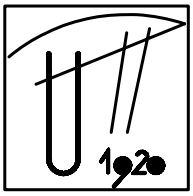

BULETINUL ŞTIINŢIFIC

al

Universităţii „POLITEHNICA” din Timişoara, România

Seria AUTOMATICĂ şi CALCULATOARE

SCIENTIFIC BULLETIN

of

The “POLITEHNICA” University of Timişoara, Romania

Transactions on AUTOMATIC CONTROL and COMPUTER SCIENCE

Vol. 57 (71), No. 2, June 2012 Frequency: 4 issues per year
ISSN 1224-600X

EDITURA POLITEHNICA

Scientific Bulletin of The "POLITEHNICA" University of Timişoara, Romania
Transactions on AUTOMATIC CONTROL AND COMPUTER SCIENCE
http://www.ac.upt.ro/journal/
Vol. 57 (71), No. 2, June 2012
ISSN 1224-600X, Frequency: 4 issues per year
Publisher: Editura Politehnica, Bd. Republicii 9, 300159 Timişoara, Romania

Address for editorial correspondence
Prof.dr.ing. Stefan Preitl
"Politehnica" University of Timişoara, Faculty of Automation and Computers, Bd. V. Parvan 2, RO-300223 Timişoara, Romania, Phone: +40-2564032-24, -29, Fax: +40-256403214, E-mail: *stefan.preitl@aut.upt.ro*
http://www.ac.upt.ro/journal/

CONTENTS

Automatic Control and Mechatronics

BULETINUL ŞTIINŢIFIC al Universităţii „POLITEHNICA” din Timişoara, România,
Seria AUTOMATICĂ ŞI CALCULATOARE
SCIENTIFIC BULLETIN of The “POLITEHNICA” University of Timişoara, Romania,
Transactions on AUTOMATIC CONTROL and COMPUTER SCIENCE, Vol. 57 (71), No. 2, June 2012, ISSN 1224-600X

Comparison of Path Tracking Flat Control and Working Point Linearization Based Set Point Control of Tumor Growth with Angiogenic Inhibition

Dániel András Drexler*, Johanna Sápi*, Annamária Szeles*, István Harmati* and Levente Kovács*,**

* Department of Control Engineering and Information Technology, Budapest University of Technology and Economics,
Magyar tudósok krt. 2., 1117, Budapest, Phone: (361) 463-4027, Fax: (361) 463-2204,
E-Mail: {drexler, sapi, harmati, lkovacs}@iit.bme.hu, szeles.annam@gmail.com
** John von Neumann Faculty of Information Technology, Óbuda University, Bécsi út 96/b, H-1034 Budapest

Abstract *– Targeted molecular therapies (TMT) represent new perspectives in cancer treatment, fighting against the specific characteristic of the investigated tumor. Antiangiogenic therapy represents a specific TMT and its role is to stop the angiogenesis of the tumor, the process of forming new blood vessels; hence, to stop tumor growth. Proper control algorithms for tumor growth control with angiogenic inhibition are analyzed in the current article in order to find optimal therapeutic protocols. Two slightly different approaches are compared: nonlinear control by exact linearization with path tracking control, and linear control by working point linearization with set point control. The control strategies are compared in terms of the characteristics of the input signal (the inhibitor, drug intake) that is crucial if the therapy will be put into practice.*

Keywords: *flat control, exact linearization, path tracking control, tumor growth control, angiogenic inhibition.*

I. INTRODUCTION

Cancer is in the front line of lethal illnesses which demands the highest number of human lives in modern societies. According to statistics of the European Union, 1.3 million people of the European Union were estimated to die from cancer in 2011, [1]. Consequently, the treatment is in focus of research even in interdisciplinary areas. In this paper we apply novel results of nonlinear control theory to a tumor growth model, in order to give therapeutic protocols for a special type of antitumor therapy, the antiangiogenic therapy. The resulting controller is compared to a linear control strategy created previously by the authors [2].

Conventional cancer fighting therapies (like chemotherapy, radiotherapy) have general attack points (for example chemotherapy works by killing rapidly dividing cells), so these treatments have a lot of side effects and affect the whole body. In addition, tumor cells can become resistant towards the drug used in chemotherapy, which makes the usage of new drugs necessary.

However, targeted molecular therapies (TMTs) fight specifically against different cancer mechanisms, so these treatments can be more effective and have limited side effects. A promising field in TMTs is antiangiogenic therapy, which had come up in the last decade [3, 4]. "Anti-angiogenesis is a form of targeted therapy that uses drugs or other substances to stop tumors from making new blood vessels. Without a blood supply, tumors can't grow" [5]. Contrary to conventional treatments, if antiangiogenic therapy is used, tumor cells can not become resistant towards the antiangiogenic drugs (this is achieved by antiangiogenic therapy if it is directed against the tumor supplying blood vessels) [6] and antiangiogenic therapy can be used with nontoxic concentrations [7].

Clinical aspects of angiogenic inhibition are discussed more detailed in [6, 8]. In [9] a model for tumor growth under angiogenic inhibition was developed, and it was validated using experiments on mice with lungs cancer (the Lewis lung carcinoma). Optimal bang-bang control was designed on a simplified model in [10]. Antiangiogenic therapy combined with radiotherapy was discussed in [11]. Application of linear control theory was investigated in [12, 13] for a simplified model. Linear control synthesis was worked out in [2, 14, 15] for the model used in this paper, while nonlinear control was investigated in [16]. The results of [2] and this paper are compared, and it is shown that nonlinear control by flat control yields much better

input signal characteristics from physiological point of view than the results with linear control.

The paper is organized as follows. In Section II, the biomedical background of the therapy is reviewed, and the nonlinear tumor growth model is examined in Section III. After checking the controllability of the model, flat control and path tracking control is applied in Section IV. Working point based linearization and linear control strategy is applied in Section V. The two control strategies are compared based on simulations in Section VI. The paper ends with the conclusion in Section VII.

II. BIOMEDICAL BACKGROUND OF ANTIANGIGENIC THERAPY

Rapidly dividing tumor cells need lots of oxygen. When proliferation begins, small sized tumor can pick up oxygen from near capillaries. After a certain size (1-2 mm diameter) tumor development stops, because a part of the tumor gets too far from capillaries and cannot pick up enough oxygen. Tumor needs own blood vessels - the process of forming new blood vessels is called angiogenesis [17]. Angiogenesis occurs normally in the human body at specific times; in adults it is a relatively infrequent event. In such cases, angiogenesis starts due to typical molecular triggers and ends when the necessary processes are completed. Tumors can break through this precise control, and by stimulating angiogenesis, new blood vessels are formed to feed the tumor cells. This process is called tumor indicated angiogenesis. The usage of angiogenic inhibitors blocks this process, and can even eliminate already existing blood vessels at the tumorous areas. However, by antiangiogenic therapy tumors cannot be totally eliminated, since angiogenic inhibition acts only on the vascular system.

In the next section, we discuss a nonlinear model, that describes the dynamics of angiogenic inhibition and tumor indicated angiogenesis.

III. NONLINEAR TUMOR GROWTH MODEL

The model of tumor growth under angiogenic inhibition was worked out in [9]. The model structure is based on a priori knowledge, and the parameters were identified based on experiments. In this article the model used for tumor growth possesses three state variables:

- x_1 is the tumor volume in mm^3;
- x_2 is the endothelial volume in mm^3;
- x_3 is the inhibitor serum level in mg/kg.

The input (u) of the system is the inhibitor intake in $mg/kg/day$, and the output (y) is the tumor volume. The dynamics is described as follows:

$$\dot{x}_1 = -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) \quad (1)$$

$$\dot{x}_2 = bx_1 - dx_1^{2/3}x_2 - ex_2x_2 \quad (2)$$

$$\dot{x}_3 = -\lambda_3 x_3 + u \quad (3)$$

$$y = x_1 \quad (4)$$

The first two equations are the same as in [9], while the third equation is the pharmacokinetic model of the inhibitor, appeared in this form in [2]. The parameters in the model are $\lambda_1 = 0.192\ day^{-1}$, $b = 5.85\ day^{-1}$, $d = 0.00873\ day^{-1}mm^{-2/3}$, $e = 0.66\ day^{-1}mg/kg$ and $\lambda_3 = 1.3\ day^{-1}$ acquired from [9].

The equations of the dynamic system may be rewritten in the following form:

$$\dot{x} = f(x) + g(x)u \quad (5)$$

$$y = h(x) \quad (6)$$

where

$$f(x) = \begin{bmatrix} -\lambda_1 \ln\left(\frac{x_1}{x_2}\right) \\ bx_1 - dx_1^{2/3}x_2 - ex_2x_3 \\ -\lambda_3 x_3 \end{bmatrix} \quad (7)$$

represents the drift vector field with

$$g(x) = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \quad (8)$$

representing the control vector field, and

$$h(x) = x_1 \quad (9)$$

representing the output of the system. It can be easily verified that these equations define a nonlinear, but input affine model [16].

Since in this paper the model is used for control synthesis, the analysis of the controllability of the system is required.

The nonlinear system has a drift vector field f and a control vector field g. Let:

$$\Delta_0 = \{g\} \tag{10}$$

denote an initial distribution composed of the control vector field. According to [18], the nonlinear system is controllable if it satisfies the Lie Algebra Rank Condition, so the distribution Δ_0 expanded with the Lie brackets $[f,g]$ and $[f,[f,g]]$ is involutive. Involutivity is checked by handling the expanded distribution as a matrix and examining its rank. If this matrix is full rank, then the distribution is involutive. In our case, the Lie bracket of the drift and the control vector fields is:

$$[f,g] = \frac{\partial f}{\partial x} g - \frac{\partial g}{\partial x} f = \begin{bmatrix} 0 \\ ex_2 \\ \lambda_3 \end{bmatrix} \tag{11}$$

The Lie bracket of f and $[f,g]$ is:

$$[f,[f,g]] = \begin{bmatrix} -x_1\lambda_1 \\ e(bx_1 + x_2\lambda_3) \\ \lambda_3^2 \end{bmatrix} \tag{12}$$

while the distribution Δ_0 expanded with $[f,g]$ and $[f,[f,g]]$ is:

$$\begin{aligned} \Delta &= \{g,[f,g],[f,[f,g]]\} \\ &= \begin{bmatrix} 0 & 0 & -x_1\lambda_1 \\ 0 & ex_2 & e(bx_1 + x_2\lambda_3) \\ 1 & \lambda_3 & \lambda_3^2 \end{bmatrix} \end{aligned} \tag{13}$$

which has full rank if $x_1 \neq 0$ and $x_2 \neq 0$, so the nonlinear system is controllable if the system is not in the state $x_1 = 0$ or $x_2 = 0$. Since $x_1 = 0$ means there is no tumor, this case is physiologically irrelevant, while if $x_2 = 0$ state is reached, the therapy can be switched to a constant dose. This constant dose may be calculated from the steady-state equations of the model [2].

IV. FEEDBACK LINEARIZATION AND PATH TRACKING CONTROL

In this section feedback linearization is applied in order to get a representation of the nonlinear system with state variables z and input v that acts like a linear system, i.e. a system of serially coupled integrators [16]. In order to do so, we choose the first variable z_1 as the output of the system, i.e. $z_1 = y$, thus $z_1 = h(x)$, and look for the derivatives of the output. The first and higher order derivatives of the output y are:

$$\dot{y} = L_f h(x) + L_g h(x) u \tag{14}$$

$$\ddot{y} = L_f^2 h(x) + L_g L_f h(x) u + L_f L_g h(x) u + L_g^2 h(x) u^2 \tag{15}$$

$$\dddot{y} = L_f^3 h(x) + L_g L_f^2 h(x) u + L_f L_g L_f h(x) u + L_g^2 L_f h(x) u^2 + L_f^2 L_g h(x) u + L_g L_f L_g h(x) u^2 + L_f L_g^2 h(x) u^2 + L_g^3 h(x) u^3 \tag{16}$$

where $L_\alpha \beta(x)$ denotes the Lie derivative of β along α, expressed in local coordinates as:

$$L_\alpha \beta(x) = \frac{\partial \beta}{\partial x} \alpha \,. \tag{17}$$

$L_\gamma L_\alpha \beta(x)$ is the Lie derivative of $L_\alpha \beta(x)$ along γ, while multiple derivation along the same vector field is denoted by the appropriate powers, i.e.

$$L_\alpha^k \beta(x) = \underbrace{L_\alpha (L_\alpha (\ldots (L_\alpha}_{k} \beta(x)) \ldots)) \,. \tag{18}$$

The system defined by (14)-(16) is analogous to a series of integrators if the input u of the original system appears only in the highest order derivative of the output. The order of the derivative of a given output where the input appears explicitly is called the relative degree of the output [18]. Hence, the representation in (14)-(16) is a series of integrators if the relative degree of y is maximal.

The relative degree of an output of a system is r, if:

$$L_g L_f^k h(x) = 0, \quad \text{if } k < r-1 \tag{19}$$

$$L_g L_f^{r-1} h(x) \neq 0 \tag{20}$$

holds [18]. If the system has maximal relative degree then it can be linearized through static nonlinear state feedback, thus no internal state variables are required in the feedback. In this particular case:

$$L_g h(x) = 0 \tag{21}$$

$$L_g L_f h(x) = 0 \tag{22}$$

$$L_g L_f^2 h(x) = -e\lambda_1 x_1 \tag{23}$$

thus the relative degree of the output is $r = 3$ if $x_1 \neq 0$. Since the $x_1 = 0$ case is already excluded, the output has maximal relative degree in all cases.

Feedback linearization is done by transforming the system to a series of integrators, thus the behavior of the z_i, $i \in \{1,2,3\}$ transformed system variables will be defined by the equations:

$$\dot{z}_1 = z_2 \tag{24}$$

$$\dot{z}_2 = z_3 \tag{25}$$

$$\dot{z}_3 = v \tag{26}$$

$$y = z_1 \tag{27}$$

where v is the input of the transformed system and y is the output of the original and the transformed system as well. The transformed system variables may be acquired by introducing the following coordinate transformation:

$$z_1 = h(x) \quad = x_1 \tag{28}$$

$$z_2 = L_f h(x) \quad = -\lambda_1 x_1 \tag{29}$$

$$z_3 = L_f^2 h(x) \quad = \lambda_1 \left(\lambda_1 \, ln\left(\frac{x_1}{x_2} \right) \right) \left(n\left(\frac{x_1}{x_2} \right) + 1 \right) + \lambda_1 \left(b \frac{x_1^2}{x_2} - d x_1^{5/3} - e x_1 x_3 \right) \tag{30}$$

The derivatives of the transformed variables are:

$$\dot{z}_1 = \quad L_f h(x) \quad = z_2 \tag{31}$$

$$\dot{z}_2 = \quad L_f^2 h(x) \quad = z_3 \tag{32}$$

$$\dot{z}_3 = \quad L_f^3 h(x) + L_g L_f^2 h(x) u \quad = a(x) + b(x) u \tag{33}$$

Since our aim is to handle the system as a series of integrators in the z_i variables, the input acts on $v = z_3$, and the nonlinear feedback is used to calculate the input of the original system as:

$$u = \frac{v - a(x)}{b(x)} \tag{34}$$

The expressions for $a(x)$ and $b(x)$ are:

$$\begin{aligned} a(x) = & -\lambda_1 b^2 \frac{x_1^3}{x_2} + \lambda_1 bd \frac{x_1^{8/3}}{x_2} - \lambda_1^2 b \frac{x_1^2}{x_2} - 4\lambda_1^2 b \frac{x_1^2}{x_2} ln\left(\frac{x_1}{x_2} \right) \\ & + \lambda_1 be \frac{x_1}{x_2} + \lambda_1^2 d x_1^{5/3} + \frac{11}{3} \lambda_1^2 d x_1^{5/3} ln\left(\frac{x_1}{x_2} \right) - 3\lambda_1^3 x_1 \left(ln\left(\frac{x_1}{x_2} \right) \right)^2 \\ & - \lambda_1^3 x_1 \left(ln\left(\frac{x_1}{x_2} \right) \right)^3 - \lambda_1^3 x_1 ln\left(\frac{x_1}{x_2} \right) + \lambda_1^2 e x_1 x_3 + 3\lambda_1^2 e x_1 x_3 ln\left(\frac{x_1}{x_2} \right) \\ & + \lambda_1 \lambda_3 e x_1 x_3 \end{aligned} \tag{35}$$

$$b(x) = -e\lambda_1 x_1 \tag{36}$$

Applying the coordinate transformation defined by (28)-(30), and the nonlinear feedback (34), the resulting system with state variables $\{z_1,z_2,z_3\}$, input v and output y can be handled as a system composed of three serially connected integrators defined by (14)-(16) that is a linear system, thus linear controller design may be applied.

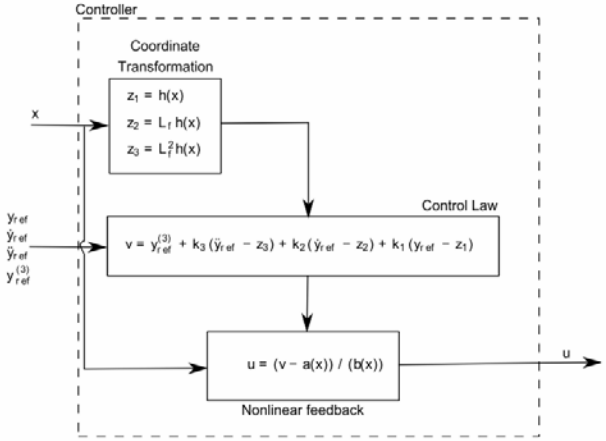

Fig. 1. Control Architecture of the path tracking with exact linearization.

The control strategy applied for the exact linearization case is path tracking [18]. Suppose that the desired evolution of tumor volume is given in advance, thus we have a reference signal $x_{1,ref} = y_{ref}$, and its derivatives up to third order are also known. The reference signals are given as a set of vectors $\{y_{ref}, \dot{y}_{ref}, \ddot{y}_{ref}, \dddot{y}_{ref}\}$. The control law applied is:

$$v = \dddot{y}_{ref} + k_3 \left(\ddot{y}_{ref} - \ddot{y} \right) + k_2 \left(\dot{y}_{ref} - \dot{y} \right) + k_1 \left(y_{ref} - y \right) \tag{37}$$

with $K = [k_3 \; k_2 \; k_1]$ being the coefficients of a Hurwitz polynomial describing the tracking error dynamics. Since applying the coordinate transformation defined by (28)-(30) results in a series of integrators, the output y and its derivatives are explicitly given by $y = z_1$, $\dot{y} = z_2$, $\ddot{y} = z_3$. Hence:

$$v = \dddot{y}_{ref} + k_3(\ddot{y}_{ref} - z_3) + k_2(\dot{y}_{ref} - z_2) + k_1(\dot{y}_{ref} - z_1) \quad (38)$$

The control architecture is depicted in Fig. 1. The inputs of the controller are the reference signal and its derivatives, and the states of the nonlinear model. The output of the controller is the actuator's signal, e.g. the level of the drug administration rate. The controller consists of the coordinate transformation, the control law and the nonlinear feedback.

V. WORKING POINT LINEARIZATION AND SET POINT CONTROL

In case of this approach, the system is linearized in a working point, and the system dynamics is defined with the first order terms of the Taylor polynomial of the nonlinear system, i.e.

$$\dot{x} = Ax + Bu \quad (39)$$

$$y = Cx + Du \quad (40)$$

with matrices:

$$A = \begin{bmatrix} -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) - \lambda_1 & \lambda_1 \frac{x_1}{x_2} & 0 \\ b - \frac{2}{3} d x_1^{-1/3} x_2 & -d x_1^{2/3} - e x_3 & -e x_2 \\ 0 & 0 & -\lambda_3 \end{bmatrix} \quad (41)$$

$$B = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \quad (42)$$

$$C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \quad (43)$$

$$D = 0 \quad (44)$$

The working point is chosen to be in a steady-state, with the less amount of inhibitor possible as:

$$A_0 = \lim_{\substack{x_1 \to x_{10} \\ x_2 \to x_{10} \\ x_3 \to 0}} A = \begin{bmatrix} -\lambda_1 & \lambda_1 & 0 \\ b - \frac{2}{3} d \sqrt[3]{x_{10}^2} & -d \sqrt[3]{x_{10}^2} & -e x_{10} \\ 0 & 0 & -\lambda_3 \end{bmatrix} \quad (45)$$

The chosen working point is x_{10} = 100 mm^3, that is desirably low among the possible tumor volumes. The applied control law was Linear Quadratic (LQ) control, with a polynomial observer, i.e. a state-feedback that minimizes:

$$J(t,x) = \int_0^\infty \left\{ x^T(t) Q x(t) + u^T(t) R u(t) \right\} dt \quad (46)$$

with the design parameters chosen as:

$$Q = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \; R = 10^5 \quad (47)$$

i.e. it is an expensive control, and the energy of x_1 and x_3 is also minimized. This is satisfied by a state-feedback $u = -Kx$, where $K = R^{-1}B^TP$, and P is the solution of the Control Algebraic Ricatti Equation (CARE):

$$PA + A^T P - PBR^{-1}B^T P + Q = 0\,. \quad (48)$$

The applied observer is a polynomial observer, with:

$$\dot{\hat{x}} = F\hat{x} + Gy + Hu\,, \quad (49)$$

and the parameters are chosen to guarantee predefined estimation error characteristics, i.e. G is designed as a pole-placement for the fictive system A^T, C^T with predefined observer poles, and $F = A - GC$, $H = B$. The observer poles are chosen to be five times faster than the poles of the closed loop system resulted with the previously defined control law.

Since we apply set point control here (we control the system to the zero state) and thus the initial error signal can be very large, this may result in large input signal. Large input signal however is physiologically meaningless, so we need to put saturation at the output of the controller. The resulting control architecture is depicted on Fig. 2.

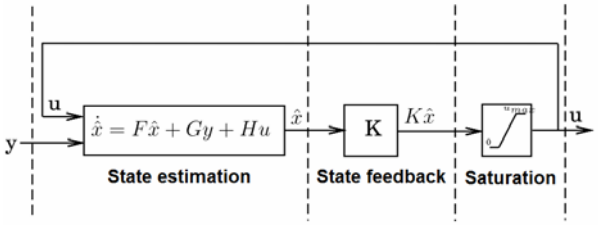

Fig. 2. The architecture of set point controller designed for the linearized model.

VI. COMPARISION OF CONTROL STRATEGIES THROUGH SIMULATION RESULTS

First we show simulation result for the flat control with path tracking control law defined in Section IV. It is assumed, that the states of the nonlinear system are

available. Note that this is not the case in the reality, since the measurement of the endothelial volume and the inhibitor serum level is expensive and difficult; however, the solution of this problem (e.g. application of a nonlinear state observer) is the subject of further research. The reference signal and its derivatives are:

$$y_{ref} = (x_{1,0} - 1)exp\left(-\frac{t}{T_{treat}}\right) + 1 \tag{50}$$

$$\dot{y}_{ref} = -\frac{1}{T_{treat}}(x_{1,0} - 1)exp\left(-\frac{t}{T_{treat}}\right) \tag{51}$$

$$\ddot{y}_{ref} = \frac{1}{T_{treat}^2}(x_{1,0} - 1)exp\left(-\frac{t}{T_{treat}}\right) \tag{52}$$

$$\dddot{y}_{ref} = -\frac{1}{T_{treat}^3}(x_{1,0} - 1)exp\left(-\frac{t}{T_{treat}}\right) \tag{53}$$

The initial tumor volume $x_{1,0}$ is chosen as the maximal tumor volume that can be reached with *0* input, numerically $x_{1,0}$ = 17347 mm^3. The T_{treat} is the time constant of the desired exponential characteristics of tumor elimination, chosen to be T_{treat} = *6 days* in the simulations. The vector *K,* defining the path tracking error dynamics, is chosen as:

$$K = [1 \quad 1 \quad 8] \tag{54}$$

This polynomial is Hurwitz, with roots:

$$k_1 = -0.5 + i \cdot 2.7839 \tag{55}$$

$$k_2 = -0.5 - i \cdot 2.7839 \tag{56}$$

The original tumor model was initiated at its equilibrium state without input, where the tumor volume and endothelial volume are equal and their value is $x_{1,0}$ = 17347 mm^3. The time swap of the simulation was *100 days*. The evolution of the tumor volume during the *100 days* of treatment is shown on Fig. 3, while the administered inhibitor is shown on Fig. 4. The tumor volume dropped drastically during the treatment, it reached *63* mm^3 in *40 days*, *2* mm^3 in *90 days*, while the inhibitor injection rate stayed considerably low during the whole period of the treatment. The inhibitor injection was *28 mg/kg/day* at the 40^{th} day of the treatment, reached its maximum of *28.72 mg/kg/day* at the 53^{rd} day of the treatment, and it was *15.88 mg/kg/day* at the 90^{th} day of the treatment, close to the value of *15.0682 mg/kg/day*, that is the inhibitor injection rate needed to maintain the tumor volume close to *0* mm^3 [2]. The total amount of inhibitor used during the *100 days* treatment period is *2253 mg/kg*.

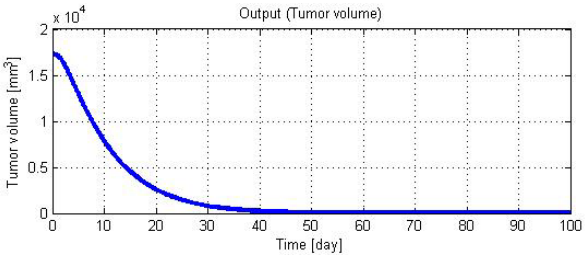

Fig. 3. The evolution of the tumor volume with flat control and path tracking.

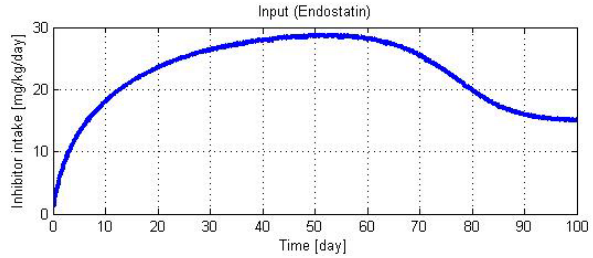

Fig 4. The drug input characteristics with flat control and path tracking.

Second, we show the simulation results for the linear controller defined in Section V. The saturation is chosen in order to get a suboptimal solution, i.e. the total amount of inhibitor used during the therapy is the lowest. This problem has already been explored in [2], where we presented, that if the tumor growth is initiated at the maximal value, then the optimal choice for the saturation is *80 mg/kg/day*. Fig. 5 shows the elimination of the tumor volume, and the drug input characteristics. The treatment is examined for *120 days*.

The speed of tumor volume elimination is nearly the same as in the case of flat control in Fig. 3; however, the drug input characteristics has some major differences. In the linear case in Fig. 5, the input is high at the beginning of the treatment (it is the achievable maximum if the saturation is present), and starts to decrease after around 3 weeks, and then slowly decreases to the minimal value that is needed to maintain the avascular tumor state.

The input characteristics in case of flat control however is much more desirable, since it yields sufficiently low drug doses even in absence of saturations, and the therapy is much more balanced.

The total amount of inhibitor used in the linear case is *2188.3 mg/kg* for *120 days* of treatment, which is lower than the value we got for the results with flat control that was only examined for *100 days*.

This is an advantage of the linear controller, but it is questionable, if its characteristics from therapeutic point of view are better than the result with flat control.

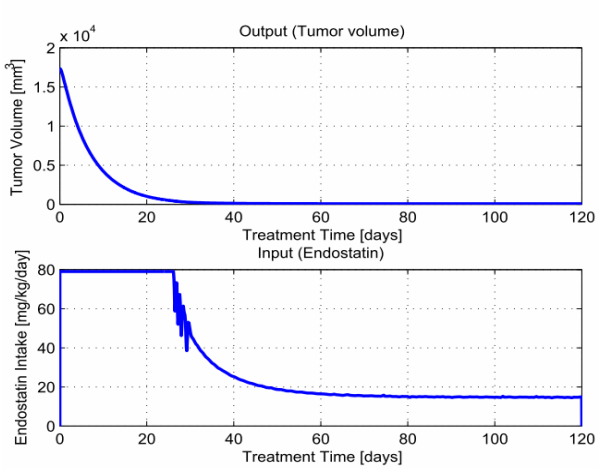

Fig. 5. The tumor volume evolution, and the drug input characteristics with the linear controller.

VII. CONCLUSIONS

We have examined the possibility of tumor therapy design with the use of control theory. Two different approaches were examined: path tracking based on exact linearization, and set point control based on working point linearization. Both approaches were successful in the sense that the tumor volume reached the lowest possible value, however their input characteristics was different. While the linear case resulted in a therapy that consumed fewer drug, the nonlinear controller resulted in much more balanced drug intake characteristics.

Further work will be related to modern robust control methods, but also on the use of nonlinear control methods and other optimal control methods [19]. Higher order model synthesis will be also performed. A further aim of research is modeling and controlling combined therapy and validate it on animal experiments.

ACKNOWLEDGEMENTS

This work was supported in part by the National Office for Research and Technology (NKTH), Hungarian National Scientific Research Foundation grants OTKA K71762 and K82066. It is connected to the scientific program of the "Development of quality-oriented and harmonized R+D+I strategy and functional model at BME" project, supported by the New Hungary Development Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

Levente Kovács is supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

REFERENCES

[1] M. Malvezzi, A. Arfé, P. Bertuccio, F. Levi, C. La Vecchia, and E. Negri, "European cancer mortality predictions for the year 2011", Annals of Oncology, doi:10.1093/annonc/mdq774, 2011.

[2] D. A. Drexler, L. Kovács, J. Sápi, I. Harmati, Z. Benyó, "Model-based analysis and synthesis of tumor growth under angiogenic inhibition: a case study", In *Proc. of the IFAC WC 2011 – 18th World Congress of the International Federation of Automatic Control*, Milano, Italy, pp. 3753-3758, August 2011.

[3] J. M. Pluda, "Tumor-associated angiogenesis: mechanism, clinical implications, and therapeutic strategies", *Seminars in Oncology*, vol. 24(2), pp. 203-218, 1997.

[4] G. J. Kellof, C. W. Boone, V. E. Steele, J. R. Fay, R. A. Lubey, J. A. Criwel and C. C. Sigman, "Mechanistic considerations in chemopreventive drug development", *Journal of Cellular Biochemistry – Supplement*, vol. 20, pp. 1-24, 1994.

[5] American Cancer Society, "Antiangiogenesis Treatment", http://www.cancer.org/acs/groups/cid/documents/webcontent/002988-pdf.pdf , 2012.

[6] R. S. Kerbel, "A cancer therapy resistant to resistance", *Nature*, vol. 390, pp. 335-336, 1997.

[7] Y. Y. Qian, H. Zhang, Y. Hou, L. Yuan, G. Q. Li, S. Y. Guo, H. Tadashi and Y. Q. Liu, "Celastrus Orbiculatus extract inhibits tumor angiogenesis by targeting vascular endothelial growth factor signaling pathway and shows potent antitumor activity in hepatocarcinomas in Vitro and in Vivo", *Chinese Journal of Integrative Medicine*, pp. 1-9, 2011.

[8] R. Kerbel and J. Folkman, "Clinical translation of angiogenesis inhibitors", *Nature Reviews, Cancer*, vol. 2, pp. 727-739, 2002.

[9] P. Hahnfeldt, D. Panigrahy, J. Folkman and L. Hlatky, "Tumor Development Under Angiogenic Signaling: A Dynamical Theory of Tumor Growth, Treatment response, and Postvascular Dormancy", *Cancer research*, vol. 59, pp. 4770-4775, 1999.

[10] U. Ledzewicz and H. Schätler, "A synthesis of Optimal Controls for Model of Tumor Growth under Angiogenic Inhibitors", In *Proc. of the 44th IEEE conference on Decision and Control, and the European Control Conference 2005*, pp. 934-939, December 2005.

[11] A. Ergun, K. Camphausen and L. M. Wein, "Optimal Scheduling of Radiotherapy and Angiogenic Inhibitors", *Bulletin of Mathematical Biology*, vol. 65, pp. 407-424, 2003.

[12] J. Sápi, D. A. Drexler, I. Harmati, Z. Sápi and L. Kovács, "Linear state-feedback control synthesis of tumor growth in antiangiogenic therapy". In *Proceedings of SAMI 2012 – 10th International Symposium on Applied Machine Intelligence and Informatics,* Herlany, Slovakia, pp. 143-148, January 2012.

[13] A. Szeles, J. Sápi, D. A. Drexler, I. Harmati, Z. Sápi and L. Kovács, "Model-based Angiogenic Inhibition of Tumor Growth using Modern Robust Control Method", In *Proc. of IFAC 2012 – 8th IFAC Symposium on Biological and Medical Systems*, Budapest, Hungary, pp. 1-6, August 2012.

[14] D. A. Drexler, I. Harmati and L. Kovács, "Optimal control of tumor growth using antiangiogenic chemotherapy", In *Proc. of MACRo 2011 – 3rd International Conference on Recent Acievements in Mechatronics, Automation, Computer Sciences and Robotics,* Targu Mures, Romania, pp. 273-284, April 2011.

[15] L. Kovács, P. Szalay, T. Ferenci, D. A. Drexler, J. Sápi, I. Harmati, Z. Benyó, "Modeling and Optimal Control strategies with High Public Health Impact", In *Proc. of INES 2011 – 15th International Conference on Intelligent Engineering System*, Poprad, Slovakia, pp. 23-28, June 2011.

[16] D.A. Drexler, J. Sápi, A. Szeles, I. Harmati, A. Kovács, L. Kovács, "Flat control of tumor growth with angiogenic inhibition", In *Proc. of SACI 2012 – 7th International Symposium on Applied*

Computational Intelligence and Informatics, Timisoara, Romania, pp. 179-183, May 2012.

[17] K. J. Gotink and H. M. W. Verheul, "Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action?", *Angiogenesis*, vol. 13, pp. 1-14, 2010.

[18] A. Isidori, Nonlinear Control Syste*ms*, Springer-Verlag London, 1995.

[19] R.E. Precup and S. Preitl, "Optimisation criteria in development of fuzzy controllers with dynamics", *Engineering Applications of Artificial Intelligence*, vol. 17(6), pp. 661-674, 2004.

Manuscript received June 5, 2012; revised June 24, 2012; accepted for publication June 28, 2012.