Backstepping Based Automatically Controlled Angiogenic Inhibition Therapy

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Abstract

In this work, we present an automatically controlled angiogenic inhibition therapy where the variation profile of the inhibitory agent is generated by a control law that is derived using a back-stepping based control methodology. The angiogenic inhibition is described by a second order model representing the dynamics of tumor and supporting vasculature volumes. Backstepping control recursively stabilizes that dynamics and generates automatic control laws that allows the tumor volume to stay at a desired value. The desired value will be kept at one thousandth of its initial value. This will lead to a very small injection at the steady state. This is important as zero injection may lead to regrow of the tumor. The results will be presented in tabular and graphical forms. Tabular results present the variation of maximum injection rate and setup time. Graphical results present the variation of tumor and supporting vasculature volumes, injection rate and the tracking error between the reference and actual tumor volumes. In addition, we will also perform a simulation to test the capability of the closed loop to accomodate the parametric uncertainties in the rate constants. The uncertainties are represented by a random deviation in the range $\pm 10\%$ times the nominal value of the effected parameter. The control laws will be kept the same and the simulations will be repeated by 1000 times and each result will be superimposed on the graph. The area occupied by the curves will show the relative capability of the designs.

1 Angiogenic Inhibition Model of Cancer Progression

In this research we will utilize the angiogenic inhibition model developed by [1] and [2]. That is a nonlinear system represented by the following differential equations:

$$\begin{aligned}\dot{x}_1 &= -\lambda_1 x_1 \ln \left(\frac{x_1}{x_2} \right) \\ \dot{x}_2 &= bx_1 - dx_1^{2/3} x_2 - ex_2 x_3 \\ \dot{x}_3 &= \int_0^t u(\tau) \exp(-\lambda_3(t-\tau)) d\tau\end{aligned}\tag{1}$$

where x_1 is the tumor volume in mm^3 , x_2 is the supporting vasculature volume in mm^3 (blood vessels stem from a regular vessel due to tumor angiogenesis after secretion of vascular endothelial growth factor to the site), x_3 the level of inhibitory agent in the blood serum in mg/kg and u is the inhibitor administration rate in $\text{mg/kg}\cdot\text{day}$. There are five parameters in (1) $\theta = [b, d, e, \lambda_1, \lambda_3]$ and their definitions, units and nominal values are available in **Table 1**.

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Table 1: The numerical values of parameters in (1). These are taken from [3] which presents a mathematical model of animal Lewis lung carcinoma.

Parameter	Unit	Value
b	day^{-1}	5.85
d	$\text{day}^{-1} \cdot \text{mm}^{-2}$	0.00873
e	$\text{day}^{-1} \cdot (\text{mg/kg})^{-2}$	0.66
λ_1	day^{-1}	0.192
λ_3	day^{-1}	1.3

The integral equation found in the $\dot{x}_3$ equation is actually not very convenient for a control application. That is a convolution operation and defines the response of a linear system expressed by the following transfer function:

$$H(s) = \frac{1}{s + \lambda_3} \quad (2)$$

to the input $u(t)$. The value of the parameter λ_3 relatively closer to unity. Because of that the steady state gain of (2) is about 0.77. This corresponds to a rise time of about 1.7 days. This seems quite fast concerning a realistic problem. So one can directly replace the plasma inhibitory agent variable x_3 by the inhibitory agent rate represented by u . This is also the case in the relevant examples presented by [4, 2]. So one can reduce the third order model in (1) to a second order one by just replacing x_3 by u in the $\dot{x}_2$ equation as:

$$\begin{aligned} \dot{x}_1 &= -\lambda_1 x_1 \ln \left(\frac{x_1}{x_2} \right) \\ \dot{x}_2 &= bx_1 - dx_1^{2/3} x_2 - ex_2 u \end{aligned} \quad (3)$$

Uncontrolled evolution of the tumor volume and supporting vasculature volumes can be seen in **Figure 1**. The parameters are taken from **Table 1**.

Figure 1: The evolution of tumor volume under no treatment conditions. The responses are obtained from (3) with the parameters in **Table 1**.

2 Application of Backstepping Control to Angiogenic Inhibition Problem

In this section, we will apply the famous backstepping technique [5] to derive automatically controlled inhibitory agent injection laws. One should note here that, the angiogenic inhibition model presented in (3) is a full relative degree model. This means that one can allow the backstepping based approach without the risk of an uncontrollable remaining dynamics.

2.1 Step 1: Stabilization of the Tumor Volume

Before proceeding one needs to define a tracking error ϵ_1 between actual and reference tumor volumes (x_1 and r_1) as shown below:

$$\epsilon_1 = x_1 - r_1 \quad (4)$$

Finding its dynamics by differentiating yields:

$$\dot{\epsilon}_1 = \dot{x}_1 - \dot{r}_1 = -\lambda_1 x_1 \ln \left(\frac{x_1}{x_2} \right) \quad (5)$$

In the above we assume that the reference tumor level r_1 is constant. Although we are in Step 1, one needs to define the tracking error between the supporting vasculature volume and a virtual input r_2 as follows:

$$\epsilon_2 = x_2 - r_2 \quad (6)$$

If one draws x_2 as $x_2 = \epsilon_2 + r_2$ and substitutes into (4), we can write the following:

$$\dot{\epsilon}_1 = -\lambda_1 x_1 \ln \left(\frac{x_1}{\epsilon_2 + r_2} \right) \quad (7)$$

To ensure the stability, one needs to define a Control Lyapunov Function V_1 as shown below:

$$V_1 = \frac{1}{2} \epsilon_1^2 \quad (8)$$

and taking its time derivative will yield:

$$\dot{V}_1 = \epsilon_1 \dot{\epsilon}_1 \quad (9)$$

After substituting (7) to above, we will obtain:

$$\dot{V}_1 = \epsilon_1 \left[-\lambda_1 x_1 \ln \left(\frac{x_1}{\epsilon_2 + r_2} \right) \right] \quad (10)$$

Concerning a standard backstepping application one needs to draw the virtual control variable r_2 from the above equation which will yield a negative definite $\dot{V}_1$. This will yield an asymptotically stable dynamics for ϵ_1 . One thing to note here is that backstepping techniques develop the control laws recursively. This recursiveness is provided by the Control Lyapunov Functions. In this step, this is obtained by equating (10) to a form shown by:

$$\dot{V}_1 = -\epsilon_2 \epsilon_1 - K_1 \epsilon_1^2 \quad (11)$$

with K_1 being a positive real number. In order to obtain this rate function, r_2 should be derived as:

$$r_2 = \lambda_1 x_1 \ln \left(\frac{x_2}{x_1} \right) + x_2 + K_1 \epsilon_1 \quad (12)$$

2.2 Step 2: Stabilization of the Supporting Vasculature Volume

One should start by taking the time derivative of the tracking error between x_2 and r_2 as shown in the following:

$$\dot{\epsilon}_2 = -\lambda_1^2 x_1 \ln^2 \left[\frac{x_1}{x_2} \right] - \frac{\lambda_1 b x_1^2}{x_2} + \lambda_1 d x_1^{5/3} - \lambda_1 e x_1 u - \lambda_1^2 x_1 \ln \left[\frac{x_1}{x_2} \right] + K_1 \lambda_1 x_1 \ln \left[\frac{x_1}{x_2} \right] \quad (13)$$

Secondly, we will need to define a Control Lyapunov Function for this step. This should be defined as an additive to that of the first one.

$$V_2 = V_1 + \frac{1}{2} \epsilon_2^2 \quad (14)$$

and its rate of change is:

$$\dot{V}_2 = \dot{V}_1 + \epsilon_2 \dot{\epsilon}_2 = -K_1 \epsilon_1^2 - \epsilon_2 \epsilon_1 + \epsilon_2 \dot{\epsilon}_2 \quad (15)$$

Substituting from (13) yields:

$$\dot{V}_2 = \epsilon_2 \left[-\epsilon_1 - \lambda_1^2 x_1 \ln^2 \left[\frac{x_1}{x_2} \right] - \frac{\lambda_1 b x_1^2}{x_2} + \lambda_1 d x_1^{5/3} - \lambda_1 e x_1 u - \lambda_1^2 x_1 \ln \left[\frac{x_1}{x_2} \right] + K_1 \lambda_1 x_1 \ln \left[\frac{x_1}{x_2} \right] \right] \quad (16)$$

If we choose an inhibitory agent injection rate as:

$$u = \frac{-K_2\epsilon_2 + \epsilon_1 + \lambda_1^2 x_1 \ln^2 \left[\frac{x_1}{x_2} \right] + \frac{\lambda_1 b x_1^2}{x_2} - \lambda_1 d x_1^{5/3} + \lambda_1^2 x_1 \ln \left[\frac{x_1}{x_2} \right] - K_1 \lambda_1 x_1 \ln \left[\frac{x_1}{x_2} \right]}{\lambda_1 e x_1} \quad (17)$$

(16) becomes:

$$V_2 = -K_1 \epsilon_2^2 - K_2 \epsilon_2^2 \quad (18)$$

with K_2 being a positive real number. (18) ensures the asymptotic stability of the closed loop.

3 Results

In this section we will present an example application together with its simulation results. First of all, we will present a scenario for the simulation environment and secondly we will present the results for different controller configurations.

3.1 Information on Simulations

One can see the information related to the initial tumor and supporting vasculature volumes and targeted treatment duration in days in **Table 2**.

Table 2: Problem scenario and simulation conditions			
Scenario Parameter	Symbol	Value	Unit
Treatment Duration	T_f	50	Days
Initial Tumor Volume	$x_1(0)$	2000	mm ³
Initial Vasculature Volume	$x_2(0)$	250	mm ³
Reference (steady state) tumor volume	r_1	$\frac{1}{1000}x_1(0)$	mm ³

The purpose of the controlled simulations is to reduce the tumor volume x_1 to 1% of its initial volume $x_1(0)$ in **Table 2** in a finite duration. The duration required to achieve this goal is called as setup time. In the control application there is a constant reference tumor volume r_1 . This will be chosen as one thousandth of the initial volume i.e. $r_1 = 2.5$ mm³.

3.2 Simulation Results: No Uncertainties Exist

A typical variation of the tumor volume $x_1(t)$, supporting vasculature volume $x_2(t)$ and injection rate of inhibitory agent $u(t)$ can be seen in **Figure 2**.

Figure 2: The variation of tumor volume $x_1(t)$, supporting vasculature volume $x_2(t)$ and injection rate of inhibitory agent $u(t)$ when $K_1 = 100$ and $K_2 = 0.5$.

In addition to 2, one is eligible to see the results associated with maximum required injection and setup times in **Table 3**. Note that some rows in this table depicts pretty unapplicable cases (i.e. instability or very large injection rates).

Table 3: Maximum value of inhibitory injection rate and setup times of backstepping based treatment procedures. Here $\max(u)$ is the maximum inhibitory agent injection rate and T_s is the setup time in days.

K_1	K_2	$\max(u)$	T_s
2.0000	0.0500	1249.3485	5.5320
2.0000	0.1000	2789.3545	5.0430
2.0000	0.2000	44372.6944	4.3100
2.0000	0.2500	4033991.5434	4.0360
5.0000	0.0500	101.4783	17.8450
5.0000	0.1000	103.2578	14.9000
5.0000	0.2000	106.8169	11.2200
5.0000	0.5000	400.8060	6.4910
5.0000	0.9000	3584.5894	4.2040
5.0000	1.5000	95733.1915	2.8020
5.0000	2.5000	19222732.9454	1.8790
5.0000	5.0000	137296569206.2600	1.2380
10.0000	0.0100	81.3145	42.0260
10.0000	0.0200	82.0646	38.5310
10.0000	0.0500	84.3149	30.8440
10.0000	0.1000	88.0653	23.1570
10.0000	0.2000	95.5661	15.4700
10.0000	0.5000	206.7063	7.7840
10.0000	1.0000	2866.5315	4.2920
10.0000	2.0000	538543.5230	2.3000
20.0000	0.0002	42.3266	93.1330
20.0000	0.0020	42.6035	89.9110
20.0000	0.0100	43.8343	77.9290
20.0000	0.0200	45.3727	66.8030
20.0000	0.0500	49.9880	46.7770
20.0000	0.1000	57.6802	31.2000
20.0000	0.2000	73.0645	18.7390
20.0000	0.5000	155.0376	8.5440
20.0000	1.0000	2113.3121	4.4980
20.0000	2.0000	385414.3820	2.3270
20.0000	4.0000	12287655310.0452	1.2020
50.0000	0.0020	9.7487	213.5450
50.0000	0.0100	10.1500	156.6040
50.0000	0.0200	10.6819	117.4580
50.0000	0.0500	12.4766	67.1270
50.0000	0.1000	16.2033	39.1650
50.0000	0.2000	27.3737	21.3710
50.0000	0.5000	131.6975	9.0520
50.0000	1.0000	1789.5742	4.6230
50.0000	2.0000	325013.6384	2.3420
50.0000	4.0000	10618811896.1328	1.1810
100.0000	0.0020	9.2806	391.9980
100.0000	0.0100	9.6517	235.2020
100.0000	0.0200	10.1496	156.8040
100.0000	0.0500	11.8434	78.4060
100.0000	0.1000	15.3737	42.7710
100.0000	0.5000	128.4096	9.2310
100.0000	1.0000	1696.9747	4.6640
100.0000	2.0000	308350.3896	2.3460
100.0000	2.2500	1131789.4217	2.0860

3.3 Simulation Results: Simulations Under Existence of Uncertainties

In this section, we will present simulations under the existence of 10% uncertainty in the rate constants (i.e. $[b, d, e, \lambda_1]$). The uncertainties are incorporated into the parameters by introducing random deviations to those parameters. This deviation is obtained by adding a uniformly distributed random number in the following fashion:

For example for parameter b , the uncertainty is incorporated as $\hat{b} = b(1 + \delta)$ where δ is a random number uniformly distributed in the interval $[-0, 1, 0, 1]$. This means that there is a 10% uncertainty assumed in the parameters. The deviated parameters are only used in the simulation of the angiogenic inhibition model itself. The controller stays same. In other words, controller's design involves the nominal values of the parameters $\theta = [b, d, e, \lambda_1]$.

Since we have randomly varying parameters, the simulation needs to be repeated. We repeat the simulations 1000 times and superimpose the results on the same figure. The `hold on/off` feature of the MATLAB environment draws each curve with a different color. As the number of runs advances, the curves may occupy a larger space. The larger the occupied area the larger the deviations.

The simulations are performed with the configurations presented in **Table 4**. If the results are not therapeutically feasible under 10% uncertainty, the situation is also indicated. The results associated with the therapeutically feasible cases are presented in **Figures 3-16** referenced in the table. It should be noted that, unstable and cases resulting negative inhibitory agent injections are not reported graphically.

Table 4: The configuration of the sliding surface parameters for the simulations under 10% uncertainty in the physiological rate constant parameters $\theta = [b, d, e, \lambda_1]$. If the results are not therapeutically feasible under 10% uncertainty, the situation is indicated in the observation column. NOTE: When the gains are swapped (i.e. $K_1 \Leftrightarrow K_2$) similar results are obtained.

K_1	K_2	Observations
1	0.05	UNSTABLE
1	0.02	UNSTABLE
1	0.1	UNSTABLE
0.5	0.02	UNSTABLE
0.5	0.05	UNSTABLE
2	0.1	UNSTABLE
2	0.05	UNSTABLE
2	0.2	UNSTABLE
2	0.4	UNSTABLE
5	0.1	UNSTABLE
5	0.2	UNSTABLE
5	0.5	UNSTABLE
5	0.9	UNSTABLE
10	0.01	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$
10	0.05	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$
10	0.1	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$
10	0.2	UNSTABLE
10	0.5	UNSTABLE
10	1	UNSTABLE
10	2	UNSTABLE
20	0.0002	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$ Very slow response

20	0.002	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$ Very slow response
20	0.01	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$ Very slow response
20	0.02	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$ Very slow response
20	0.05	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$
20	0.1	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$
20	0.2	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$
20	0.5	UNSTABLE
20	1	UNSTABLE
20	2	UNSTABLE
20	4	UNSTABLE
50	0.002	NEGATIVE INJECTION
50	0.01	NEGATIVE INJECTION
50	0.02	NEGATIVE INJECTION
50	0.05	NEGATIVE INJECTION
50	0.1	NEGATIVE INJECTION
50	0.2	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$ Relatively faster.
50	0.5	Sudden decrease in the inhibitory agent administration rate $u(t)$. Sudden jumps in the vasculature volume $x_2(t)$ Smoother responses
50	1	UNSTABLE
50	2	UNSTABLE
50	5	UNSTABLE
100	0.002	NEGATIVE INJECTION
100	0.01	NEGATIVE INJECTION
100	0.02	NEGATIVE INJECTION
100	0.05	NEGATIVE INJECTION
100	0.1	NEGATIVE INJECTION
100	0.5	Fast and smoother responses, no jumps.
100	1	UNSTABLE
100	2	UNSTABLE
100	5	UNSTABLE
100	10	UNSTABLE
200	0.2	NEGATIVE INJECTION
200	0.5	Fast and smoother responses, no jumps. Relatively larger injection rate.
200	1	UNSTABLE
200	2	UNSTABLE
200	5	UNSTABLE
200	10	UNSTABLE
500	0.2	NEGATIVE INJECTION
500	0.5	Fast responses, jumps reappear. Relatively larger injection rate.
500	1	NEGATIVE INJECTION

500	2	UNSTABLE
500	5	UNSTABLE

Figure 3: Simulations under the existence of 10% uncertainty when $K_1 = 10$ and $K_2 = 0.01$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 4: Simulations under the existence of 10% uncertainty when $K_1 = 10$ and $K_2 = 0.05$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 5: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.0002$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 6: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.002$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 7: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.01$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 8: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.02$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 9: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.05$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 10: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.1$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 11: Simulations under the existence of 10% uncertainty when $K_1 = 20$ and $K_2 = 0.2$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 12: Simulations under the existence of 10% uncertainty when $K_1 = 50$ and $K_2 = 0.2$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 13: Simulations under the existence of 10% uncertainty when $K_1 = 50$ and $K_2 = 0.5$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 14: Simulations under the existence of 10% uncertainty when $K_1 = 100$ and $K_2 = 0.5$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 15: Simulations under the existence of 10% uncertainty when $K_1 = 200$ and $K_2 = 0.5$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

Figure 16: Simulations under the existence of 10% uncertainty when $K_1 = 500$ and $K_2 = 0.5$. $x_1(t)$: Tumor volume, $x_2(t)$: Supporting vasculature volume, $u(t)$: Inhibitory agent rate

4 Results, Discussion and Observation

In this text, we presented an automatically controlled angiogenic inhibition problem where the control laws are derived recursively using a back-stepping based approach. The mechanism samples the tumor and supporting vasculature volumes and generates an inhibitory agent variation profile. One can have the following observations:

1. Among the cases in **Table 4**, the most feasible configuration seems the one with $K_1 = 100$ and $K_2 = 0.5$. The variations of the variables are relatively faster, smooth and lowest dispersion seen under various parametric deviation. The setup time seems 9.23 days and highest level of inhibitory agent injection is 128.4 mg/kg·day. See **Figure 14**.
2. Most of the cases in **Table 4** yields sudden decreases in the inhibitory agent administration rate $u(t)$ and jumps in the supporting vasculature volume $x_2(t)$.

3. A robust control approach with better uncertainty accommodation such as sliding mode may be preferred.

References

- [1] P. Hahnfeldt, D. Panigrahy, J. Folkman, L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer research* 59 (19) (1999) 4770–4775.
- [2] A. Szeles, D. A. Drexler, J. Sápi, I. Harmati, L. Kovács, Model-based angiogenic inhibition of tumor growth using adaptive fuzzy techniques, *Periodica Polytechnica Electrical Engineering and Computer Science* 58 (1) (2014) 29–36.
- [3] B. Rashidi, M. Yang, P. Jiang, E. Baranov, Z. An, X. Wang, A. Moossa, R. Hoffman, A highly metastatic lewis lung carcinoma orthotopic green fluorescent protein model, *Clinical & experimental metastasis* 18 (1) (2000) 57–60.
- [4] S. Herdjunto, Simple control design using double feedback structure for reducing tumor size, in: *Proceedings of 2016 1st International Conference on Biomedical Engineering: Empowering Biomedical Technology for Better Future, IBIOMED 2016*, 2017.
URL www.scopus.com
- [5] P. Kokotović, M. Arcak, Constructive nonlinear control: a historical perspective, *Automatica* 37 (5) (2001) 637–662.