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Study of Modern Control Methodologies Applied to Tumor Growth under Angiogenic Inhibition ⋆

Annamária Szeles *, **Dániel A. Drexler** *, **Johanna Sápi** **, **István Harmati** *, **Levente Kovács** **

* *Department of Control Engineering and Information Technology, Budapest University of Technology and Economics, Budapest, Hungary (e-mails: szeles.annam@gmail.com, {drexler, harmati}@iit.bme.hu)*

** *John von Neumann Faculty of Informatics, Óbuda University, Budapest, Hungary (e-mail: sapi.johanna@phd.uni-obuda.hu, kovacs.levente@nik.uni-obuda.hu)*

Abstract: Cancer treatment is one of the most important research fields of modern medicine. In the last decades, targeted molecular therapies showed prosperous results. These treatments achieve tumor regression with limited side-effects. Mathematical models were posed which describe the dynamics of tumor regression under the applied control. The current paper investigates antiangiogenic therapy, which inhibits the tumor to grow its own endothelial capillaries and thus inhibits tumor to grow over a certain size. Many different control approaches were elaborated and published since the model formulation was posed. The aim of this paper is to give an overview of these methods and results, and to review the work carried out by the authors.

Keywords: tumor therapy, biomedical systems, LQ regulation, robust control, flat control

1. INTRODUCTION

Modern medical research aims to find harmless and effective therapies to fight cancer. Targeted molecular therapies propose better solutions than conventional treatments, Gerber (2008); Li et al. (2012). These therapies apply drugs which are non-toxic towards normal cells, hence these cause limited side-effects. Antiangiogenic therapy influences the life cycle of the tumor in a way which secures that the tumor can not grow over a certain size (1-2 mm^3), Pluda (1997). Antiangiogenic drugs (endostatin, O'Reilly et al. (1997) or bevacizumab, Ellis and Haller (2008)) inhibit the tumor to develop own blood vessels, thus the tumor is not able to take up more nutriants and oxygen over a certain amount, Wu et al. (2008).

The mathematical formalism which describes angiogenic signalling in case of an in vivo tumor was posed in Hahnfeldt et al. (1999). The model was investigated and reformulated many times, d'Onofrio and Cerrai (2009); d'Onofrio et al. (2009). Different control methodologies were elaborated to design optimal dosaging for a simplified second-order model. Bang-singular-bang control was designed in Ledzewicz and Schättler (2005), and set-valued protocol was proposed in Kassara and Moustafid (2011). Optimal state-feedback design was carried out in Sápi et al. (2012), and robust methodologies were presented in Szeles et al. (2012). Flatness based techniques were elaborated in Szeles et al. (2013), and for the original model flat control design was presented in Drexler et al. (2012).

These techniques involve different approaches towards the nonlinearity of the system, these are: application of nonlinear control, Ledzewicz and Schättler (2005); Kassara and Moustafid (2011), working point linearization, Sápi et al. (2012); Szeles et al. (2012), and exact linearization, Drexler et al. (2012); Szeles et al. (2013).

The aim of this paper is to give an overview of the techniques applied by the authors. The differences, advantages and disadvantages of each methodology is to be emphasized.

Section 2 describes the mathematical model of tumor growth under antiangiogenic treatment. Section 3 presents the different control techniques (LQ regulation, $\mathcal{H}_\infty$ control, and flatness based control methodologies), related simulation results are detailed in Section 4. Based on the results, a detailed comparison is proposed including the effects of model parametric perturbations. The paper ends with the conclusions in Section 5.

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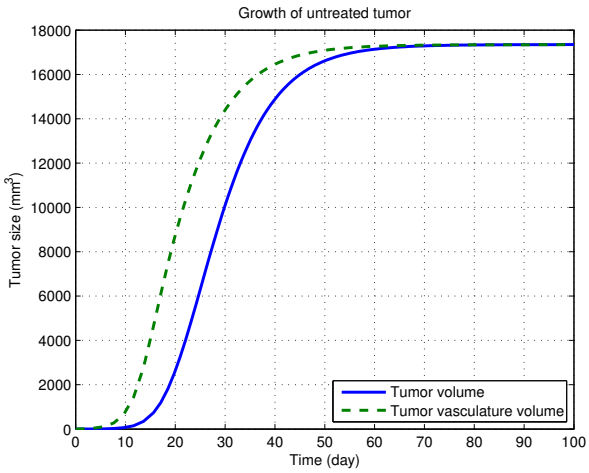


Fig. 1. Growth of untreated tumor

2. MATHEMATICAL MODEL OF TUMOR GROWTH

The mathematical model which describes tumor growth dynamics was posed in Hahnfeldt et al. (1999). The model was biologically validated through experiments in which mice were injected with Lewis lung carcinoma cells. This paper uses a simplified second-order model. The simplification originates from the fact that instead of first-order, zero-order pharmacokinetics is applied. The description of tumor growth dynamics is based on a Gompertzian growth (1), which captures the phenomenon of tumor growth slowdown. Tumor stimulated growth and regression and the effects of the antiangiogenic inbihition are summarized in (2). The measured output of the system is the tumor volume (3). Thus, the model formulation becomes:

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

$$\dot{x}_2 = bx_1 - dx_1^{\frac{2}{3}} x_2 - ex_2 u \tag{2}$$

$$y = x_1 \tag{3}$$

where x_1 is the tumor volume (mm^3), x_2 is the vasculature volume (mm^3), and u is the serum level of the administered inhibitor (mg/kg). The parameters λ, b and d are characteristic for the animals and the Lewis lung carcinoma, the parameter e is characteristic for the applied inhibitor, that was endostatin:

$$\begin{array}{ll} \lambda = 0.192\,(\mathrm{day}^{-1}) & d = 0.00873\,(\mathrm{day}^{-1}\mathrm{mm}^{-2}) \\ b = 5.85\,(\mathrm{day}^{-1}) & e = 0.66\,(\mathrm{day}^{-1}(\mathrm{mg/kg})^{-1}) \end{array}. \tag{4}$$

The dynamics of an untreated tumor comprised by the model is presented in Fig. 1.

3. APPLIED CONTROL TECHNIQUES

3.1 Linear control methods

The first approach was using linear control methodologies in the following way:

(1) working point linearization was carried out,
(2) the control design was performed for this linear model,
(3) the designed controller was wired to the nonlinear model.

The behavior of the system in different working points was analyzed in Drexler et al. (2011). The chosen working point and the characteristics of the linearized system were detailed in Szeles et al. (2012).

LQ regulation The aim of the regulation is to find the optimal u^* control input which minimizes the $J(x,u)$ cost function, Zhou (1996). The cost function is the following:

$$J(x,u) = \frac{1}{2}\int_0^\infty [< Qx(t), x(t) > + < Ru(t), u(t) >]\mathrm{d}t \tag{5}$$

To determine the optimal control input, the Algebraic Riccati Equation has to be solved whose solution is the $P > 0$ positive definite matrix,

$$PA + A^T P - PBR^{-1}B^T P + Q = 0 \tag{6}$$

Thus, the control input (and the optimal state feedback) becomes:

$$u^* = -Kx = -R^{-1}B^T Px \tag{7}$$

The output is minimized in a quadratic sense, from which $Q \geq 0$ is determined, and $R > 0$ is tuned accordingly, hence the applied weighting matrices are:

$$Q = C^T C \qquad R = 10000 \tag{8}$$

$\mathcal{H}_\infty$ design The aims of robust control design are the following, Zames (1981); Zhou (1996):

- handle model uncertainty,
- eliminate disturbances and measurement noise,
- minimize the controller output.

The goal of the design is to find a stabilizing controller which minimizes the $\mathcal{H}_\infty$-norm of the closed-loop system,

$$\min_{K_s} \|\mathcal{F}_\ell(P,K)\|_\infty \tag{9}$$

where K is the controller, P refers to the nominal model of the system including the input and output weighting functions and not including model uncertainty and disturbances, and the operation $\mathcal{F}_\ell$ is the lower linear fractional transformation.

The input and output weighting functions are responsible for transforming the signal magnitudes into a desired domain and to realize signal filtering if necessary. These are the following:

$$\begin{array}{llll} W_n = 0.1 & W_{unc} = 0.01\frac{s+2}{s+8} \\ W_u = \frac{1}{50} & W_{perf} = 6.5\cdot 10^{-7}\frac{s+8}{s+1} \end{array} \tag{10}$$

where W_n penalizes the wide-band measurement noise, W_{unc} weights the disturbances originating from model uncertainties, W_u weights the control input, and W_{perf} decreases the deviation of the output signal from the desired output.

The state-space description of the controller resulting from the $\mathcal{H}_\infty$ design is:

$$\dot{v} = K_A v + K_B \begin{bmatrix} r \\ y \end{bmatrix} \tag{11}$$

$$u = K_C v + K_D \begin{bmatrix} r \\ y \end{bmatrix} \tag{12}$$

where r is the reference signal (constant zero), y is the output of the tumor model, u is the control input, v is the state-space variable of the controller, and the matrices are:

$$K_A = \begin{bmatrix} -15.80 & 0.19 & 0 & 0 & 0 \\ -653.18 & -1.77 & 0.01 & -0.01 & -170.81 \\ 0 & 0 & -0.07 & 0 & 0 \\ 0 & 0 & -0.11 & -1 & 0 \\ 0.03 & 0.01 & 0 & 0 & -7.37 \end{bmatrix}$$

$$K_B = \begin{bmatrix} 0 & 0.89 \\ 0 & 37.43 \\ 2.88 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \quad K_C = [\,2.27\ 0.42\ 0\ 0\ 44.96\,] \quad K_D = [\,0\ 0\,] \tag{13}$$

The investigation of parametric sensitivity, the steps of controller design and stability related issues are detailed in Szeles et al. (2012). However, simulations were recalculated to compare the controllers under standardized circumstances (observed tumor range changed, see Section 4).

3.2 Flatness based control methods

The second approach was using exact linearization; hence, the nonlinear system could be transformed into a series of integrators, Isidori (1995). Each step of the transformation was calculated in Szeles et al. (2013), the resulting linearizing feedback is:

$$u = \frac{v - a(x)}{b(x)} \tag{14}$$

where u is sent to the nonlinear system, and the closed-loop interconnection between v and the output of the system y can be handled as a series of integrators, and

$$a(x) = (\lambda \ln \frac{x_1}{x_2} + \lambda)\lambda x_1 \ln \frac{x_1}{x_2} + \lambda x_1 \frac{1}{x_2}(bx_1 - dx_1^{\frac{2}{3}} x_2) \tag{15}$$

$$b(x) = -e\lambda x_1. \tag{16}$$

Flat control In the case of flat control, path tracking is realized according to prescribed error dynamics. The reference signal describes exponential decrease from the initial tumor volume to the plateau of 1 mm^3, Drexler et al. (2012); Szeles et al. (2013). The mathematical form of the reference signal is:

$$y_{ref} = (x_0 - 1)e^{-\frac{t}{T}} + 1 \tag{17}$$

$$\dot{y}_{ref} = -\frac{1}{T}(x_0 - 1)e^{-\frac{t}{T}} \tag{18}$$

$$\ddot{y}_{ref} = \frac{1}{T^2}(x_0 - 1)e^{-\frac{t}{T}}. \tag{19}$$

The Hurwitz polinomial which defines the error dynamics is:

$$s^2 + k_2 s + k_1 = 0. \tag{20}$$

The simulation and design parameters are:

$$\begin{aligned} T &= 1/0.35 \quad x_0 = 2000 \\ k_1 &= 18.25 \quad k_2 = 8 \end{aligned} \tag{21}$$

and the reason behind the applied error dynamics is detailed in Szeles et al. (2013).

Flatness based switch control Since the controlled system shows nonlinear behavior, in different tumor volume domains different error dynamics are advantegous. Thus, it is prosperous to divide the observed tumor volume domain into several regions, as presented in Fig. 2 and prescribed in Table 1, where the most appropriate error dynamics and reference signal can be defined. In our case, this means that in lower tumor volume ranges both the reference signal and the error dynamics can be fastened.

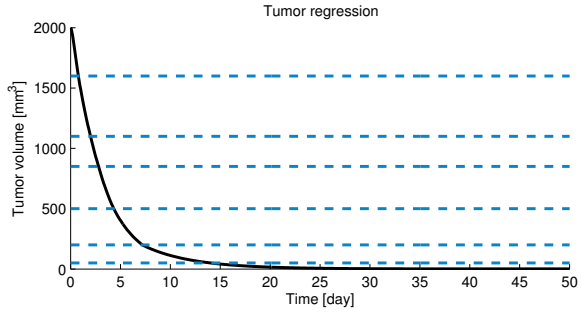


Fig. 2. Division of the tumor domain

Table 1. Simulation parameters

	Domain					
	1	2	3	4	5	6-7
Limit	2000	1600	1150	850	500	200,50
s_1	-0.15	-0.25	-0.3	-0.35	-0.32	-0.2
s_2	-8	-8.75	-11	-12.5	-12.7	-19
T	1/0.35	1/0.45	1/0.5	1/0.7	1/0.8	1

To avoid discontinuities, the affine combination of the control inputs calculated in the neighboring intervals is sent to the system ($u = \lambda u_i + (1 - \lambda)u_{i+1}$) such that in the middle of the i^{th} interval $\lambda = 1$. Table 1 shows the upper limits of the tumor regions, the time constant of the reference signal, and the poles of the Hurwitz polinomial which describe the error dynamics in each domain. The chosen error dynamics and time constants are further detailed in Szeles et al. (2013).

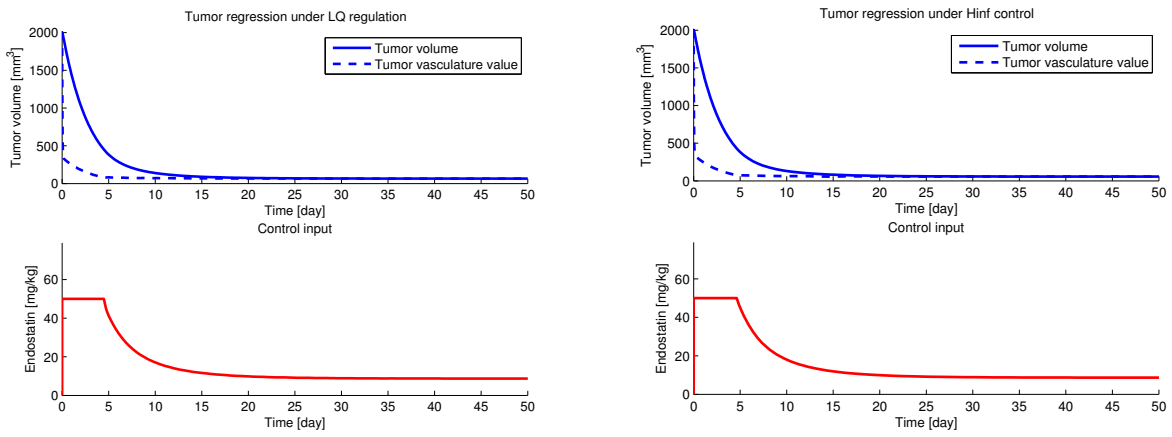
4. SIMULATION RESULTS

Simulations were carried out in the [0 2000] mm^3 tumor volume domain. Because of physiological reasons, the inhibitor serum level shall not be greater than 50–70 mg/kg, however linear controllers may generate significantly higher control input (over 600 mg/kg), thus control input saturation of 50 mg/kg was applied for the linear controllers. Tumor regression (tumor volume and vasculature volume) and corresponding control inputs are presented in Fig. 3.

The designed controllers are compared according to the following aspects:

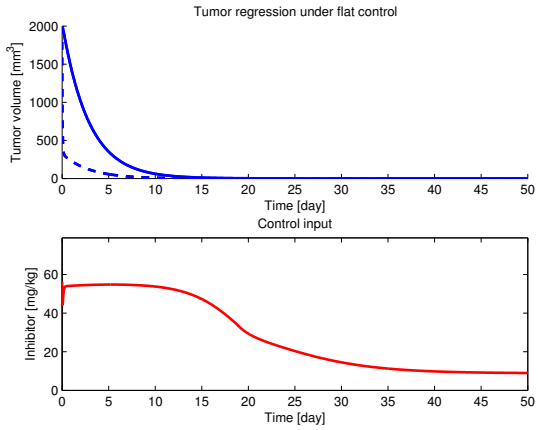
- time until tumor volume decreased to 1% (20 mm^3) of initial tumor volume (days);
- time until achieving the plateau of 1 mm^3 (days);
- tumor volume achieved in 50 days (mm^3);
- time while daily endostatin inlet is over 40 mg/kg measured in days;
- total endostatin inlet (mg/kg);
- minimal total endostatin inlet (mg/kg) in the perturbed cases;
- maximal total endostatin inlet (mg/kg) in the perturbed cases.

In the cases of LQ and $\mathcal{H}_\infty$ control, Fig. 3(a) and 3(b), the control inputs needed to be saturated, since initial serum levels exceeded 600 mg/kg, while the control inputs

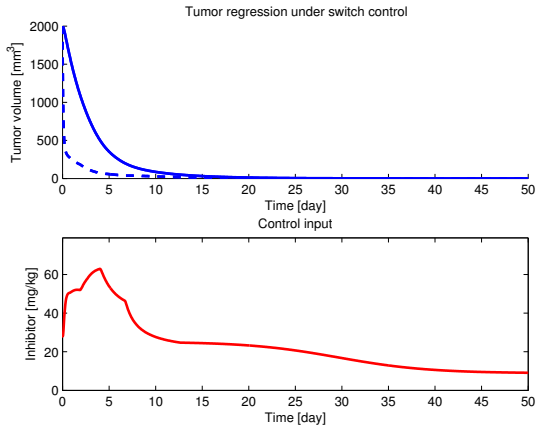


(a) LQ regulation

(b) $\mathcal{H}_\infty$ design



(c) Flat control



(d) Flatness based switch control

Fig. 3. Comparison of the performance of the applied control techniques

of flatness based techniques remained under 65 mg/kg, Fig. 3(c) and 3(d).

Though linear controllers generate lower control inputs at the final part of the therapy and presented low total drug inlets, these were unable to reduce the tumor volume under 1% of the initial tumor volume. However, flatness based techniques were able to attain the desired plateau of 1 mm^3. The performance of switch control suits the requirements the best: the tumor volume decreased to 1 mm^3 using relatively low daily and total inhibitor inlets, without external saturation.

4.1 Effects of parameter perturbation

To investigate the effects of parametric changes, simulations were carried out where the four model related parameters (λ, b, d, e) were perturbed independently in the range of $\pm 25\%$. The effects of the parameter changes on the tumor regression and control input can be seen in Fig. 4. Compared to the nominal behavior of the model, some model parameter combinations appear to influence both the performance of tumor regression and the inhibitor inlets (daily and total) advantegously. In those cases, where inhibitor inlets increased, the total inlet is still lower than inlets published in Ledzewicz and Schättler (2005); Kassara and Moustafid (2011), latter inlets were over 3000 mg/kg. Minimal and maximal total inhibitor inlets are detailed in the last rows of Table 2.

In the cases of linear control, tumor regression showed the nominal performance despite the parametric changes during most of the simulations. However, the total inhibitor inlet showed high variance. The characteristics of the control input did not change significantly due to the saturation that is needed to avoid physiologically unacceptable input serum levels.

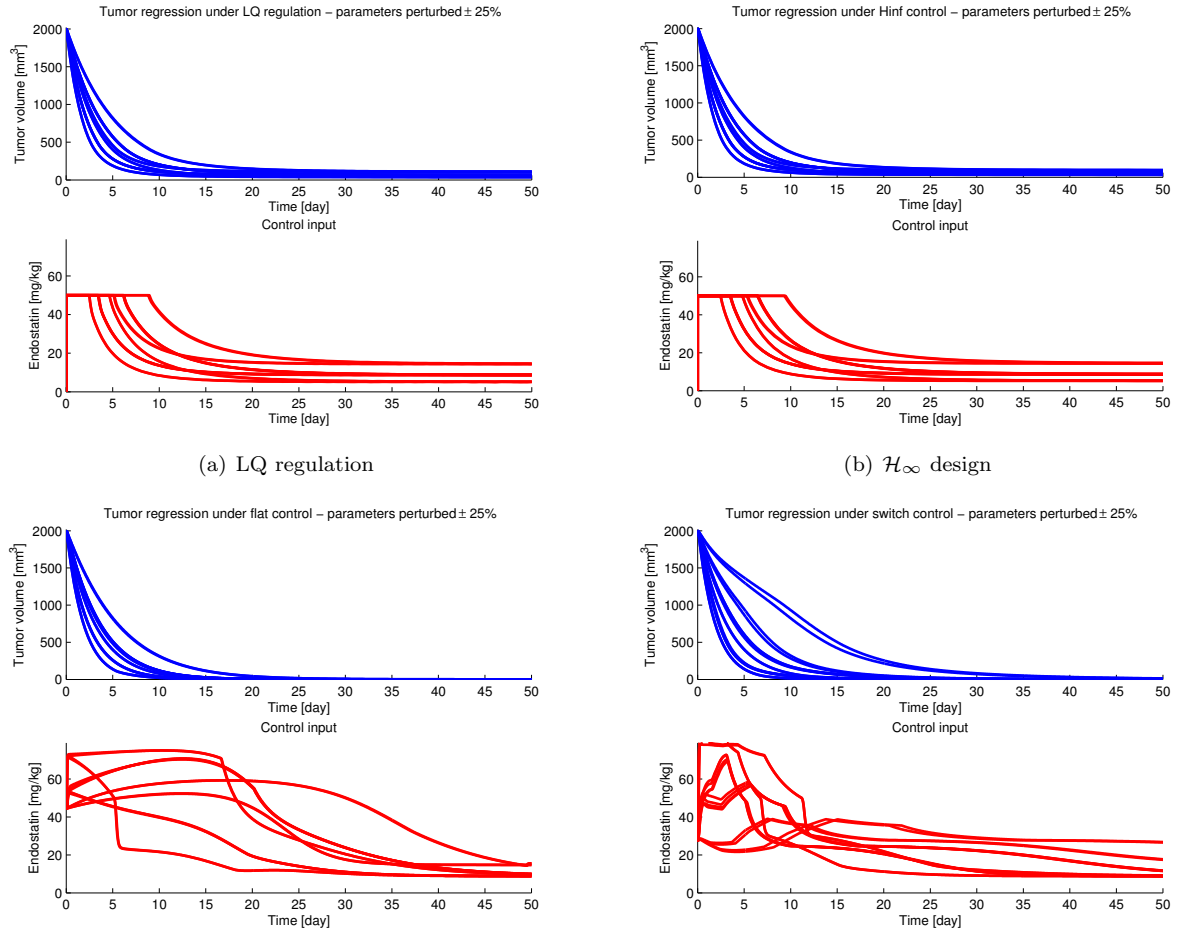
Flatness based techniques (especially switch control) outperformed linear methods in the following aspect: if model parameters changed advantegously (e.g. d increased, b decreased, e increased), the control algorithms resulted in far lower control inputs, while linear controllers did not adapt to changes appropriately.

In the case of switch control, two model parameter combinations caused significant performance deterioration, while in the case of flat control, the performance of tumor regression remained nearly unchanged (three parameter combinations caused relevant difference in tumor volume changes, and two of them showed amelioration in the speed of regression).

However, flat control based methodologies may result in greater total inlet compared to linear techniques.

Property	$\mathcal{H}_\infty$ control	LQ regulation	Flat control	Switch control
Time to 1% (days)	-	-	13	17
Time to 1 mm^3 (days)	-	-	19	39
Size after 50 days (mm^3)	58	65	1	1
Daily inlet high (days)	5	5	17	7
Total inlet (mg/kg)	671	644	1412	1148
Minimal total inlet (mg/kg) – model parameters perturbed ±25%	493	482	902	1020
Maximal total inlet (mg/kg) – model parameters perturbed ±25%	1258	1231	2252	1479

Table 2. Comparison of the applied control techniques



(a) LQ regulation

(b) $\mathcal{H}_\infty$ design

(c) Flat control

(d) Flatness based switch control

Fig. 4. Tumor regression and control inputs in the case of model parameter perturbation in the range of ±25%

5. CONCLUSION

In this paper, different control methodologies were compared through a biomedical model. The two different approaches towards the nonlinearity of the system were working point linearization and exact linearization.

Working point linearization is a plausible solution to handle nonlinear systems. However, if the initial states of the system are far from the chosen working point, the control input may exceed certain limits which have to be taken into consideration. Despite the low inhibitor inlets, the presented linear methods were not able to attain the desired tumor volume plateau of 1 mm^3. Although, these techniques are able to tolerate parameter perturbations of high degree.

Flatness based techniques adapt better to the nonlinearity of the presented system. The minimal tumor volume was reached by both techniques, using higher total drug inlet, though. The disadvantage of this solution is that it is more sensitive towards parametric changes.

Since the expected perturbation of the model parameters is far lower than ±25%, we can state that flatness based switch control is a favorable solution for the posed biomedical problem.

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