Parameter optimization of H_∞ controller designed for tumor growth in the light of physiological aspects

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***Abstract*—According to the fact that cancer diseases are leading causes of death all around the world, development of cancer fighting therapies is necessary. Beside the medical knowledge, there is an extra need for engineering approach to solve this complex problem. The aim of this paper is to design controller for tumor growth under angiogenic inhibition, which on the one hand minimizes the input signal as far as possible (in order to have less side effects and greater cost-effectiveness) and on the other hand results in appropriately low tumor volume. Since the model contains uncertainties and measurement noise, the controller was designed using modern robust control methodology. Choosing of the ideal system and the weighting functions were done in the light of physiological aspects.**

I. INTRODUCTION

Cancer diseases are leading causes of death nowadays all around the world. In the EU the total predicted number of cancer deaths in 2013 is 1.314.236 compared with 1.281.694 in 2009 [1]. In Hungary, cancer was the second most common cause of death after cardiovascular diseases in 2012 [2].

Protocols for medical treatment comprise constant drug dosage, which can be effective in terms of reducing the progression of the diseases; however, nowadays the problem seems more complex. From multidisciplinary point of view the aim is to design a controller which is on the one hand able to minimize the input signal as far as possible (in order to have less side effects and greater cost-effectiveness) and on the other hand results in appropriately low tumor volume. We have investigated the applicability of several control methods in this specific field and designed controllers using LQ control method and state observer [3], [4], flat control [5], and modern robust control method [6].

In biomedical applications experts always faced with two major problems: understanding the physiological behavior of a system and transform it into a model; and finding sufficiently sensitive methods and sensors to detect the required states and values. However, there always will be model uncertainties and measurement noises; thus, there is a need for systems which satisfy the requirements not only for its nominal values but also in the presence of perturbations. These aspects can be taken into account using H_∞ control methodology that represents the goal of the current paper as well.

The paper is organized as follows. In Section II, we review the biomedical background of the antiangiogenic therapy. In Section III, we analyze the nonlinear model of tumor growth under angiogenic inhibition, and describe a linear model which is acquired by working point linearization. Section IV contains the description of the design structure, the theoretical H_∞ suboptimal solution, and the choice of the ideal system and the weighting functions in the light of physiological aspects. In Section V, we present the simulation results. The paper ends with the conclusion in Section VI.

II. BIOMEDICAL BACKGROUND

Angiogenesis is the process of forming new blood vessels, which occurs normally in the human body at specific times. During embryogenesis vasculogenesis plays an important role; however, angiogenesis also takes place in adults. The process of angiogenesis is precisely controlled by proangiogenic and antiangiogenic factors, thus, normally there is an angiogenic balance in the body.

All cells need oxygen and nutrients, which can be picked up from nearby capillaries. Tumor cells are dividing rapidly, so there is an extra need for oxygen. When proliferation begins, small sized tumor can pick up enough oxygen – in this phase tumor is an avascular nodule (dormant), in a steady-state level of proliferating and apoptosing cells [7]. After a certain size (1-2 mm diameter), tumor development stops, because the diffusion of oxygen through tissues is limited. Tumor needs own blood vessels to grow, however forming new vessels is inhibited by the body's antiangiogenic factors. Tumor have to break through this strict control – the process when tumor become able to form own blood vessels is called angiogenic switch. This switch ensures exponential tumor growth. The aim of antiangiogenic therapy is to prevent tumors from forming new blood vessels, because without angiogenesis tumor growth is inhibited [8], [9].

III. DYNAMICAL MODEL OF TUMOR GROWTH UNDER ANGIOGENIC INHIBITION

P. Hahnfeldt et al. created a dynamic model for tumor growth in antiangiogenic therapy [10]. In their experiment mice were injected with Lewis lung carcinoma cells and they have investigated the effect of three different angiogenic inhibitors (angiostatin, endostatin and TNP-470). The original model was analyzed and modified in several studies [11], [12], [13]. The most important alteration is the continuous infusion therapy [12], where the input (the inhibitor administration rate) is equal to the concentration of administered inhibitor (serum level of inhibitor).

The model which takes into account the continuous infusion therapy is the following second-order system:

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

$$\dot{x}_2 = bx_1 - dx_1^{2/3}x_2 - ex_2 g \quad (2)$$

$$y = x_1 \quad (3)$$

where x_1 is the tumor volume (mm^3), x_2 is the endothelial volume (mm^3), g is the concentration of the administered inhibitor (mg/kg). The model contains the following parameters: λ_1 is the tumor growth rate ($1/day$), b is the stimulatory capacity of the tumor to the vasculature ($1/day$), d is the endogenous inhibition of previously generated vasculature ($1/day \cdot mm^2$), e is the antiangiogenic effect of the administered inhibitor on the tumor vasculature ($kg/day \cdot mg$).

Parameter values for the considered Lewis lung carcinoma and the mice used in the experiment are [10]: $\lambda_1 = 0.192$ 1/day, $b = 5.85$ 1/day, $d = 0.00873$ 1/day·mm^2. The experiment has shown that the most effective inhibitor was endostatin; therefore, we have applied this antiangiogenic drug in controller design ($e_{endostatin} = 0.66$ kg/day·mg).

From equation (1) it can be seen that the system is in steady-state if the tumor volume and the vascular volume are equal. (We will use 'endothelial' and 'vascular' words as synonyms during the article). Steady-state can be reached in two different ways (Fig. 1). Tumor growth without antiangiogenic therapy leads to high steady-state tumor volume ($1.734 \cdot 10^4$ mm^3) and it represents the lethal steady-state case. Using angiogenic inhibition, tumor size can be reduced from a high tumor volume to a low value. In the lower part of Fig. 1 we have simulated the effect of constant 5 mg/kg endostatin inhibition.

Since H_∞ control design requires a linear nominal model, we have applied working point linearization [14] in the $g_0 = 0$ working point. The matrices of the linear model are:

$$A = \begin{bmatrix} -\lambda_1 \log\left(\frac{x_1}{x_2}\right) - \lambda_1 & \lambda_1 \frac{x_1}{x_2} \\ b - \frac{2}{3} d \cdot x_1^{-\frac{1}{3}} \cdot x_2 & -d \cdot x_1^{\frac{2}{3}} \end{bmatrix} \quad (4)$$

$$B = \begin{bmatrix} 0 \\ -ex_2 \end{bmatrix} \quad (5)$$

$$C = \begin{bmatrix} 1 & 0 \end{bmatrix} \quad (6)$$

$$D = [0] \quad (7)$$

The assessed working point is $x_1 = x_2 = 100$ mm^3. Eigenvalues of the linearized system are $p_1 = -1.2384$ and $p_2 = 0.8584$; because of p_1 has positive real part, the system is unstable. Investigating the controllability and the observability matrices, we have found that they are full rank for every $x_1 \neq 0$, thus the linearized system is controllable and observable in every working point [4].

IV. H_∞ CONTROL DESIGN

A. Design structure

For controller design, we have created the closed-loop interconnection structure (Fig. 2).

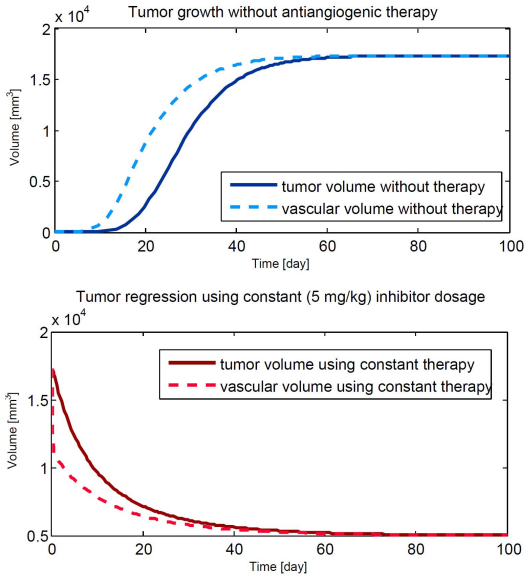

Figure 1. Tumor growth without and under angiogenic inhibition

The closed-loop system includes the feedback structure of the nominal model G_n. K is the two-degrees of freedom controller, which consists of two parts: K_r is the feedforward branch and K_y is the feedback branch. Differences between the nominal model and the real system are taken into account using input multiplicative uncertainty, G_{unc} [15]:

$$G_{unc}(s) = W_{unc}(s) \cdot (I + \Delta_{unc}(s)) \quad (8)$$

Weighting function W_n seeks to minimize the influence of sensor noise. Limitation of the control input is achieved by the weighting function W_u, which penalizes larger deflections. Ideal system is described by T_{id} transfer function. Weighting function W_{perf} seeks to penalize differences between the output of the nominal model and the ideal plant.

Signals of the system are the following: r is the reference signal, u is the control input, y is the output of the nominal model, n is the measurement noise, e is the modeling error, d is the disturbance caused by the uncertainty of the model, z_u is the penalized control input and z_e is the penalized difference between the output of the nominal model and the ideal model.

The generalized structure of H_∞ control design is formulated in Δ-P-K structure (Fig. 3). The detailed Δ-P-K structure is described as follows:

$$\begin{bmatrix} e \\ z_e \\ z_u \\ r \\ y \end{bmatrix} = \left[\begin{array}{ccc|c} 0 & 0 & 0 & W_{unc} \\ W_{perf}G_n & -W_{perf}T_{id} & 0 & W_{perf}G_n \\ 0 & 0 & 0 & W_u \\ \hline 0 & 1 & 0 & 0 \\ G_n & 0 & W_n & G_n \end{array}\right] \begin{bmatrix} d \\ r \\ n \\ u \end{bmatrix}. \quad (9)$$

P is called the generalized plant and partitioned as:

$$P = \left[\begin{array}{c|c} P_{11} & P_{12} \\ \hline P_{21} & P_{22} \end{array}\right]. \quad (10)$$

Input of the generalized plant is:

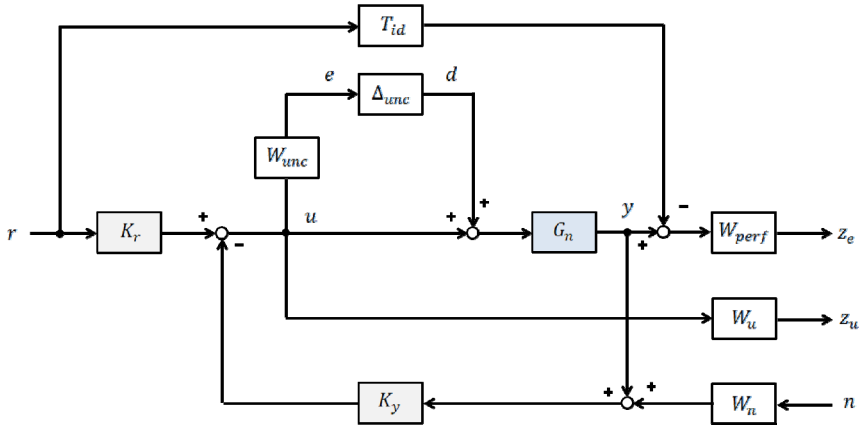

Figure 2. The closed-loop interconnection structure for controller design

$$w = \begin{bmatrix} d \\ w^* \\ u \end{bmatrix}, \tag{11}$$

where $w^* = [r\ n]^T$ is the external input and $w_{min} = [d\ w^*]^T$.

Output of the generalized plant is:

$$z = \begin{bmatrix} e \\ z^* \\ r \\ y \end{bmatrix}, \tag{12}$$

where $z^* = [z_e\ z_u]^T$ is the external output to be penalized and $z_{min} = [e\ z^*]^T$.

The closed-loop function M can be derived as the lower linear fractional transformation of the pair (P,K):

$$z_{\min} = \left[P_{11} + P_{12}K\left(I - P_{22}K\right)^{-1}P_{21}\right]w_{\min} = F_l(P,K)w_{\min} \tag{13}$$

$$M = F_l(P,K) \tag{14}$$

B. H_∞ suboptimal solution

The objective is to find a stabilizing controller K to minimize the output z_{min}, in the sense of $||w||_\infty \le 1$. It is equivalent to minimizing the H_∞-norm of M from w_{min} to z_{min}:

$$\min_{K_s} \| F_l(P,K) \|_\infty, \tag{15}$$

where K_s is an element of the set of stabilizing K controllers; this is called the H_∞ optimization problem [16]. Since the solution of the optimization problem is not obvious, in practice, it is usually satisfactory to find a stabilizing controller K such the H_∞-norm of the closed-loop function is less than a given positive number [16]:

$$\| M \|_\infty = \| F_l(P,K) \|_\infty < \gamma, \tag{16}$$

where $\gamma > \gamma_0 = min_{Ks}||F_l(P,K)||_\infty$; it is called as the H_∞ suboptimal problem.

System-performance specifications can usually be interpreted as a reduction of z^* with respect to w^*. Robustness and performance can be investigated by the partition blocks of M:

$$\begin{bmatrix} e \\ z^* \end{bmatrix} = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix} \begin{bmatrix} d \\ w^* \end{bmatrix}. \tag{17}$$

The scope of the H_∞ controller design is to guarantee robust performance of the system. This can be realized by fulfilling the conditions of robust stability and nominal performance. To guarantee nominal stability the system must be internally stable, which means that the created transfer function is stable from all inputs to all outputs.

Robust stability is achieved by fulfilling the following condition:

$$\| M_{11} \|_\infty \le 1 \tag{18}$$

Nominal performance is achieved if the performance objective is satisfied:

$$\| M_{22} \|_\infty \le 1 \tag{19}$$

The upper linear fractional transformation of the pair (M, Δ) can be described as:

$$z^* = \left[M_{22} + M_{21}\Delta\left(I - M_{11}\Delta\right)^{-1}M_{12}\right]w^* = F_u(M,\Delta)w^* \tag{20}$$

Robust performance is achieved by fulfilling the following condition:

$$\| F_u(M,\Delta) \|_\infty < 1 \tag{21}$$

C. Choosing of the ideal system and the weighting functions in the light of physiological aspects

From engineering point of view, the ideal system (T_{id}) is needed to be a fast system for fast reduction of the tumor volume. Nevertheless, on the one hand it is physically impractical, on the other hand fast transients need high control signal and in medical treatments the input is always limited. Besides these, researches have shown that in the case of antiangiogenic therapy low-dose treatments can be more effective ([17] states it exactly in the context of Lewis lung carcinoma). According to the fact that tumor regression has exponential characteristics, our ideal system was found to have a relatively slow exponential decay:

$$T_{id}(s) = \frac{K}{sT + 1}, \tag{22}$$

where K is the initial tumor volume and T is the time constant of the ideal system ($T = 100$ days). Weighting function W_u (which penalizes large deflections of the control input) was chosen to constant value and we have run iteration to find the greatest possible value to penalize deflections. Finally we set $W_u = 0.02$.

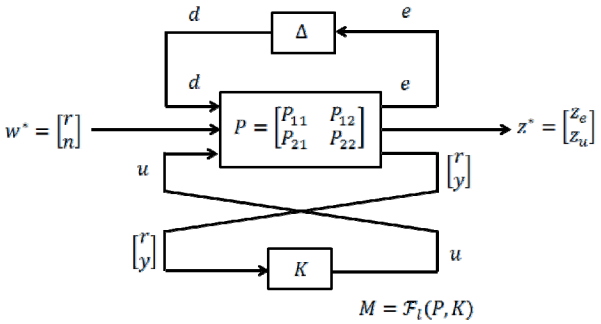

Figure 3. The generalized Δ-P-K structure

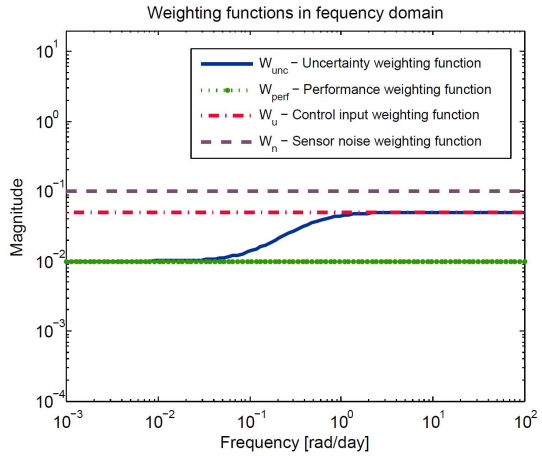

Figure 4. Weighting functions of the controller

Sensor-noise, as a wide-band signal, can be modeled with a constant value. The effect of the weighting function W_n was investigated in the range of [*0.0 0.2*], Section V contains the results of this analysis.

In the case of weighting functions W_{unc} and W_{perf}, tuning of the crossover frequencies was carried out to reach better performance and robustness.

$$W_{unc} = 0.05 \cdot \frac{s + 0.1}{s + 0.5} \tag{23}$$

$$W_{perf} = 0.01 \tag{24}$$

The chosen weighting functions can be seen in Fig. 4.

V. Simulation Results

Frequency domain analysis (Fig. 5) showed that the conditions of robust stability (18), nominal performance (19) and robust performance (21) are fulfilled, because all the corresponding norms are smaller than *1* for every frequency.

The reached γ value was *0.0781* and the *K* controller was stable, thus the designed structure provides a suboptimal H_∞ solution. According to the minimal size criteria for diagnosis in the case of Lewis lung carcinoma (tumor size has to be bigger than *3* cm [18]) and assuming a spherical shape, simulations were run from the initial tumor volume $x_0 = 14137$ mm^3.

Time domain analysis showed that control input saturation is necessary, because one-off high dose can be tolerated by the patient; however, continuous dosage of angiogenic inhibitor is limited in concentration to around *10* mg/kg [19]. The saturation, which was resulting in the least possible control signal, but still effective H_∞ control, is *13* mg/kg; every simulation results were run with this value.

The effect of the weighting function W_n was investigated in the range of [*0.0 0.2*], since subcutaneous tumor volume measurement is usually carried out by calipers. Width and length of the tumor can be measured, but the third dimension is estimated; and tumor volume is approximated with a spherical shape or an ellipsoid [20]. The results have shown that the designed H_∞ controller can handle the sensor noise in a robust way until 15%: we have found that if $W_n \leq 0.15$, tumor volume (output of the system) decreased exactly the same rate in every cases. Above this value, the control signal was not applicable. This result also shows how important the precise tumor volume measurement is, and if it is possible, Magnetic Resonance Imaging (MRI) has to be preferred as measurement method against to caliper [21].

Effect of the initial tumor volume at the beginning of the therapy was examined in the [*100 17340*] mm^3 range. The results are shown in Fig 6. Steady-state tumor volume is independent from the initial tumor volume; in every case tumor volume was *25.6* mm^3 ± *0.1*% (Fig 6.a). Steady-state inhibitor concentration (Fig 6.b) has showed the same result, viz. minimal deviation (8.759 mg/kg ± *0.07*%). It is clear that the period of maximal inhibitor dose (Fig 6.c) have to increase as the simulations start from higher initial tumor volumes to ensure the appropriate steady-state tumor volume. However, a breakpoint can be determined at *2000* mm^3: below this value, initial tumor value has greater impact on the maximal inhibitor period than above this point.

Similar results can be seen in (Fig 6.d); total concentration of the administered inhibitor depends more on initial tumor volume below the *2000* mm^3 breakpoint than above (of course the former last two functions are not independent). Summarizing the results of these figures: at lower initial working points the dynamics of the change is larger and the controller should administer more inhibitor; however, nearly the same tumor outputs can be provided.

We have compared our previous result, when optimal LQ controller was designed for angiogenic inhibition of tumor growth [4], with the H_∞ suboptimal solution. The outcome can be seen in Fig. 7. The numerical results are the following. Steady-state tumor volume: $V_{LQ} = 7.491$ mm^3, $V_{H\infty} = 25.64$ mm^3.

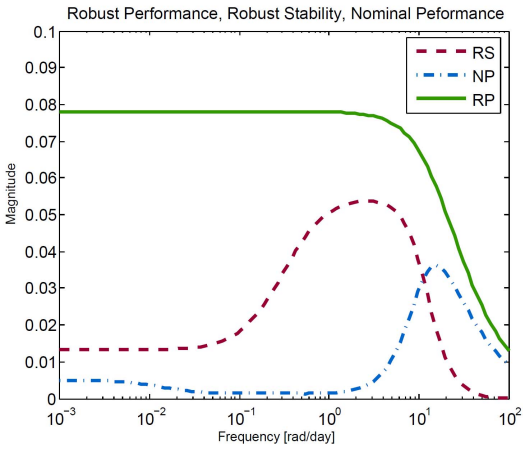

Figure 5. Robust Performance, Robust Stability and Nominal Performance

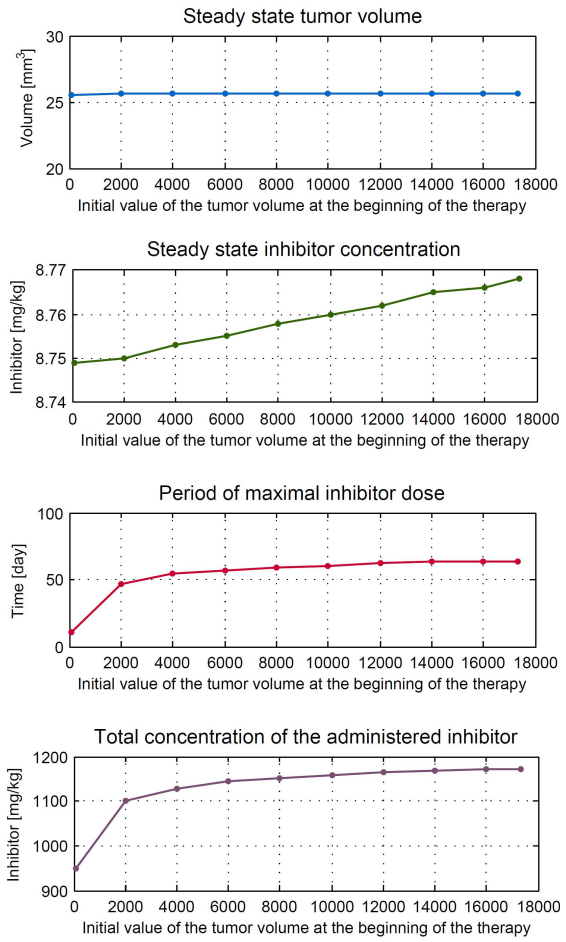

Figure 6. Investigating the effect of different working points on the
a) steady-state tumor volume,
b) steady-state inhibitor concentration,
c) period of maximal inhibitor dose and
d) total concentration of the administered inhibitor

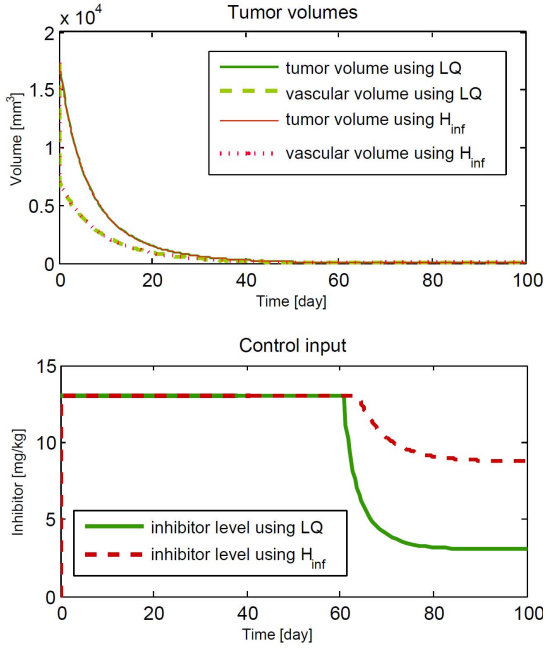

Figure 7. Comparison of control inputs and tumor volumes in the cases of Linear Quadratic optimal control and suboptimal Robust Control method

Steady-state inhibitor concentration: $SC_{LQ} = 3.093$ mg/kg, $SC_{H\infty} = 8.768$ mg/kg. Period of maximal inhibitor dose: $T_{LQ} = 60$ days, $T_{H\infty} = 64$ days. Total concentration of the administered inhibitor: $SC_{LQ} = 915$ mg/kg, $SC_{H\infty} = 1173$ mg/kg. As it would expected, LQ optimal control provides better results, but only in the case of good model identification and minimal sensor noise. If the system contains significant uncertainties and the measurement noise is large, only robust control method can provide near-optimal results. Last but not least, we have simulated and compared the changes in full-grown tumor volume after making the diagnosis (*14137* mm^3) in three different cases; Fig. 8. shows the results. The first case was a therapy when the inhibitor was administered by the H_∞ controller. In the second case the therapy was based on the Hungarian OEP protocol for antiangiogenic monotherapy [22]. The third case was the simulation without therapy. From Fig. 8 it is clear, that the intermittent dosing used by the chemotherapy protocol is not effective.

The tumor volume reduced slightly as a result of one-day dose, but between the treatment phases, tumor grows back again. At the end of the whole treatment period, there is no large difference between the therapy with OEP protocol and the case without therapy.

VI. Conclusion

H_∞ controller was designed for the problem of tumor growth under angiogenic inhibition, considering the physiological aspects. Robust stability, nominal performance and robust performance were achieved. Frequency domain analysis and time domain analysis were carried out. We have investigated the effect of the sensor noise weighting function on the robustness. We have also examined the effect of the initial tumor volume on the steady-state tumor volume, on the steady-state inhibitor concentration, on the period of maximal inhibitor dose and on the total concentration of the administered inhibitor. We have compared the results of the H_∞ controller with the results of LQ optimal control and the therapy with OEP protocol. Further research will focus on other control strategies like fuzzy control [23], robust multiobjective optimization questions [24], system identification problems, but real world applicability challenges [25] as well.

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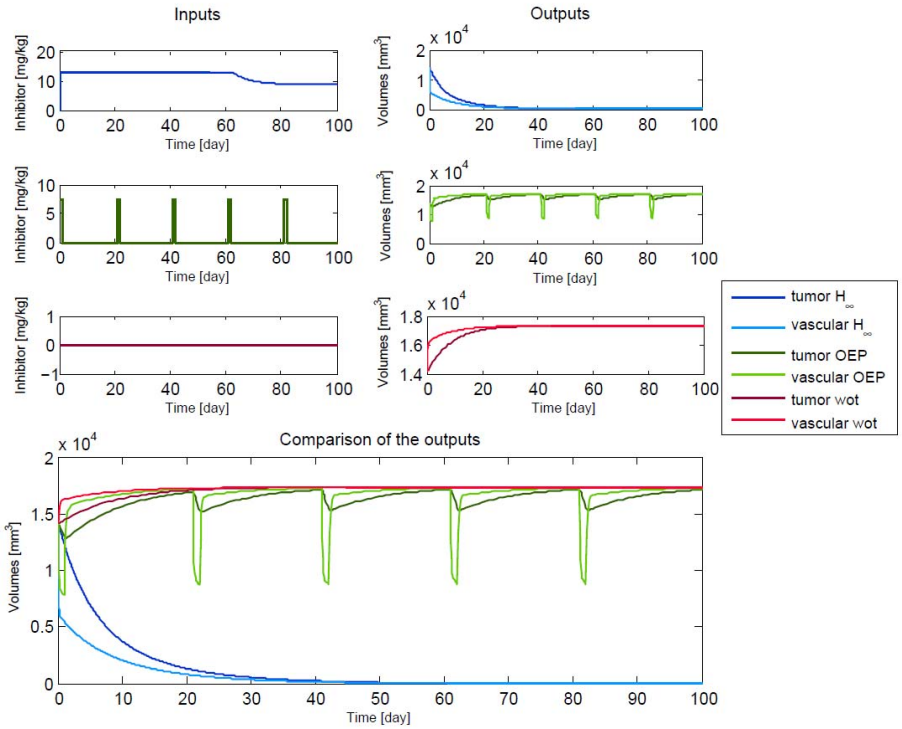

Figure 8. Comparison of changes in tumor volume after making the diagnosis (*14137* mm^3) in three different cases:
a) therapy using the controller which was designed with Robust Control method
b) therapy based on the Hungarian OEP protocol for antiangiogenic monotherapy
c) without therapy

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