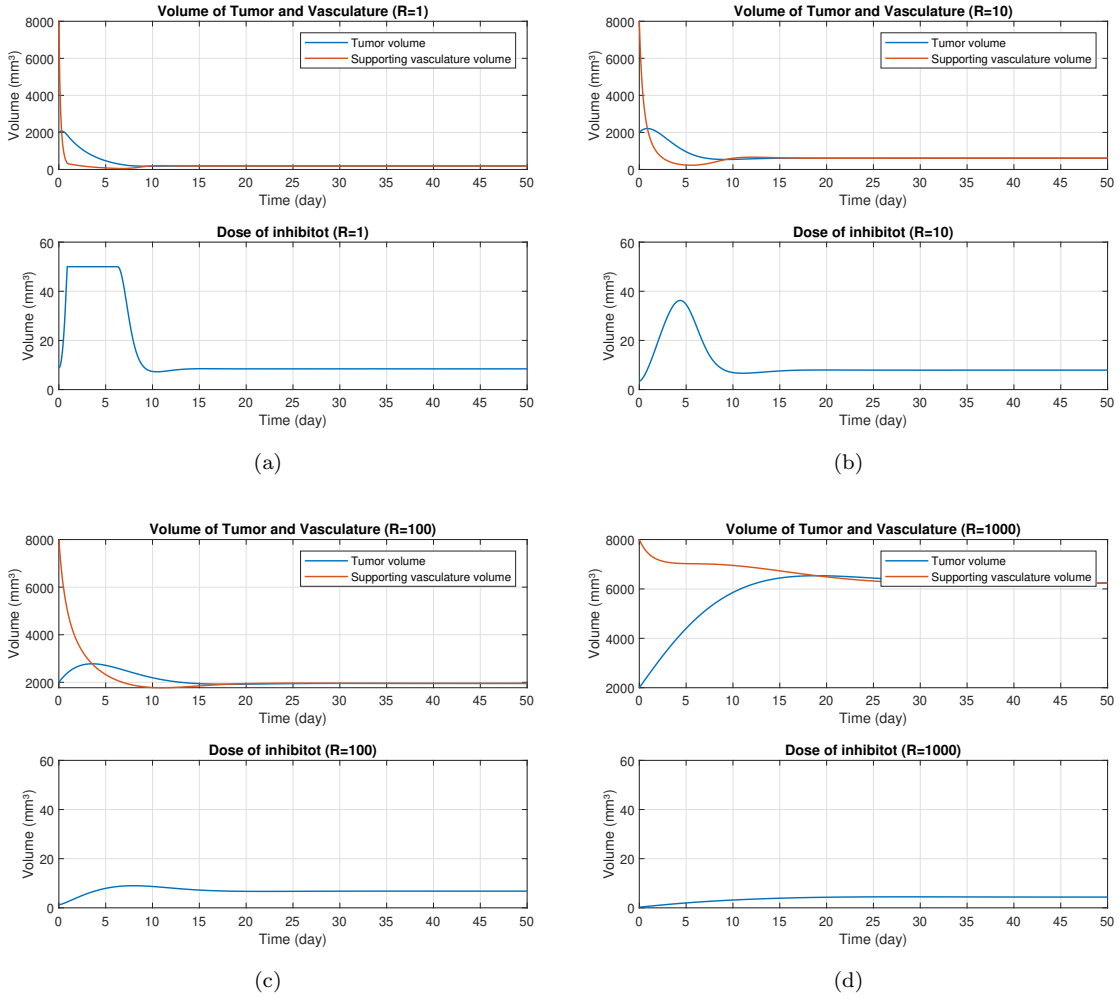


Figure 4: Response of tumor volume and supporting vasculature volume under the optimal level of inhibitor dose for different values of input-weighting scalar R: (a) $R = 1$, (b) $R = 10$, (c) $R = 100$, (d) $R = 1000$, using the formulas showed in [6] for computing the control gain G, but correcting the typo in the $\alpha(x)$ term of the linearizing feedback.

A.2 Differences on $\alpha(x)$

Finally in figure 5 are depicted the results without correcting the typo in the expression of $\alpha(x)$ term. In this case, since the dynamics of the system is clearly affected by this term, we obtain a completely different and meaningless behaviour, from the biological model point of view.

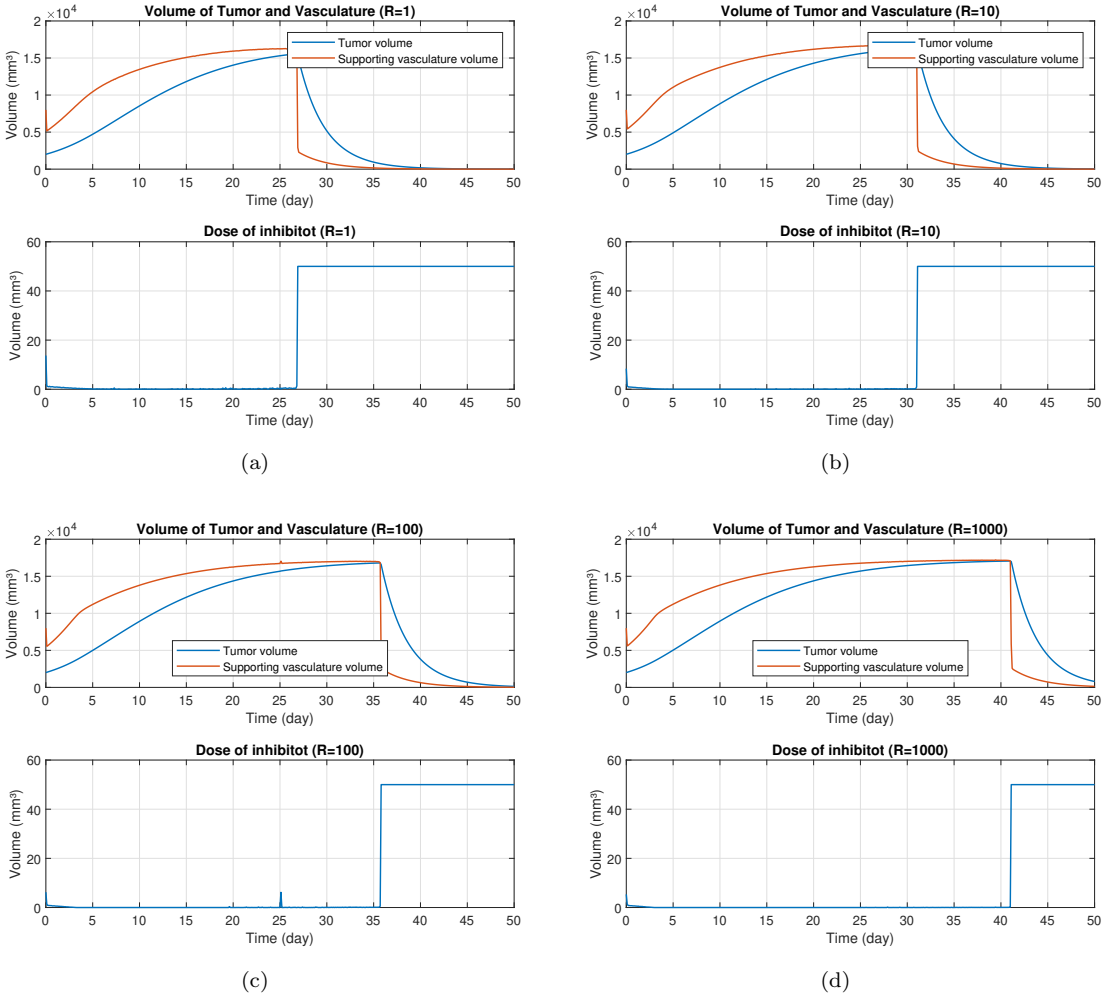
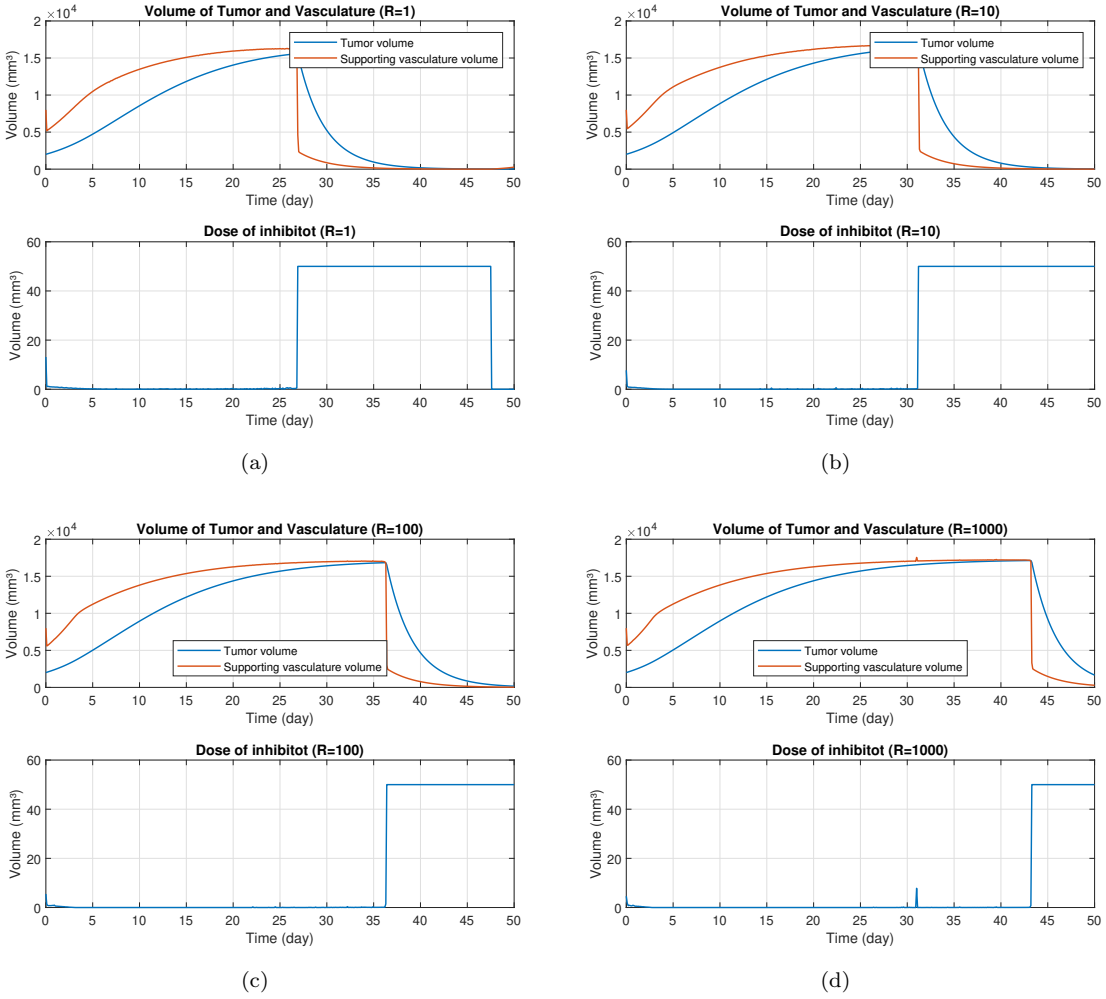


Figure 5: Response of tumor volume and supporting vasculature volume under the optimal level of inhibitor dose for different values of input-weighting scalar R: (a) $R = 1$, (b) $R = 10$, (c) $R = 100$, (d) $R = 1000$, using the formulas showed in [6] of the $\alpha(x)$ term, but using the different expression for computing G.

A.3 Differences on G and $\alpha(x)$

Firstly, in figure 6 we can appreciate the results when using the same formulas as described in [6], which are clearly different with respect to the one claimed in their article and which we obtain, instead, by correcting those erros, as showed in previous sections.



(a) (b) (c) (d)

Figure 6: Response of tumor volume and supporting vasculature volume under the optimal level of inhibitor dose for different values of input-weighting scalar R: (a) $R = 1$, (b) $R = 10$, (c) $R = 100$, (d) $R = 1000$, using all the exact formulas showed in [6].

Appendix B - Matlab Code

Functions:

Dynamical Model of Tumor Growth Dynamics

```
function tumorModelstate = tumorModel(t,state,params)
tumorModelstate = [
    -params{1}*state(1)*log(state(1)/state(2));
    params{2}*state(1)-params{3}*state(1)^(2/3)*state(2)-params{4}*state(2)* ...
            control_u(state(1),state(2),params{1},params{2},params{3}, ...
            params{4}, params{5},params{6},params{7},params{8},params{9})
    ];
end

function tumorModelstate_constant_u = tumorModel_constant_u(t,state,params,u)
tumorModelstate_constant_u = [
    -params{1}*state(1)*log(state(1)/state(2));
    params{2}*state(1)-params{3}*state(1)^(2/3)*state(2)-params{4}*state(2)*u
    ];
end
```

Discrete LQR with set-point

```
function [K,G]=dlqr_sp(A_d,B_d,C,Q,R,H)
    S_i=H;
    K_i=[1,1];
    N=0;
    buffSize = 20;
    circBuff = zeros(1,buffSize);
    while abs(sum(K_i*(buffSize/2))-sum(circBuff))>10^-7
        N=N+10;
        for i=N-1:-1:0
            S_i=A_d'*(S_i-S_i*B_d*1/(B_d'*S_i*B_d+R)*B_d'*S_i)*A_d+Q;
            circBuff = [circBuff(3:end),K_i];
            K_i=(1/(R))*B_d'/(A_d')*(S_i-Q);
        end
    end
    K=K_i;
    G=1/(C/(eye(2)-A_d+B_d*K)*B_d);%G=1/(C/(B_d*K-A_d)*B_d)
end
```

Control Function

```
function u=control_u(x1,x2,lambda,b,d,e,K,G,r,A_d,B_d)
beta = -e*lambda*x1;
alpha = (lambda*log(x1/x2)+lambda)*lambda*x1*log(x1/x2) ...
                  +lambda*(x1/x2)*(b*x1-d*(x1^(2/3))*x2);

z1 = x1;
z2 = -lambda*x1*log(x1/x2);
z=[z1;z2];
I2=eye(2);
```

```
gamma=inv(I2+B_d*K);
A_new=gamma*A_d;
B_new=gamma*B_d*G;
z_new=A_new*z+B_new*r;

v=-K*z_new+G*r;
u=(v-alpha)/beta;
if u<0
    u=0;
end
if u>50
    u=50; %saturation
end
end
```

System integration

```
function [states,u,t,total_inhibitor_dose,days]=tumor_growth_simulation(A_d, ...
                                B_d,C_d,Q,R,H,lambda,b,d,e,r,tspan,state_0,plot,verbose)

    [K,G]=dlqr_sp(A_d,B_d,C_d,Q,R,H);
    index_days_to_1perc=tspan(end);
    first_time=true;
    params = {lambda,b,d,e,K,G,r,A_d,B_d};
    [t,states]=ode45(@(t,state)tumorModel(t,state,params),tspan,state_0);
    u=zeros(size(t'));
    for i=1:size(states,1)
        u(i)=control_u(states(i,1),states(i,2),params{1},params{2},params{3}, ...
                    params{4},params{5},params{6},params{7},params{8},params{9});
        if states(i)<=(state_0(1)/100) && first_time
            index_days_to_1perc=i;
            first_time=false;
        end
    end
    total_inhibitor_dose=sum(u);
    days=t(index_days_to_1perc);
    if verbose
        K
        G
        total_inhibitor_dose
        days
    end
    if plot
        plot_inhibitor(t,states,u,R)
    end
end
```

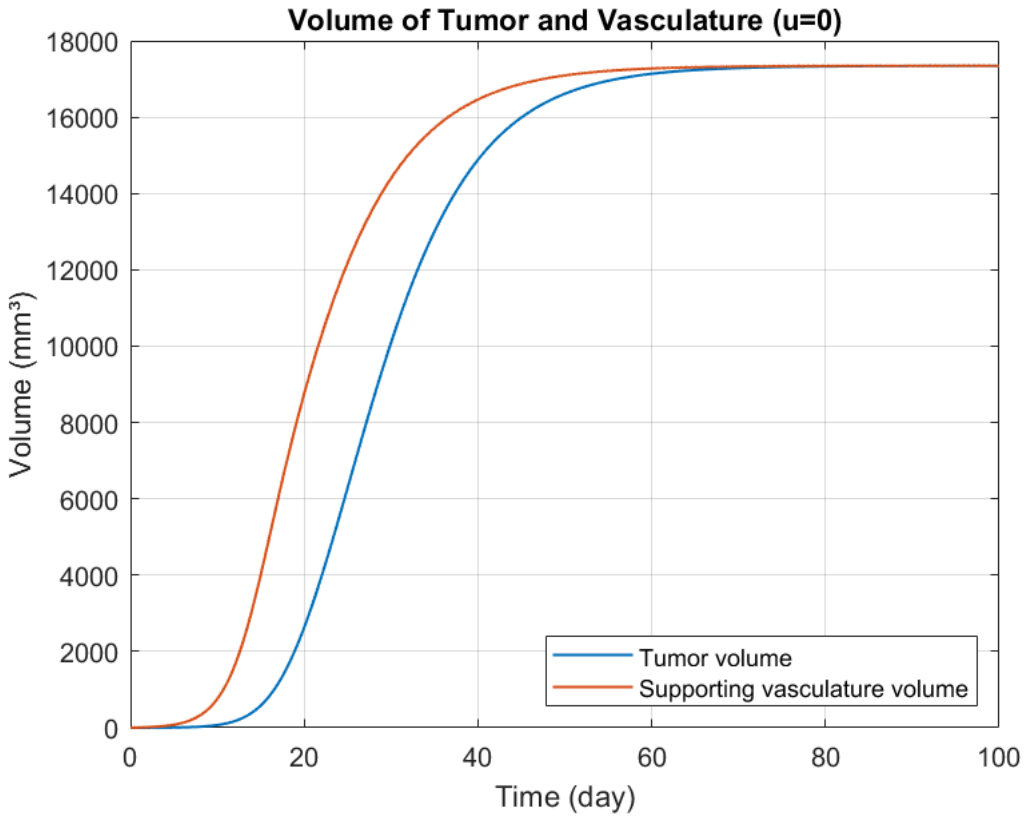
Main Function

```
clear all

lambda=0.192;
b=5.85;
d=0.00873;
```

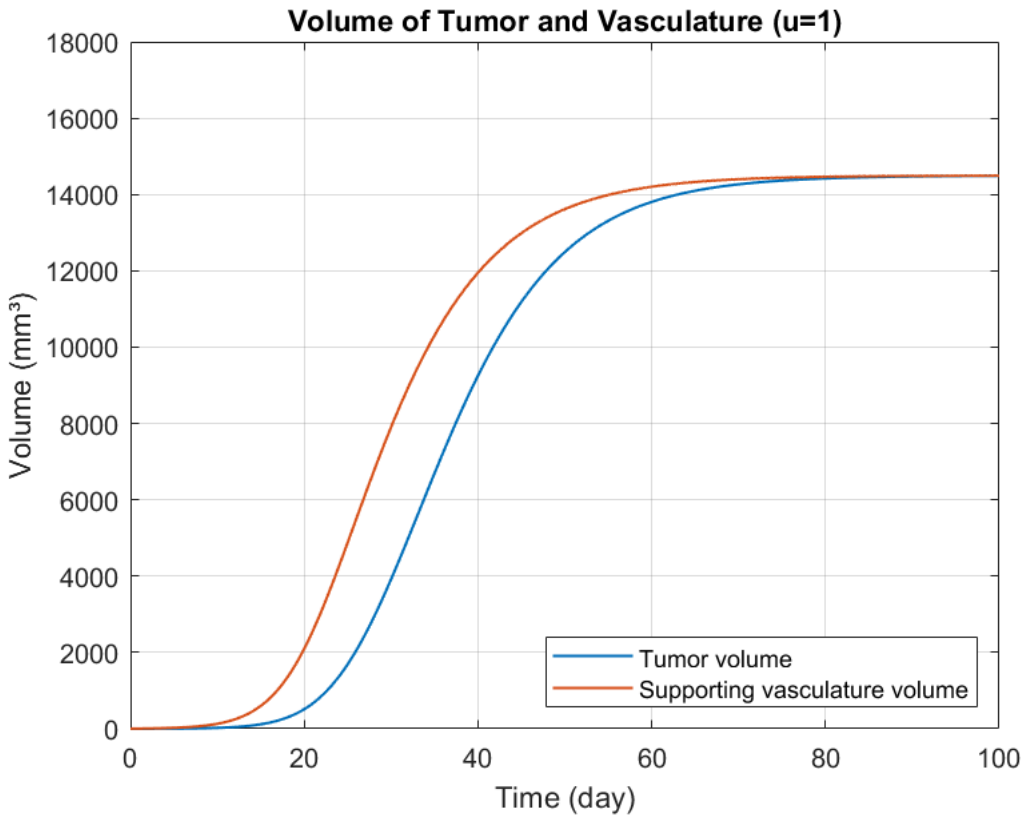
```
e=0.66;
r=1;
params_constant_u = {lambda,b,d,e};
```

Response of tumor volume and supporting vasculature volume without and under inhibitor doses of various constant levels

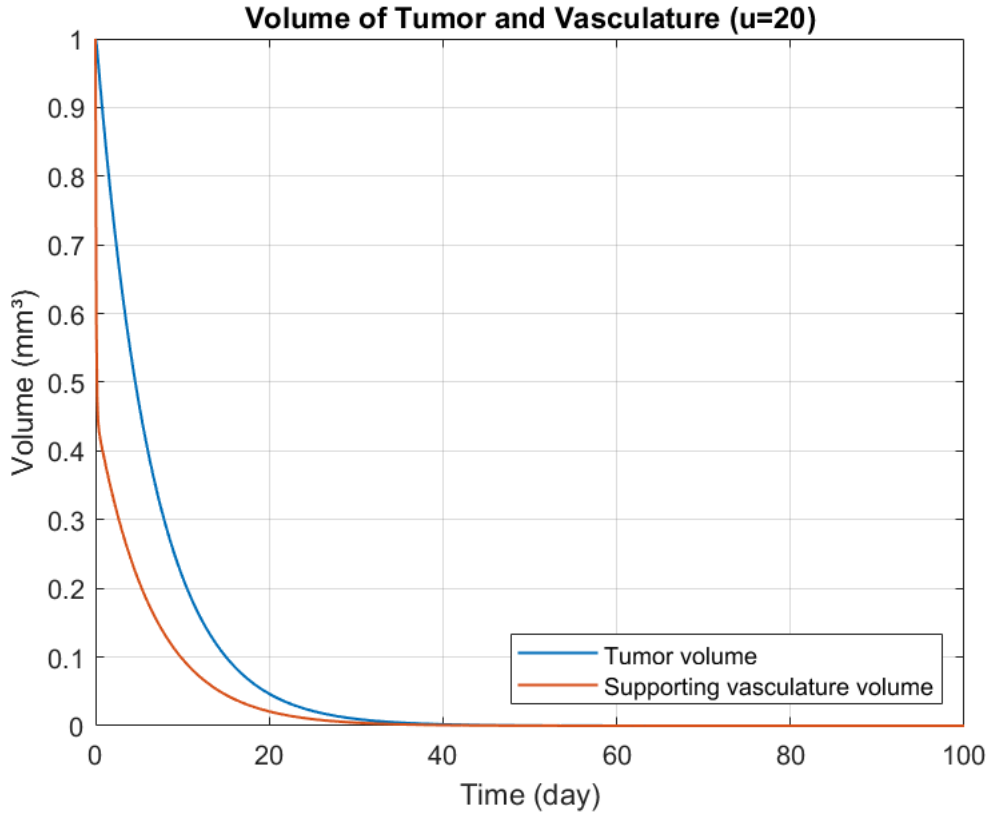
```
state_0_constant_u =[1; 1];
tspan_constant_u = [0:0.1:100];
plot_constant_inhibitor(0,params_constant_u,tspan_constant_u,state_0_constant_u,[0,18000])
```



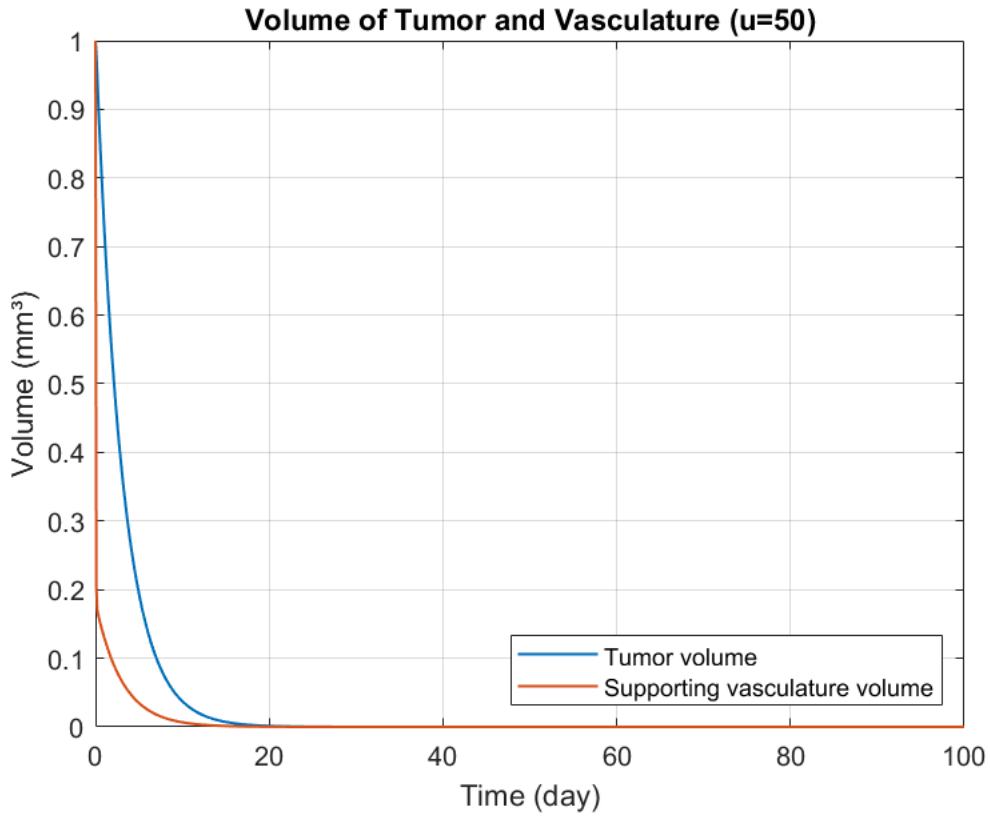

```
plot_constant_inhibitor(1,params_constant_u,tspan_constant_u,state_0_constant_u,[0,18000])
```




```
plot_constant_inhibitor(20,params_constant_u,tspan_constant_u,state_0_constant_u,[0,1])
```



```
plot_constant_inhibitor(50,params_constant_u,tspan_constant_u,state_0_constant_u,[0,1])
```



Feedback linearized model in z coordinates:

```
A = [0 1; 0 0];
B = [0; 1];
C = [1 0];
D = 0;
```

Optimal discrete state-feedback design

```
discrete_time_system = c2d(ss(A,B,C,D),0.1)
```

```
discrete_time_system =

  A =
       x1   x2
   x1   1  0.1
   x2   0    1

  B =
         u1
   x1  0.005
   x2    0.1

  C =
       x1  x2
   y1   1   0

  D =
       u1
```

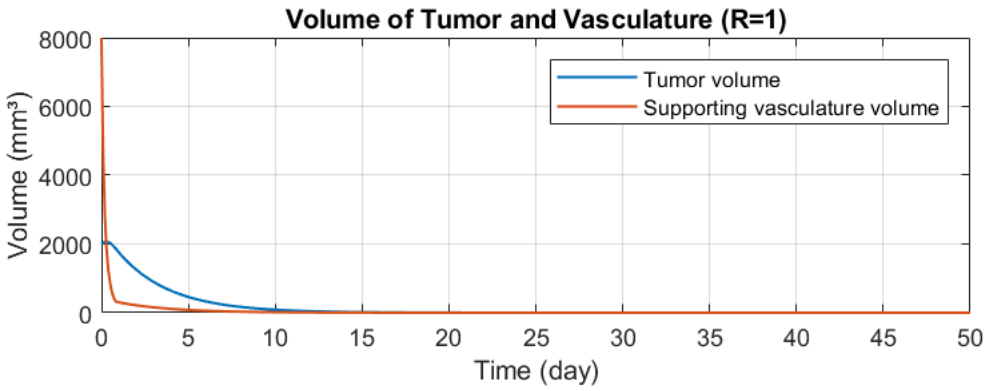
```
   y1   0

Sample time: 0.1 seconds
Discrete-time state-space model.
```

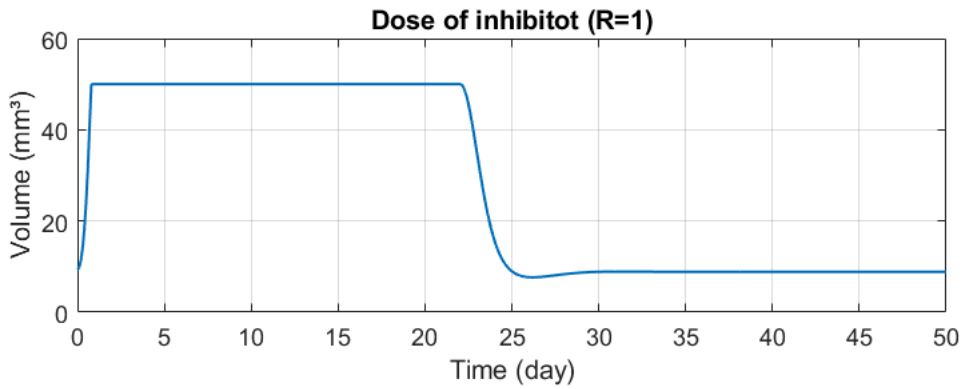
```
A_d=discrete_time_system.A;
B_d=discrete_time_system.B;
C_d=discrete_time_system.C;
Q=[1,0;0,0];
H=[1,0;0,0];
r=1;
state_0 =[2000; 8000];
tspan = [0:0.1:50];
lambda=0.192; b=5.85; d=0.00873; e=0.66;
```

Case R=1

```
[states,u,t,total_inhibitor_dose,days_to_1perc]=tumor_growth_simulation(A_d, ...
                                    B_d,C_d,Q,1,H,lambda,b,d,e,r,tspan,state_0,true,true);
```

```
K = 1×2
     9.317451415091824e-01     1.365097169808200e+00
G =
     9.317451415091825e-01
total_inhibitor_dose =
     1.377649765946793e+04
days =
     1.450000000000000e+01
```



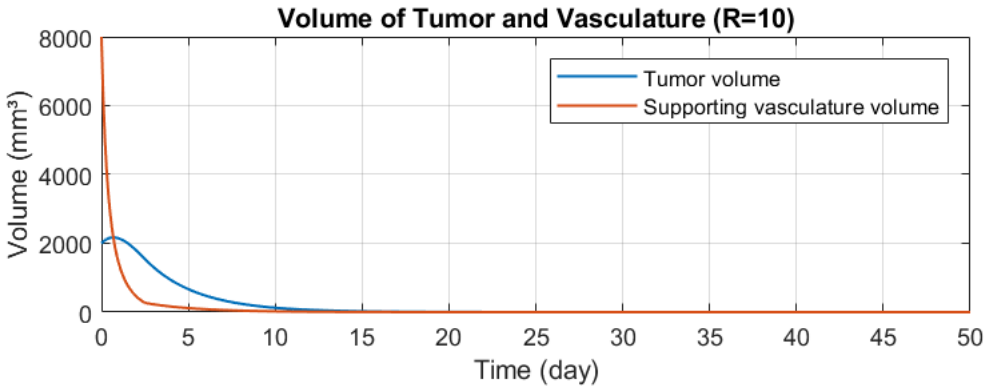


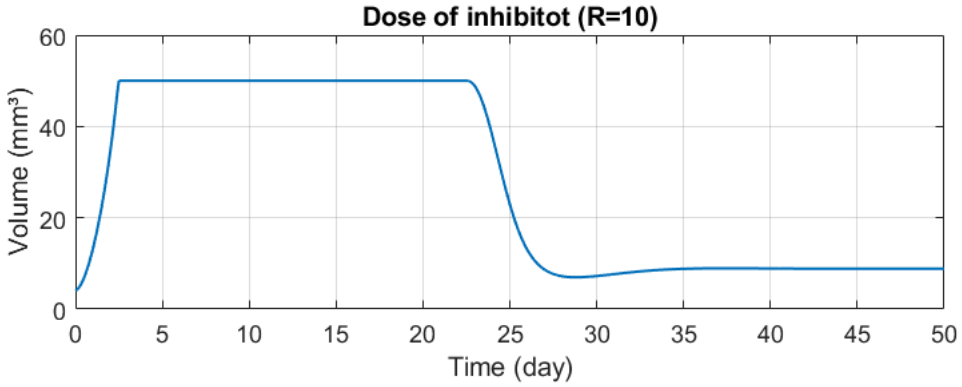
Case R=10

```
[states,u,t,total_inhibitor_dose,days_to_1perc]=tumor_growth_simulation(A_d, ...
```

```
                                    B_d,C_d,Q,10,H,lambda,b,d,e,r,tspan,state_0,true,true);
```

```
K = 1×2
     3.039009467385543e-01     7.796165038749431e-01
G =
     3.039009467385543e-01
total_inhibitor_dose =
     1.374866791775597e+04
days =
     1.560000000000000e+01
```

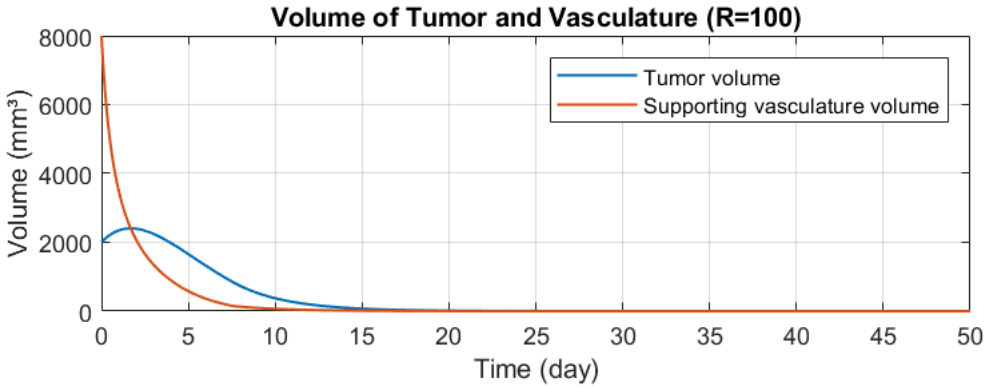


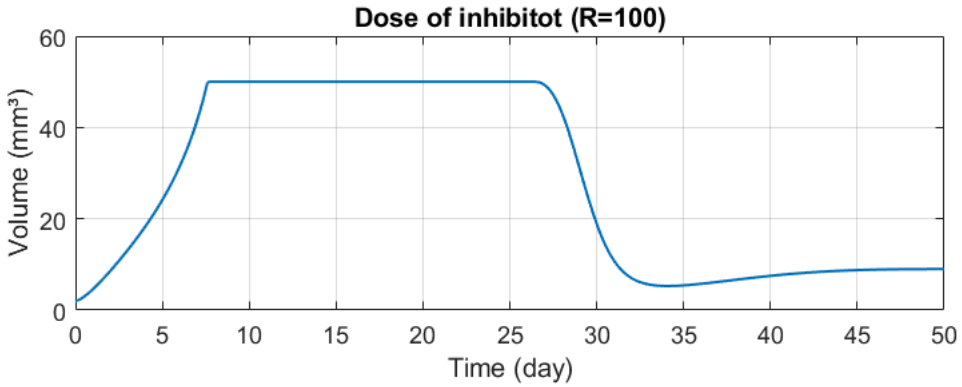


Case R=100

```
[states,u,t,total_inhibitor_dose,days_to_1perc]=tumor_growth_simulation(A_d, ...
                                    B_d,C_d,Q,100,H,lambda,b,d,e,r,tspan,state_0,true,true);
```

```
K = 1×2
     9.778879137876374e-02     4.422415403734525e-01
G =
     9.778879137876374e-02
total_inhibitor_dose =
     1.385700361523058e+04
days =
     1.890000000000000e+01
```

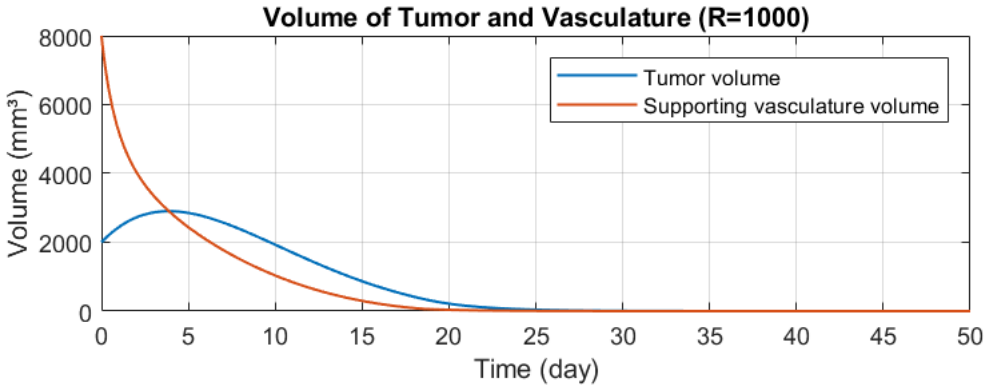


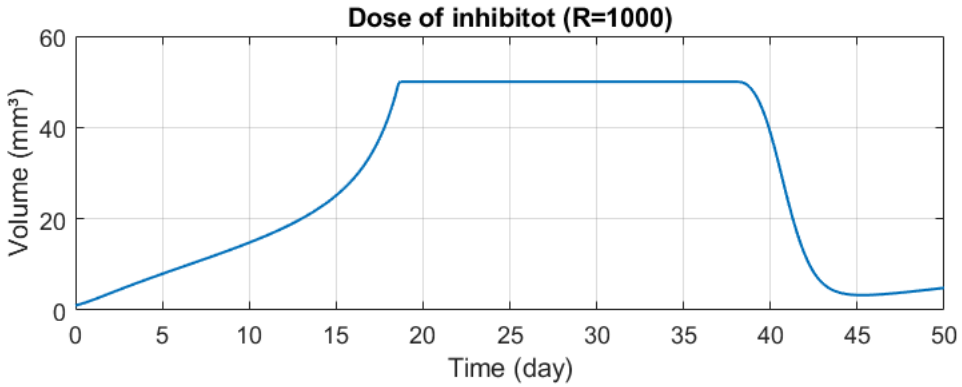


Case R=1000

```
[states,u,t,total_inhibitor_dose,days_to_1perc]=tumor_growth_simulation(A_d, ...
                                    B_d,C_d,Q,1000,H,lambda,b,d,e,r,tspan,state_0,true,true);
```

```
K = 1×2
     3.122763054129877e-02     2.499104993415736e-01
G =
     3.122763054129877e-02
total_inhibitor_dose =
     1.447128225611787e+04
days =
     2.720000000000000e+01
```





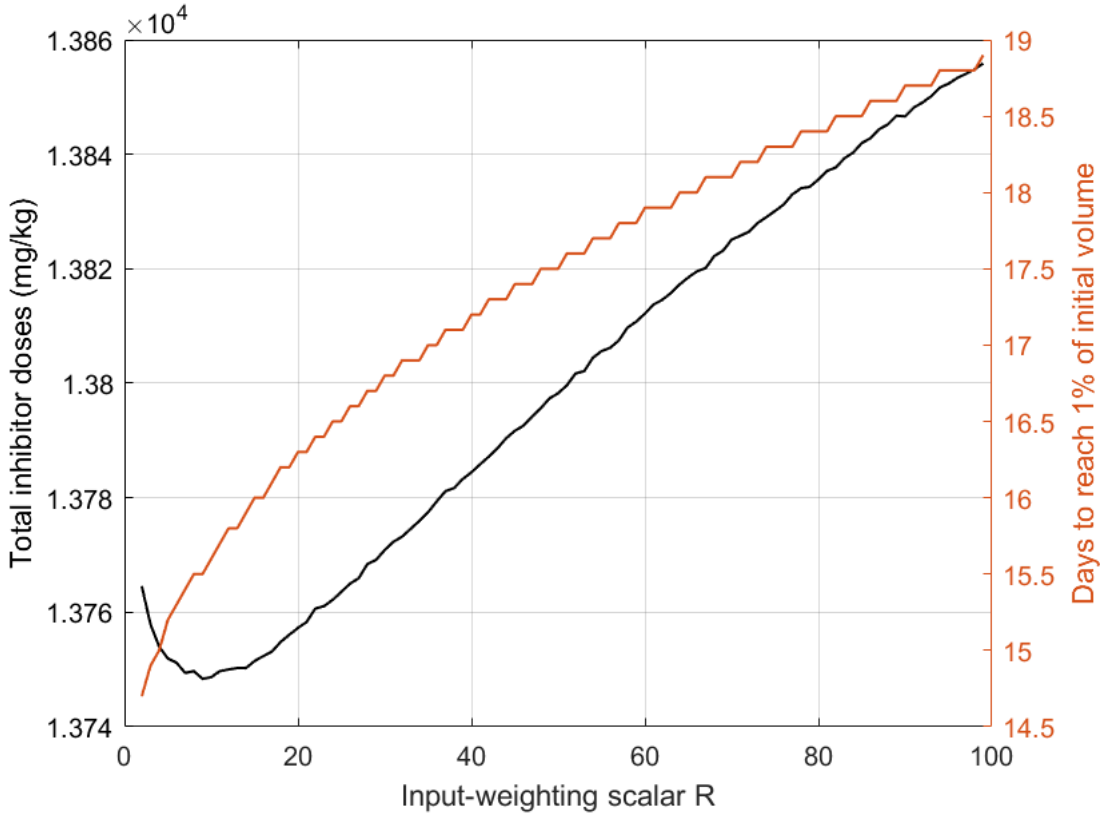

```
R_list=[2:99];%[1,10:10:100];
total_inhibitor_doses=zeros(size(R_list));

time_lenghts=zeros(size(R_list));
for i=1:size(R_list,2)
    [states,u,t,total_inhibitor_dose,days]=tumor_growth_simulation(A_d, ...
                    B_d,C_d,Q,R_list(i),H,lambda,b,d,e,r,tspan,state_0,false,false);
    total_inhibitor_doses(i)=total_inhibitor_dose;
    days_to_1perc_list(i)=days;
end
total_inhibitor_doses
```

```
total_inhibitor_doses = 1×98
    1.376456231560103e+04    1.375790273189442e+04    1.375401769631372e+04 ···
```

```
days_to_1perc_list
```

```
days_to_1perc_list = 1×98
    1.470000000000000e+01    1.490000000000000e+01    1.500000000000000e+01 ···
```

```
[min_tid, idx_min_tid]=min(total_inhibitor_doses);


plot_total_inhibitor_doses(total_inhibitor_doses,R_list,days_to_1perc_list)
```




```
disp(['The minimum total inhibitor dose is ',num2str(min_tid), ...
              ' for a choice of R=',num2str(R_list(idx_min_tid))])
```

```
The minimum total inhibitor dose is 13748.3797 for a choice of R=9
```

Plot functions

```
function plot_inhibitor(t,states,u,R)
    figure
    tiledlayout(2,1)
    % Top plot
    ax1 = nexttile;
    plot(ax1,t,states,'LineWidth',1)
    title(ax1,['Volume of Tumor and Vasculature (R=',num2str(R),')'])
    ylabel(ax1,'Volume (mm³)')
    xlabel(ax1,'Time (day)')
    legend('Tumor volume','Supporting vasculature volume')
    grid on
    % Bottom plot
    ax2 = nexttile;
    plot(ax2,t,u,'LineWidth',1)
    title(ax2,['Dose of inhibitot (R=',num2str(R),')'])
    ylabel(ax2,'Inhibitor dose (mg/kg)')
    ylabel(ax2,'Volume (mm³)')
    xlabel(ax2,'Time (day)')
```

```
    ylim([0,60])
    grid on

end

function plot_total_inhibitor_doses(total_inhibitor_doses,R_list,days_to_1perc_list)
    figure

    %xx=linspace(R_list(1),R_list(end),1000);
    %yy=interp1(R_list,total_inhibitor_doses,xx,'spline');

    %days_to_1perc_list_yy=interp1(R_list,xx,'spline');
    plot(R_list,total_inhibitor_doses,'LineWidth',1)

    ylabel('Total inhibitor doses (mg/kg)')
    xlabel('Input-weighting scalar R')
    grid on
    yyaxis right
    plot(R_list,days_to_1perc_list,'LineWidth',1)
    ylabel('Days to reach 1% of initial volume')
end

function plot_constant_inhibitor(constant_u,params_constant_u, ...
                        tspan_constant_u,state_0_constant_u,y_lim)
    [t_constant_u,states_constant_u]=ode45(@(t_constant_u, ...
              state_constant_u)tumorModel_constant_u(t_constant_u,state_constant_u, ...
              params_constant_u,constant_u),tspan_constant_u,state_0_constant_u);
    figure
    plot(t_constant_u,real(states_constant_u),'LineWidth',1)
    xlabel('Time (day)')
    ylabel('Volume (mm³)')
    legend({'Tumor volume','Supporting vasculature volume'},'Location','southeast')
    grid on
    title(['Volume of Tumor and Vasculature (u=',num2str(constant_u),')'])
    ylim(y_lim)
end
```