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Tumor control by means of an observer-based control law

Advisor
Prof. Pasquale Palumbo

Co-Advisor
Dr. Valerio Cusimano

Candidate
Islam Ibrahim Sultan

Matricola
227466

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Laurea Magistrale in Ingegneria Matematica
Dipartimento di Ingegneria e Scienze dell'Informazione e Matematica
Università degli Studi dell'Aquila

Dedication

To my beloved parents for their
support, encouragement, and sacrifices

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Abstract

The thesis proposes a closed-loop control law of tumor growth with the aim of tumor volume reduction by means of antiangiogenic administration. To cope with discrete sampled measurements, the mathematical problem is restated by means of time-varying delays on the measurements. A tumor growth model accounting for angiogenic stimulation and inhibition is considered. A control law, based on output feedback linearization is formulated and discussed: the control law is made of an observer-controller cascade, where the observer is a high gain observer of the chain type, and the controller is the classic state linearizing scheme. It has been shown in the literature that under suitable conditions on the system, the observer is globally exponentially convergent, additionally replacing the true state with the observer one in the control law leads to an exponentially stabilizing feedback scheme. Different simulations for various values of the delay were done, additionally, different input functions were considered including continuous and discrete. Simulation results show a noticeable robustness against a wide range of the initial state estimate for different values of the delay.

Contents

Chapter 1

Introduction

Tumor, also known as a neoplasm, is an abnormal mass of tissue which may be solid or fluid-filled. A tumor does not mean cancer, tumors can be benign (not cancerous), premalignant (precancerous), or malignant (cancerous). There are many different types of tumors and a variety of names for them, their names usually reflect their shape and the kind of tissue they appear in. Put simply, a tumor is a kind of lump or swelling, it does not necessarily pose a health threat.

For the fact that Tumor is usually can be dangerous even the benign type (if they press on vital organs), searching and developing a therapy for it has a great interest among the biology scientists. There are many treatment types for tumors include surgery, chemotherapy, radiation therapy and other types of treatment. The focus of this thesis is on the chemotherapy, specially The effects of the angiogenic inhibitors endostatin, angiostatin, and TNP-470 on tumor growth dynamics, these kind of therapies are called Anti-angiogenic therapies.

Anti-angiogenic therapies are relatively new cancer treatments [15] which aim at inhibiting the development of the vascular network necessary to support tumor growth during the vascular phase, so providing a way to control the heterogeneous and growth unconstrained tumor population throughout the control of the homogeneous and growth-constrained population of endothelial cells [16, 10].

Tumors have the capability to resist the conventional chemotherapeutic drugs. Due to the indirect action of the anti-angiogenic drugs, the outcome of the therapy should not be impaired by the capability of tumor cells to generate resistant phenotypic variants [21, 22]. Moreover, anti-angiogenic therapies have limited side effects with respect to the conventional chemotherapies and radiotherapies. Conventional chemotherapies may also have antiangiogenic effects on the vascular network [23, 24, 1].

The main aim of the thesis work is to design a closed-loop control of the tumor growth based on angiogenic inhibitors as input, In the case of the delayed output. Further simulations and tests were carried out as well, these simulations includes replacing the continuous input drug intake with discrete input in both cases of delayed and continuous output measurements.

The concept of the carrying capacity has been first introduced in [18], which assume that the volume of the tumor is sustainable to the vasculature, hence vascular control is playing a role in tumor growth. And since the carrying capacity is highly dependent on the extension of the vasculature, its dynamics can be assumed to represent the vascular network dynamics.

The model [18] is one of the first attempts to model, with a minimal number of parameters, the interplay between the dynamics of the tumor volume and of the carrying capacity, with or without administration of antiangiogenic drugs. and since then it this model has been widely exploited in theoretical studies in order to predict the effectiveness of new antiangiogenic therapies. Some model modifications have been proposed after that for example, conditions for the eradication of the tumor under a periodic antiangiogenic treatment are provided, while combining radiotherapy and antiangiogenic treatment problem is formulated by exploiting a suitable modified version of the original model [13]. Another extensions proposal was suggested, with the aim to describe the interplay between the tumor cells populations and endothelial cells and this time as well in environment combining therapy of chemotherapeutic and antiangiogenic drugs. Since the wok of the thesis is to design a closed-loop model-based feedback control law with a delayed output measurements, it was a must to review the previous attempts for closed loop tumor control design, this has been done in [12, 36], where robust control techniques were proposed by exploiting a Linear Quadratic controller and an H∞ methodology applied to the model after linearization.

The model [18] will be exploited here, the goal of the control is to reduce the tumor volume through a closed-loop, model-based approach, exploiting as well the feedback linearization theory [19]. A similar approach has been carried out before In [9], where tumor volume measurements were exploited, with the carrying capacity was estimated by a state observer designed for nonlinear system according to [8, 31], and the input was adjusted after a feedback from the observed state. The closed-loop control law then was designed to achieve an aimed low level of tumor volume. The realistic approach used in this thesis is based on taking into account that the output measurements will not be always available but instead only at certain amounts of time taking into account the cost and time required for such measures, for that reason State estimation and control of nonlinear systems with measurement delays [7] will be exploited here, a desired low level tumor volume similar to the level in case of continuous measures is tracked.

the separability principle which allows to set independently the control and the observer parameters, is proven in the used control scheme [9] thanks to the tumor growth model special properties that guarantee the separability of estimation and feedback control algorithms. Numerical simulations have been carried out starting from running some tests used in [9] to check the robustness of the system with additional test have been firstly carried in this thesis, the results have shown noticeable level of robustness against a wide range of the initial state estimate and of the actual value of the carrying capacity.

The thesis has the following structure, After this introduction, The sec-

ond chapter is devoted for a background on tumor therapy, in which there are discussed the different ways to fight the tumor cells, with focusing on the chemotherapy more specifically on antiangiogenic treatment. The first section of this chapter is for discussing the development of the tumor under the angiogenic signals, the second section is devoted for the derivation of the dynamical system of the tumor growth which led to the mathematical model chosen for designing the closed loop control law, and follows a section for studying the treatment response. The third chapter is the place where the control design of our system will be discussed, firstly the control by means of antiangiogenic drug administration, follows a discussion for the mathematical model used for the control law, and the chapter ends by defining the control algorithm, The fourth chapter is where the results are presented and discussed, first by defining the the observer design and results in the continuous output measurements case and after a more detailed overview on the observer design in the case of delayed output, follows a presentation and discussion of the simulation results, non continuous input is discussed after this and the last chapter for the conclusion and the future scope.

Chapter 2

Tumor therapy

Since Cancer (malignant tumor) is one of the most leading causes of illness-related death (Cancer is the second most common cause of death in the US)[1], It's major public health problem, furthermore there are many non deadly tumors which could cause many bad effects. Therefore searching for therapy and developing many treatments was the concern for many scientific entities, and for various scientific fields, including chemistry, biology, mathematics and engineering. These many efforts have ended with wide range of solutions for the tumor disease, include surgery, radiation therapy, chemotherapy beside other types of treatment. There are many modalities for cancer treatment, all sharing the same main intent, which is to stop tumor cells proliferation or directly kill the tumor cells. For that reason the kinetic understanding of tumor control has been directed toward understanding the tumor cell proliferation and the sensitivity analysis of those cells.

However, there are many factors determines a tumor population, like its micro environmental heterogeneity, genetic and evolving spectrum of tumor cell behaviors ad expressions. This led to a raised concern about the real effect of the current therapeutic attempts which are targeting an expanding array of tumor expressions with customized molecular attacks towards largely temporal events. On the other hand tumor therapy types which are directed against tumor vasculature do not exploit sensitivity characteristics of tumor cells, but instead depending on suppression of tumor following inhibition of the associated vasculature [14, 16, 11, 21, 1]. By knowing how to control an exceptionally diversified, unconstrained and unstable tumor population through controlling endothelial population which are constrained and relatively homogeneous. Antiangiogenic therapy lets us to neglect an immense array of temporal and spatial details of tumor cell expression. As well, the strength of the angiogenic control dynamics lies in governing means into how such therapy could be implemented independently of the specific details of the tumor. For the mentioned reasons, we will speak in details in the next section about the antiangiogenic therapy,

[1] Based on an online report for the year 2013.

how the therapy is developed and how far it reached today, how important it is in treating tumors in general, but first we will speak about what is angiogenic signaling and how is the tumor developed under such signaling.

2.1 Tumor Development under Angiogenic Signaling

Angiogenesis, is a biological process in which the recruitment of new blood vessels happens. These vessels provide the principal route by which tumor cells exit the primary tumor site and enter the circulation, angiogenesis is a complex process that involves many stages, like activation, proliferation, and directing endothelial cells to form new capillaries from existing blood vessels. This growth of capillaries from the already existing vessels happens during the embryonic development. Angiogenesis is a critical process for embryonic development and its survival. As well it iss an important step in many pathologic processes, specially in tumors. The cell signaling pathways involving in angiogenesis are now a targets for medicine making with many current clinical trials.

Therapies that attack a tumor's blood supply are called antiangiogenesis. Antiangiogenic agents target the blood supply to tumors, mainly by blocking the process of angiogenic growth factors and their signaling pathways. Antiangiogenic therapy, although they are more tolerated compared to other traditional chemotherapy, mainly due to their selectivity in their cellular effects. Nonetheless, they are associated with various side effects that require control.

Since antianiogensis and chemotherapy do not target the same parts of the body due to the first is more selective, both can be taken together in some cases, chemotherapy drugs and antiangiogenic drugs do not work in the same way, cause the tumors to shrink or even disappear, where the second may cause tumor shrinkage, but sometimes they just stop tumor from growing anymore.

Although this may be helpful in some cases, but it is not easy to decide the period of treatment to stop tumor from growing. Sometimes patients need to spend very long times taking the drugs to reach to that stage. some studies have shown that a certain antiangiogenic drug when used alone didn't help people to live longer, where when the same drug used along chemotherapy it did help people to live longer than the case when the chemotherapy was used alone. The reason behind that may not be fully revealed, but there is the assumption that this due to the ineffectiveness of the chemotherapy drugs getting to the cells in the middle of the tumor, and that by turn due to the unsuitability of the tumor blood vessels when compared to the normal blood vessels and this assumption give an answer why using chemotherapy and antiangiogenic drugs together is more effective than using any of them alone, since maybe the antiangiogenic drug somehow stabilize the tumor blood vessels for a certain period of time, enabling the chemotherapy drug to reach more in the middle tumor cells and be more effective.

The idea of antiangiogenic treatment was first proposed by Folkman [15].

The idea was that by cutting off blood supply, nutrients will not reach to the tumor cells, then the tumor size will shrink or at least tumor will not grow further. His efforts have been awarded when bevacizumab, an antibody targeting vascular endothelial growth factor, was approved in 2004 as antiangiogenic therapy for the colon cancer treatment. Since then a carious antiangiogenic inhibitors, as monotherapy or in combination with additional chemotherapy drugs, have been made and developed, tested, and approved for cancer treatment. Although antiangiogenic was a big step in cancer treatment, there are still many obstacles on the way of antiangiogenic therapy to became a cancer therapy.

2.2 Dynamical system of tumor growth

The investigated model is nonlinear and represented by a system of ordinary differential equations accounting for both angiogenic stimulation and inhibition [18], the design of the model targeted the following key features:

- Being minimally parameterized.
- recognizing the distinct kinetics for angiogenic stimulation and inhibition.
- providing a time dependent carrying capacity under angiogenic control.

2.2.1 Model design

The model under investigation departs from earlier considerations of an effective vascular support (carrying capacity), for the tumor to be time-dependent in explicit way and under the control of distinct angiogenic signals for stimulation and inhibition arising from the tumor. Other models [27, 29, 2] have structured the potential dynamics of the tumor by explicitly merge a vascular dependence to tumor growth.

However the model under investigation instead included a dynamic versus a static support, by freeing support levels from a basic dependence on tumor volume, to bring the theory more towards the applications of angiogenic therapy, and by reducing number of parameters while still including unique terms for the distinct actions of stimulation and inhibition.

Model curve Generation

The presented model used numerical integration to determine the values of the model parameters, interval resolution of 0.00001 day was used to plot the curve points. About 1,000,000 runs of Monte-Carlo algorithm in each instance were used.

Model Equations

Starting from the "generalized logistic" equation:

$$\dot{V} = PV \tag{2.1}$$

Where

$$P = \lambda(1 - (\frac{V}{V_{max}})^{\alpha}) \tag{2.2}$$

Where $\dot{V}$ is the rate of change in tumor mass, and P is a decreasing factor of the tumor mass V, This relationship considers the phenomenology of tumor growth slowdown to a hypothetical limit V_{max}.

The more accurate details of the slowdown are added to the exponent α, for small value of the exponent α we have the familiar Gompert formula:

$$P = -\lambda\alpha \log(\frac{V}{V_{max}}) \tag{2.3}$$

The growth represented with Eqs. 2.1, 2.2 and 2.3 is closely describing the tumor growth slowdown, this has been observed through research and experiments for the past 100 years [32, 35].

Here we show the proposition that the Gompertzian growth may be understood in terms of a bidirectional control process where the tumor may cause vascular growth or suppression, while in turn the vasculature control the growth of the tumor through its usual nutritive function. It has been found that a variation from the Gompertz form that takes into account the above considerations present form that best explains the data and moreover provides a form for anticipating the effectiveness of antiangiogenic agents in tumor therapy.

Since tumor controls the level of the maximum carrying capacity V_{max} it is better to not consider it as fixed value, but instead replace it by a variable carrying capacity $K(t)$ where this variable depend on the rate change of $K(\dot{K})$ on K, V and t as follows:

$$\dot{V} = -\lambda_1 V \log(\frac{V}{K}),\ \dot{K} = f(K, V, t) \tag{2.4}$$

Where the variable carrying capacity K represents the effective vascular support subject to the tumor and reflected by the potential tumor size subjected to it. This definition ignores the microcirculation and account only for the effective tumor sustenance. It follow from the last equation that the value of K equal that one of V when it is just adequate to support the tumor, greater than V for growing tumor, and less than V for regressing tumor. to write an explicit form for *f(K,V,t)*, We need to account for the biological processes controlling the effective vascular compartment size, which include stimulation and inhibition signals from the tumor cells, intrinsic loss rate and inhibition due to administered drugs.

An explicit form for *f(K, V,t)* motivated with that effects can then be written as:

$$f(K,V,t) = -\lambda_2 K + bS(V,K) - dI(V,K) - eKg(t) \tag{2.5}$$

The first term stands for the functional vasculature spontaneous loss, the second term represents the stimulation of the tumor caused by vasculature, the third term is for the endogenous inhibition of previously generated vasculature and the last term reflects the tumor vasculature inhibition due to the administered drug, considered to be proportional to K and depends on the concentration *g(t),* as usually done on chemotherapy models [33]. Under the usual pharmacokinetic assumptions, the expression for *g(t)* is:

$$g(t) = \int_0^t c(t') \exp(-clr(t-t'))\, dt' \tag{2.6}$$

Here *c(t′)* represents the concentration of the administered inhibitor and *clr* for the clearance rate. After writing the form for *g(t)* in Eq. 2.5 we still need forms for both *S(V,K)* and *I(V,K).* there are some arguments which lead to some restrictions on these forms, these arguments include that tumor-derived inhibitors act more systemically, on the other hand tumor-derived stimulators act more locally to the tumor individual secreting sites.

After detailed derivation and explanation represented in [18], The final form for the expression for $\dot{K}$ in Eqs. 2.4 and 2.5 is:

$$\dot{K} = -\lambda_2 K + bV - dKV^{\frac{2}{3}} - eKg(t) \tag{2.7}$$

By writing this equation we complete the model, since Eqs. 2.4, 2.5, 2.6 and 2.7 represents the complete model formulation for control of tumor growth under the actions of angiogenic stimulation and inhibition.

2.3 Treatment Response

The effects of the three angiogenic inhibitors endostatin, angiostatin, and TNP-470 on the dynamics of the tumor growth were investigated experimentally and theoretically. The analysis done in [18] propose a ranking of the relative effectiveness of the three inhibitors. Moreover the existence of limitation the tumor size was revealed under the angiogenic control. The control of the three inhibitors and their treatment data, showing the effects of systemic administration of antiangiogenic agents on the growth the tumor through modulation of stimulation and inhibition balance, will be discussed in this section. Three main experiments have been done in [18], the first experiment was to test the effectiveness of the three different inhibitors relative to each other when they are given as treatment with similar dose and on the same initial conditions. Treatment regimens were 20 mg/kg/day for angiostatin, 20 and 4 mg/kg/day for endostatin, and 30 mg/kg/q.o.d.[2] for TNP-470. The measures for the tumor size were on day 0, day 4, and every third after that. Control of the tumor

[2]The abbreviation q.o.d. means every second day.

growth has been seen in the treatment regimens of 20 mg/kg/day of endostatin or angiostatin. Combination of 20 mg/kg/day for each of endostatin and angiostatin contrl the growth as well with better results. As well full regression were observed after the treatment. On the other hand, 4 mg/kg/day of endostatin or 30 mg/kg/q.o.d. did not control the tumor growth.

The observations of the results for endostatin 4 mg/kg/day and for the combination of the angiostatin and endostatin each, support the assumption that these agents act linearly and together have additive action on the vasculature. The comparative speed of the vascular response versus the tumor response to the inhibitors raises the question whether some of the potency of dosing is wasted via unproductively oscillating the vasculature over the period of treatment. In the second experiment, TNP-470 delivered at 30 mg/kg/q.o.d. was tested versus continuous delivery at the same integrated dose, it has been shown that in the first case the tumor volume is predicted to be 1840 mm^3at day 13 versus 1300 mm^3in the second case. Detailed analysis and data are represented in [18] here just the needed results for the thesis will be presented.

Additionally to the comparisons and quantification of each inhibitors effectiveness, the analysis done in [18] demonstrated a principle of tumor growth control the qualitative features of which exceed the details of the treatment. Tumor growth deceleration with size has been shown as predicted. This happen under sufficient treatment, and even naturally in some cases. Tumor size converges to a limit point relative to the available vascular support. Where the available vascular support is relevant to the final offsetting of vascular simulation by a more rapidly increasing level of vascular inhibition coming from the tumor. The administered angiogenic agents act on tumor to reach a lower final point. Although the predicted naturally occurring tumor final size may be so large to be compatible with the host viability, Antiangiogenic therapy provide the probability of reducing the tumor final set point to a clinically tolerable level. This tumor level is reached due to the balance happens between the stimulator and the inhibitor, tumor in that state would be dormant yet vascularized. simulations and graphs showing the tumor size behavior and conversion will be presented in the fourth chapter of the thesis.

2.4 Postvascular Dormancy

Extrapolating both the TNP-470 (30 mg/kg/q.o.d.) treatment regimen as well a theoretical angiostatin (14 mg/kg/day) regimen based on the data from the angiostatin (20 mg/kg/day). After the treatment It has seen that a fixed final tumor size is the expected results of the continuous treatment in each case, where the influences of the stimulation agents as well as the inhibition ones comes into balance. These final tumor size is not dependent on the initial size on the start of the treatment. More specifically, there is a monotonic descent or ascent to the same final tumor set point, or volume, approximately of 12300 mm^3 whether the treatment started at a volume smaller, larger, or the same as that value. The calculated angiostatin regimen (14 mg/kg/day) tend as well to

approach a fixed final size (240) also independent from the initial volume.

The results show the tendency of tumors growth in each case to slowdown with possible approach to a final tumor set point asymptotically. This may be interpreted in terms of the net influence of the angiogenic agent upon the tumor becoming more inhibitory over time, independently of the specific details of the tumor cells. At the end, naturally occuring tumor set points mostly occur too late in patients to prevents morality and morbidity, where the advantage of the antiangiogenic therapy may appear in its ability to create set point at small or even vanishing tumor sizes.

It has been developed a quantitative theory of the growth of the tumor and its treatment response under angiogenic development and inhibitor control. the developed theory is clinically implantable, offered a ranking of angiogenic inhibitors and showed a trend to better treatment response for more continuous dosing. The model discussed in this chapter will be the model to design the feedback control in this thesis.

Chapter 3

Closed-loop control of tumor growth

The model considered here to design the control law is a tumor growth model accounting for both angiogenic simulation and inhibition, the closed-loop control law presented in [9] is here discussed, the aim of such control law is the reduction of the the tumor volume by means of antiangiogenic administration. The classic feedback linearization theory is used here, where the feedback is designed on the basis of a state observer for nonlinear system. Thanks to the special properties of the tumor growth model that guarantee the separability principle of the control algorithms of the estimation and the feedback control, we can set independently the control and the observer parameters. Results and sensitivity analysis will be discussed as well, where the observer shows noticeable level of robustness with a wide range of different initial state estimations.

In this chapter, it is discussed the closed loop control design exploiting the tumor growth model. The data of the tumor volume were assumed to be measured continuously, which is not applicable or practical due to the cost of the measurements, the next chapter will discuss the case of the control design taking into account that, the measurements are available only after certain period of time.

3.1 Control by means of antiangiogenic administration

Antiangiogenic therapy proposed first by Folkman [15], is a relatively new cancer treatment, supported after that by many findings on the main principles regulating tumor angiogenesis [25], moreover it has been discussed in several experimental and theoretical studies. Antiangiogenic therapy aim is the inhibition the development of the vascular network which is necessary in the vascular phase to support the tumor growth, in this by turn provide a way to control

the growth of the heterogeneous unconstrained tumor population through the control of the homogeneous and constrained tumor population of the endothelial cells [10]. Tumors have the ability to develop resistance to the classical chemotherapy mainly due to the rapidity of tumor cells in developing new resistant phenotypes. Since antiangiogenic drugs has an indirect action on the tumor cells, the effectiveness of this therapy should not be impaired by the ability of the tumor cells to develop resistant phenotypic variants, as the effectiveness of the antiangiogenic treatment on the control of experimental tumors has been demonstrated [22]. Additional advantage of the antiangiogenic therapy is that it has limited side effects with respect to the conventional chemotherapy and radiotherapy.

3.2 The tumor growth mathematical model

The mathematical model under investigation [18] and its derivation have been presented in the second chapter of this thesis but, in this section, the model will be written in simpler form as it is written in [9], the reason of this simplification is because the notations of the model will be used in the next section for presenting the control algorithm and the theorem that the separability principle holds true for the considered model.

The model is given by the following system of Ordinary Differential Equations

$$\dot{x}_1 = -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \tag{3.1}$$

$$\dot{x}_2 = bx_1 - \left(\mu + dx_1^{\frac{2}{3}}\right) x_2 - cx_2x_3 \tag{3.2}$$

where $x_1$and $x_2$denote the tumor volume and the carrying capacity of the vasculature, respectively. λdenoting the tumor growth rate. In the second equation the first term represents the stimulation capacity of the tumor upon the inducible vasculature (bx_1), the second term represents the spontaneous loss (μx_2)and the tumor-dependent endogenous inhibition ($dx_1^{\frac{2}{3}}x_2$)of the previously generated vasculature; where the third term represents the vasculature inhibitory action preformed by drug administration (cx_2x_3)with $x_3$represents the serum level of the administrated inhibitor. μdenoting the spontaneous vascular rate. According to [18], without loss of generality, μwill be set equal to zero in the following.

Being the antiangiogenic drug not directly administered in vein, a further compartment is considered to account for drug diffusion, as follows

$$x_3(t) = \int_0^t e^{-\eta(t-t')} u(t')dt' \tag{3.3}$$

with u being the actual control law and η being the diffusion rate into serum. The system represented by Eqs. (3.1), (3.2) and (3.3) can be written in the following compact form

$$\begin{cases} \dot{x}_1 = -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ \dot{x}_2 = bx_1 - dx_1^{2/3}x_2 - cx_2x_3 \\ \dot{x}_3 = -\eta x_3 + u \end{cases} \tag{3.4}$$

In the following, system (3.4) will be also referred to as

$$\dot{x} = f(x) + g(x)u \tag{3.5}$$

with $f : \mathbb{R}^3 \mapsto \mathbb{R}^3$ and $g : \mathbb{R}^3 \mapsto \mathbb{R}^{3\times 1}$ defined by

$$f(x) = \begin{bmatrix} -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ bx_1 - dx_1^{\frac{2}{3}}x_2 - cx_2x_3 \\ -\eta x_3 \end{bmatrix} \qquad g(x) = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \tag{3.6}$$

3.3 The control algorithm

The main goal of the control law is the designing of the feedback control input that stabilize the closed loop system and to allow the tumor volume (x_1) to track a desired level. Such a feedback is synthesized by exploiting only the data from the output (tumor volume), which is the available measurements from the following model

$$y = h(x), \quad h : \mathbb{R}^3 \mapsto \mathbb{R}, \quad h(x) = x_1 \tag{3.7}$$

Let r be the desired tumor volume to be tracked, smaller than the non-trivial equilibrium state coming from the uncontrolled system

$$x_{1,ss} = x_{2,ss} = (b/d)^{\frac{3}{2}} \tag{3.8}$$

The control algorithm is synthesized by exploiting the feedback linearization theory for the nonlinear system [19], where the feedback is synthesized by means of a state observer [8, 31]. To do that, consider a domain D in $\mathbb{R}^3$, where $x_1 = 0$ and $x_2 = 0$ are excluded from D. Then, the single-input single-output system has full relative degree in D, and the hypothesis for the feedback linearization is satisfied, $\forall x \in D$ we have

$$\begin{aligned} L_g h(x) = L_g L_f h(x) = 0 \\ L_g L_f^2 h(x) = -\lambda c x_1 \neq 0 \end{aligned} \tag{3.9}$$

where $L_f^k h(x)$, $k = 1, 2, ...$ denotes the Lie derivatives of order k of the function $h : \mathbb{R}^3 \mapsto \mathbb{R}$ along the vector field $f : \mathbb{R}^3 \mapsto \mathbb{R}^3$.

In fact [19], the following nonlinear map $\Theta : \mathbb{R}^3 \mapsto \mathbb{R}^3$

$$\Theta(x) = \begin{bmatrix} h(x) - r \\ L_f h(x) \\ L_f^2 h(x) \end{bmatrix} = \begin{bmatrix} x_1 - r \\ -\lambda x_1 \ln(x_1/x_2) \\ \Theta_1(x) \end{bmatrix} \tag{3.10}$$

where

$$\Theta_1(x) = \lambda^2 x_1(\ln(\frac{x_1}{x_2}))^2 + \lambda^2 x_1 \ln(\frac{x_1}{x_2}) + b\lambda\frac{x_1^2}{x_2} - \lambda d x_1^{5/3} - \lambda c x_1 x_3 \tag{3.11}$$

is a diffeomorfism in D with a Jacobian given by

$$J_\Theta = \frac{d\Theta}{dx} = \begin{bmatrix} 1 & 0 & 0 \\ -\lambda(1+\ln(x_1/x_2)) & \lambda x_1/x_2 & 0 \\ J_1 & J_2 & -\lambda c x_1 \end{bmatrix} \tag{3.12}$$

with

$$J_1(x) = \lambda^2(3\ln(\frac{x_1}{x_2}) + \ln(\frac{x_1}{x_2})^2) - \frac{5}{3}\lambda d x_1^{\frac{2}{3}} + \lambda^2 - \lambda c x_3 + \frac{2\lambda b x_1}{x_2} \tag{3.13}$$

$$J_2(x) = -\frac{\lambda^2 x_1}{x_2}(2\ln(\frac{x_1}{x_2}) + 1) - \frac{\lambda b x_1^2}{x_2^2} \tag{3.14}$$

Thus, $z = \Theta(x)$ is a state transformation and system (3.5) can be written in z-coordinates as

$$\dot{z} = A_b z + B_b[L_f^3 h(\Theta^{-1}(z)) + L_g L_f^2 h(\Theta^{-1}(z))u(t)] \tag{3.15}$$

with A_b and B_b are the brunowski matrices written as

$$A_b = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix} \quad B_b = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \tag{3.16}$$

and $L_f^3 h(x)$ is the third order Lie derivative of the scalar function h.
Since $L_g L_f^2 h(x) \neq 0$, the following state feedback control law is well defined

$$u(t) = \frac{-K_c z(t) - L_f^3 h(x(t))}{L_g L_f^2 h(x(t))} \quad z = \Theta(x) \tag{3.17}$$

and let us to write the closed loop system in z-coordinates

$$\dot{z} = (A_b + B_b K_c)z \tag{3.18}$$

The pair (A_b, B_b) is controllable, thus K_c can be designed such that the closed loop matrix will be Hurwitz. This by turn ensures that z components asymptotically converges to zero and thus will converge the first component $z_1 = x_1 - r$, which ensure the convergence of the tumor volume x_1 to the desired level r.

The drawback of the represented control law is the required complete knowledge of the state $x(t)$; which is not possible in our particular case since the carrying capacity (x_2) as well (x_3) are not directly measurable. Therefore a state

observer is must here to overcome this problem. The observer for nonlinear systems [8, 31] are exploited here, the equation for such observer is

$$\dot{\hat{x}} = f(\hat{x}) + g(\hat{x})u(t) + J_{\Theta}(\hat{x})^{-1}K_o(y(t) - h(\hat{x})) \tag{3.19}$$

with $K_o \in \mathbb{R}^{3\times 1}$is the desired observer gain, and $J_{\Theta}^{-1}$is the inverse of the Jacobian matrix defined in [18], and whose existence is ensured in D due to the full relative degree hypothesis, this implies that Θ is an observability map, and system (3.5) is drift-observable.

By applying the state observer (3.19) to design the closed loop control, the control input will be written as

$$\hat{u}(t) = \frac{K_c\hat{z}(t) - L_f^3h(\hat{x}(t))}{L_gL_f^2h(\hat{x}(t))} \quad \hat{z} = \Theta(\hat{x}) \tag{3.20}$$

Although this control law is implementable by means of only measured state variable, it would not ensure the separability principle and this for the reason that such principle does not hold true for nonlinear systems, but some cases. The following theorem [9] shows how to modify the control scheme to overcome this drawback.

Theorem 3.1. *Consider the control input*

$$u(t) = \frac{K_c\hat{z}(t) - L_f^3h(\hat{x}(t))}{H(y(t))} \quad \hat{z} = \Theta(\hat{x}) \tag{3.21}$$

with $H(y) = -\lambda cy$ and $\hat{x}(t)$is provided by

$$\dot{\hat{x}} = f(\hat{x}) + J_{\Theta}(\hat{x})^{-1}B_bH(y)u(t) + J_{\Theta}(\hat{x})^{-1}K_o(y(t) - h(\hat{x})) \tag{3.22}$$

provided that the following hypothesis holds true

H1) $L_f^3h(\Theta^{-1}(z))$ is uniformly Lipschitz in $\Theta(D)$, that is, there exists $\gamma_1$such that $\forall z, \bar{z} \in \Theta(D)$

$$\left\|L_f^3h(\Theta^{-1}(z)) - L_f^3h(\Theta^{-1}(\bar{z}))\right\| \leq \gamma_1 \left\|z - \bar{z}\right\| \tag{3.23}$$

Then, it is possible to design the gain matrix K_c in (3.21) and the observer gain K_o in (3.22) to ensure the asymptotic convergence of the observer independently of the exponential convergence of $x_1(t) \mapsto r$.

The proof of the theorem is organized in two steps. The first step is to show that it is possible to design the observer gain so that ensure the asymptotic convergence of the observer error to zero; the second step is to show how to design the control gain independently of the observer gain in order to ensure the exponential convergence of the tumor volume to the desired level. The detailed proof is presented in [9].

Remark 3.2. In case that Θ^{-1} is Lipschitz in $\Theta(D)$, that is

$$\left\|\Theta^{-1}(z) - \Theta^{-1}(\bar{z})\right\| \leq \gamma_2 \left\|z - \bar{z}\right\| \quad \forall z, \bar{z} \in \Theta(D) \tag{3.24}$$

then the observer error $e(t) = x(t) - \hat{x}(t)$ converges exponentially to zero, since

$$\|e(t)\| \leq \gamma_2 \left\|e_z(t)\right\| \mapsto 0 \tag{3.25}$$

where $e_z(t) = z(t) - \hat{z}(t)$ represents the observer error in the z-coordinates.

Chapter 4

State estimation of the tumor system

In order to validate the algorithm, simulations are carried out setting the parameters of the model to the values estimated in [18]. As discussed in Chapter 2, these estimations were based on experimental data of Lewis lung carcinoma implanted in C57BL/6 mice. The data referred to volume measurements of both untreated control tumors as well treated control tumors under a regimen with endostatin. Treatment lasts for 13 days. In first section of this chapter continuous measurements simulation which have been performed in [9] will be replicated, a similar results have been noticed even with different control parameters. The produced fitting curves showed a final tumor volume approximately 135 mm^3, the initial value of the carrying capacity has been set to 625 mm^3.

4.1 Continuous output measurements simulations

The work started by replicating the model present in [9], all the performed Simulations after setting the model parameters to the values estimated in [18] and used in [9] and represented in table 1. Figs (4.1), (4.2), (4.3) and (4.4) and table 2 (a, b and c) represent the replication of the findings of [9]. In the following simulations, matrices K_c and K_o are designed in order to ensure the eigenvalues of $A_b - K_o C_b$ and $A_b - B_b K_c$ to be equal to $0.5[-1, -2, -3]$ and $0.1[-1, -2, -3]$, respectively.

λ day^{-1}	b day^{-1}	d $day^{-1}mm^{-2}$	μ day^{-1}	c $day^{-1}(mg/kg)^{-1}$	η day^{-1}
0.192	5.85	0.00873	0	0.66	1.7

Table 4.1: Model parameters

4.1.1 Simulation results

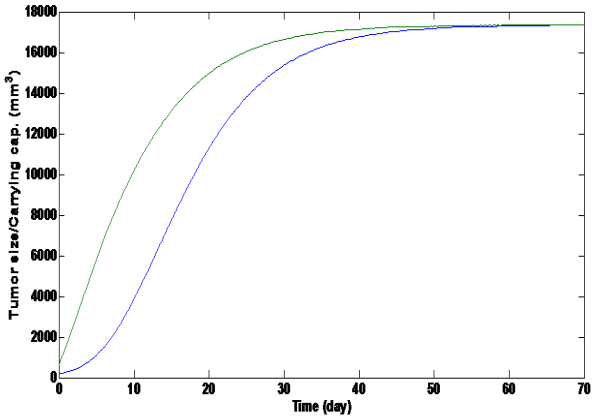

Figure 4.1: Growth of an untreated tumor and its vascular support, as fitted to the control data, the tumor and vascular growth curves are both extended to show the theoretical set point value reached, where the vascular support (green) converges with the tumor burden (blue), as a balance between angiogenic simulation and inhibition is approached

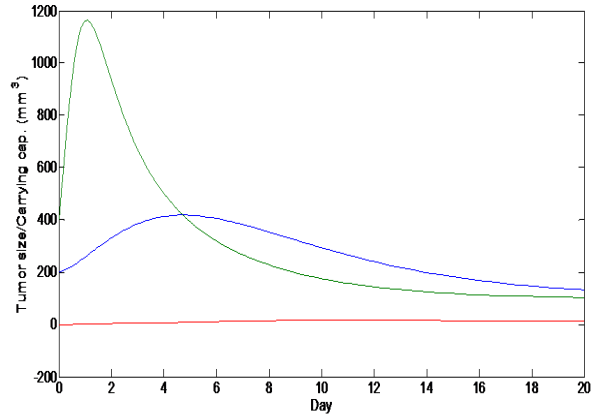

Figure 4.2: Graphical representation of the real tumor volume and real carrying capacity under the action of the closed loop control law

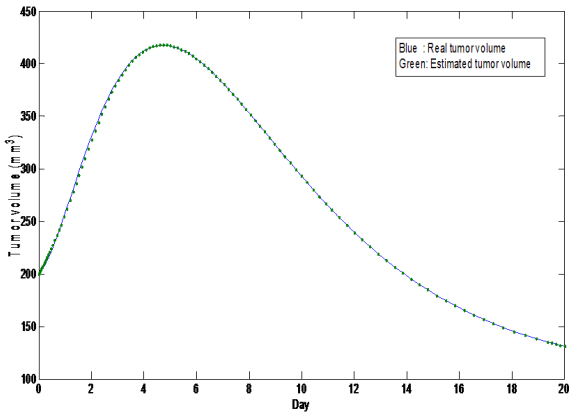

Figure 4.3: Graphical comparison of the real and estimated tumor volume under the action of the closed loop control law

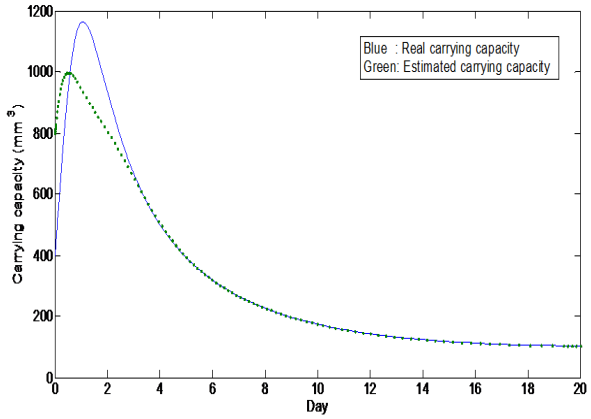

Figure 4.4: Graphical comparison of the real and estimated carrying capacity under the action of the closed loop control law

Accounting for different initial conditions of x_2 and its estimated value, table 4.2 (a) and table 4.2 (b) report the values of x_1 (13Δ) and m (total amount of administered drug per 13 days), respectively, and Table 4.2 (c) refers to the maximum value (out of 13 average daily delivered amounts) of m_d daily amount

of the administered drug. In each table the columns represent $\Delta x_2(0)(\%)$, where rows represent $\Delta \hat{x}_2(0)(\%)$.

	-40	-20	0	50	100	200
-40	136.4613	136.4666	136.4702	136.4746	136.4748	136.4687
-20	136.4527	136.4576	136.4609	136.4649	136.4653	136.4603
0	136.4611	136.4658	136.4690	136.4729	136.4734	136.4687
50	136.5007	136.5057	136.5091	136.5136	136.5145	136.5106
100	136.5433	136.5489	136.5529	136.5583	136.5600	136.5572
200	136.6181	136.6250	136.6301	136.6379	136.6413	136.6412

(a) Final value of tumor volume x1 (13Δ), At the end of the treatment.

	-40	-20	0	50	100	200
-40	240.7940	243.2291	245.3715	249.8904	253.6337	259.7510
-20	239.7226	242.0395	244.0746	248.3576	251.8970	257.6661
0	239.3104	241.5787	243.5695	247.7554	251.2106	256.8356
50	239.0815	241.3119	243.2684	247.3795	250.7704	256.2854
100	239.1345	241.3561	243.3050	247.4005	250.7786	256.2732
200	239.3246	241.5383	243.4810	247.5652	250.9357	256.4209

(b) Total amount of the administered anti-angiogenic drug.

	-40	-20	0	50	100	200
-40	23.0733	23.4265	23.8812	24.9383	25.9613	27.6481
-20	22.7703	23.0859	23.3701	24.1746	25.0018	26.6394
0	22.6397	22.9380	23.2063	23.7907	24.5690	26.1152
50	22.5406	22.8228	23.0761	23.6267	24.1006	25.5465
100	22.5342	22.8115	23.0603	23.6004	24.0647	25.3236
200	22.5703	22.8442	23.0897	23.6226	24.0803	25.1159

(c) Maximum average daily amount of anti-angiogenic drug.

Table 4.2: Data for continuous measurements case

4.2 Delayed output measurements simulations

This section deals with the problem of time-varying measurements delay of the output feedback control of nonlinear systems. A control law from [7] will be written and discussed in this section, that control law is made of an observer-controller cascade, where the observer is a high gain observer of the chain type, and the controller is the classic state linearizing scheme. It has been shown in [7] that under suitable conditions on the system, the observer the observer is globally exponentially convergent, additionally replacing the true state with the observer one in the control law, leads to an exponentially stabilizing feedback scheme. We will discuss as well the main limitation of the single observer which is the existence of a bound for the delay, this bound depends on the nonlinear system Lipschitz constant. the solution for this limitation will be discussed as well, which is to resort to a chain of observers which will allow to compensate any delay on the cost of more convergence time and growing realization space, while in [7] known and constant delay is discussed as well time varying delay. We will just focus on the known and constant case since this is the type of observer required for thesis, the design of such observer in the case of constant and known delay, specifically when the delay is not constant with respect to time, as it happens frequently in the applications is straightforward, not like the time-varying case which requires special attention. Therefore a classification of the delay functions with respect to the available output data will be discussed, and the design of the cascade of the elementary observers will be presented to solve the reconstruction problem. There is a class of delay function [7] for which this approach is not implementable.

4.2.1 Overview

State estimation and control for nonlinear systems with delayed output measurements is required in many areas of control systems. For that the state reconstruction in the existence of delays in time in the system equations and in the measurements is becoming more important issue every day. In this section we will discuss the extension of the classical approach for systems without delay, which based on state feedback and state estimation, to the delayed systems. Since the delay function plays an important role here, we will discuss first in the next subsection the classification of the delayed functions from the state reconstruction point of view, based on the work done in [7]. First work done in this area, of state estimation of delayed systems, was the prediction of the state evolution for stable linear systems with delays [5, 6, 34, 20, 28, 38]. With respect to this problem, after the classification, an observer of the high gain type will be discussed, such observer guarantees exponential convergence of the estimation error to zero in the existence of uniform bounded variable delays.

Many approaches for this issue have been done before,the problem common to them is the existence of a bound on the delay, which by turn depends on how system non linearity. This common problem is a big drawback, specially when this bound is not known with precision. There is an idea of a cascade of two or

more observers to achieve the state estimation convergence in the existence of constant delays, this idea was first introduced in [17, 37, 26]. The function of each observer in the chain is to predict the system state for a suitable portion of he total time.

4.2.2 Classification of the delay functions

Now the analysis of the delay functions from the available output information point of view will be done, this analysis is based on the work done in [7]. The systems under consideration have the following form

$$\dot{x}(t) = F(x(t), u(t)),\ t \geq -\Delta \tag{4.1}$$

$$\bar{y}(t) = h(x(t - \delta(t))),\ t \geq 0 \tag{4.2}$$

$$x(-\Delta) = \bar{x} \in \mathbb{R}^n \tag{4.3}$$

where $x(t) \in \mathbb{R}^n$ is the system state, $u(t) \in \mathbb{R}^p$ represents the input, and the function $F : \mathbb{R}^n \times \mathbb{R}^p \mapsto \mathbb{R}^n$ is affine in the input, i.e.

$$F(x, u) = f(x) + G(x)u = f(x) + \sum_{k=1}^{p} g_k(x)u_k \tag{4.4}$$

where $f(x)$ and $g_k(x)$ are C^∞ vector fields, $\bar{y}(t) \in \mathbb{R}$ is for the measured output available at time t, which is a delayed function of the state, $\delta(t)$ is a time varying measurement delay. The function $h : \mathbb{R}^n \to \mathbb{R}$ is C^∞. For simplicity a scalar output is assumed, but the framework can be extended to vector output functions with a certain delay on each component.

The problem for the system represented by Eqs. 4.1 and 4.2 is the reconstruction of the state at time t by using the knowledge of the input $u(\tau)$, $\tau \in [-\Delta, t]$, and the output $\bar{y}(\tau)$, $\tau \in [0, t]$, moreover the stabilization of the simultaneous system through a function of the reconstructed state.

Here $y(t) = h(x(t))$ represents the not delayed output, where $\bar{y}(t) = y(t - \delta(t))$. Here as well it is assumed that the delay is upper bounded by known value, which mean that $\delta(\mathrm{t}) \in [0, \Delta]$ where Δ is known. It is not needed to assume the previous knowledge of the function $\delta(t)$, it is only assumed that $\delta(t)$ is known at the same time t at which $\bar{y}(t)$ is available. Therefore the new information on the system at time t is the pair $(\bar{y}(t), \delta(t))$. Additionally it is needed to assume that $\delta(t)$ is continuous, although we need it to be piecewise continuous for the existence and uniqueness of the solution of a state observer in a differential form.

Note that when the function $\delta(t)$ is continuous and bounded the information flux will not be interrupted, in that at time t all the previous measurements to $y(t - \delta(t))$ are available.

Proposition 4.1. *If $\delta(t) \in [0, \Delta]$ is continuous, then at any time $t > \Delta$ the measurement $y(t-\sigma)$ is available, if $\sigma > \delta(t)$. that is, there exists $t* < t$ such that $\bar{y}(t*) = y(t-\sigma)$.*

This indicates that the measurements will be available at most after time Δ, and the information is never lost. Therefore, the continuous delay case is not too different from the continuous delay case. Specifically, any state observer designed for the constant delay case can work with the continuous delay functions by retarding the measurement $\bar{y}(t)$ with a delay $\theta(t) = \Delta - \delta(t)$, obtaining $\bar{y}(t-\theta(t)) = y(t-\Delta)$. Although this way is not always efficient, but it shows that continuous delays are not so different from continuous ones in the sense that the output information is completely available after a certain period of time. This property can be formally characterized with the notion of lossless delay functions (LDF).

Definition 4.2. A delay function $\delta(t)$ is said to be LDF if $\forall t > 0, \exists t* \geq t$ such that $\bar{y}(t*) = y(t)$.

The LDF case implies that the output data can be fully reconstructed after a certain time interval. In fact any continuous $\delta(t)$ is LDF, but not vice versa, in that not all discontinuous delay functions cause information loss. As an example for discontinuous LDF is the transmission delay over a network when there no data packets are lost but the order of packets is not maintained.

Sampled measurements can be modeled by discontinuous delay functions as originally suggested in [30]. The delay function used when the sampling interval is T can be written as $\delta(t) = mod(t, T)$.

In this case $\bar{y}$ is defined for any $t \geq 0$ by means of a piecewise constant function consisting of the last available measurements, so that $\delta(t)$ has a sawtooth shape.It is clear that delay functions that model sampling are not LDF.

This idea can be extended to the case of missing output measurements. Suppose that the measurements are available with a constant delay $\bar{\delta}$, and are lost in interval $[t_1, t_2]$, this can be modeled with a delay function $\delta(t) = \bar{\delta}$ for $t \notin [t_1, t_2)$ and $\delta(t) = t - t_1 + \bar{\delta}$ for $t \in [t_1, t_2)$. It is evident that the difficulty of estimating the state in the existence of non LDF delays depends on the frequency and amplitude of the loss of the information.

4.2.3 Single step exponential observer

In this section we will discuss the single-step observer for the system represented by Eqs. 4.1 and 4.2, as well the convergence results of the observer. It is crucial in order to design a chain of observers that the estimation error of the single-step observer is exponentially stable. Here it's presented a high-gain observer, such an observer is based on the drift observability map and has been proposed first in [4]. This observer is an exponentially convergent version of version of the observer presented in [3].

We need now to recall the definition of the Lie derivative of a C^∞ function $\lambda(x)$ with respect to the C$^\infty$ vector field $\varphi : \mathbb{R}^n \to \mathbb{R}^{n \times p}$, $L_\varphi \lambda(x) = d\lambda/dx$.

$\varphi(x)$ is a function from from $\mathbb{R}^n$ to $\mathbb{R}$. Where the symbol $L_\varphi^k \lambda(x)$ is the k- times repeated iteration of $L\varphi\lambda(x)$. For a C^∞matrix function $G : \mathbb{R}^n \to \mathbb{R}^{n\times p}$, the Lie derivative $L_G\lambda(x) = \left[L_{g1}\lambda(x).....L_f^{n-1}h(x)\right]$ is a function from $\mathbb{R}^n$ to $\mathbb{R}^p$.

For system (4.4) the drift observability map $z = \Phi(x)$ is defined as

$$z = \Phi(x) = \left[h(x)\, L_f h(x).....L_f^{n-1}h(x)\right]^T \tag{4.5}$$

Definition 4.3. The system (4.1) is said to be globally drift observable if the function $z = \Phi(x)$ is a diffeomorphism in all $\mathbb{R}^n$. While a system is said to be globally uniformly Lipschitz drift observable which is abbreviated as (GULDO) if it is globally drift observable and the maps Φ and $\Phi^{-1}$are uniformly Lipschitz.

When the system is globally drift observable, the map $z = \Phi(x)$ defines a global change of coordinates, where the Jacobian

$$Q(x) = \frac{d\Phi(x)}{dx} \tag{4.6}$$

is nonsingular for all $x \in \mathbb{R}^n$.

Definition 4.4. The triple $(f(x), G(x), h(x))$ is said to have observation relative degree r in a set $\Omega \subseteq \mathbb{R}^n$ if

$$L_G L_f^k h(x) = 0,\ k = 0, ..., r-2\ \forall x \in \Omega \tag{4.7}$$

$$L_G L_f^{r-1} h(x) \neq 0,\ for\, some\, x \in \Omega \tag{4.8}$$

If $\Omega = \mathbb{R}^n$ then the triple is said to have observation relative degree r.

If the system (4.1) is globally drift observable and the observation relative degree in $\mathbb{R}^n$ is n, then the following function is well defined

$$p(z,u) = (L_f^n h(x) + L_G L_f^{n-1} h(x))u)_{x=\Phi^{-1}(z)} \tag{4.9}$$

and with similarities to the non delayed nonlinear case [31], the z-coordinates representation is

$$\dot{z}(t) = A_b z(t) + B_b p(z(t), u(t)),\ t \geq -\Delta \tag{4.10}$$

$$\bar{y}(t) = C_b z(t - \delta(t)) \qquad t \geq 0 \tag{4.11}$$

with $z(-\Delta) = \Phi(\bar{x})$.

To summarize, for the construction of the proposed observer, the following hypothesis are needed.

- The nonlinear delay free system (f, G, h) is GULDO.

- The function $p(z,u)$ defined in (4.9) is globally uniformly Lipschitz in z, additionally the the Lipschitz coefficient $\gamma_p$is a non decreasing function of $\|u\|$.
- The triple (f,G,h) has uniformly observation degree at least equal to n.

The observer proposed in [7] is, for $t>0$,

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + G(\hat{x}(t))u(t) + Q^{-1}(\hat{x}(t))K_\delta(t)[\bar{y}(t) - h(\hat{x}(t-\delta(t)))] \quad (4.12)$$

where $\hat{x}(\tau) = \chi(\tau)$, $\tau \in [-\Delta, 0]$, $K_\delta(t) = e^{-\eta\delta(t)}K_o$.

$\chi : [-\Delta, 0] \to \mathbb{R}^n$ is a vector continuous and bounded function to initiate the observer. The vector $K_o \in \mathbb{R}^n$ and the constant η is a desired exponential decay rate for the observation error .

4.2.4 Simulation results

The next step was to simulate the observer for the nonlinear system [7], in the case that the output is not always available, or in other words when there is a delay in the output measurements. Simulations and robustness analysis were carried out for different values of the delay (0.5, 1 and 1.5) days. Figs. (4.5), (4.6), (4.7) and (4.8) and Tables. (4.3), (4.4) and (4.4) represent the results for the delayed measured output equal to (0.5) day. Where Figs. (4.9), (4.10), (4.11) and (4.12) and Tables. (4.6), (4.7) and (4.8) represent the results for the delayed measured output equal to (1) day, and Figs. (4.13), (4.14), (4.15) and (4.16) and Tables. (4.9), (4.10) and (4.11) represent the results for the delayed measured output equal to (1.5) day. In the following Simulations, Matrices K_c and K_o are designed in order to ensure the eigenvalues of $A_b - K_o C_b$ and $A_b - B_b K_c$ to be equal to $0.4[-1,-2,-3]$ and $0.1[-1,-2,-3]$, respectively.

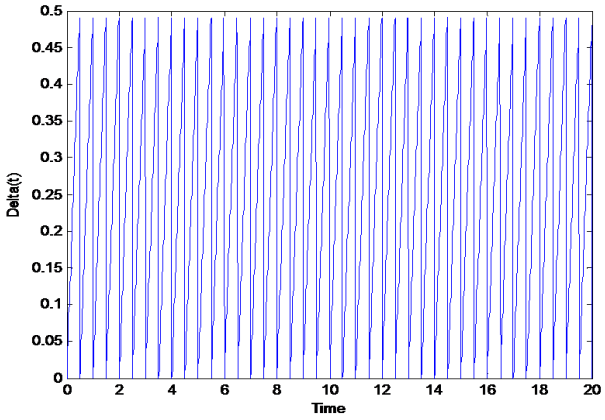

Figure 4.5: Discontinuous delay function represent the delay of the measured output (Delay=0.5 day)

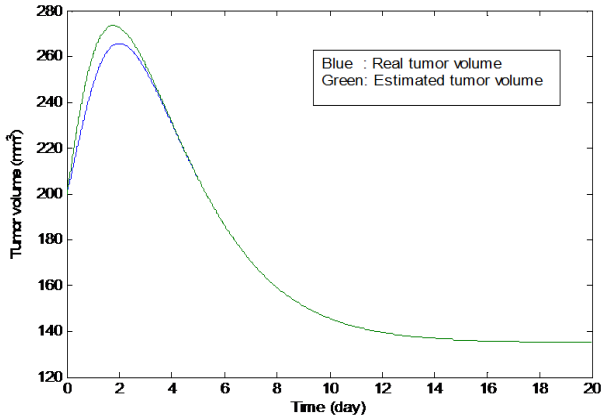

Figure 4.6: Graphical comparison of the real and estimated tumor volume under the action of the closed loop control law (in the case of delayed measure of output=0.5 day)

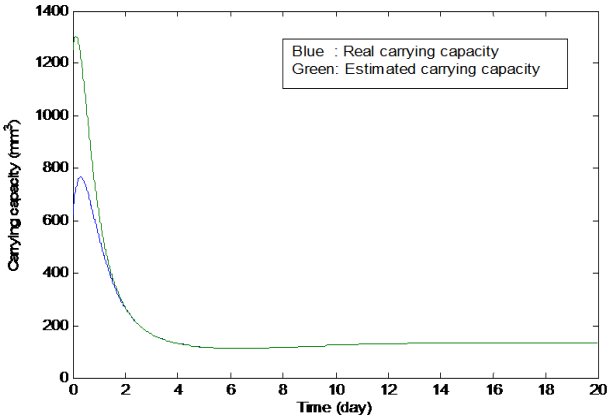

Figure 4.7: Graphical comparison of the real and estimated carrying capacity under the action of the closed loop control law (in the case of delayed measure of output=0.5 day)

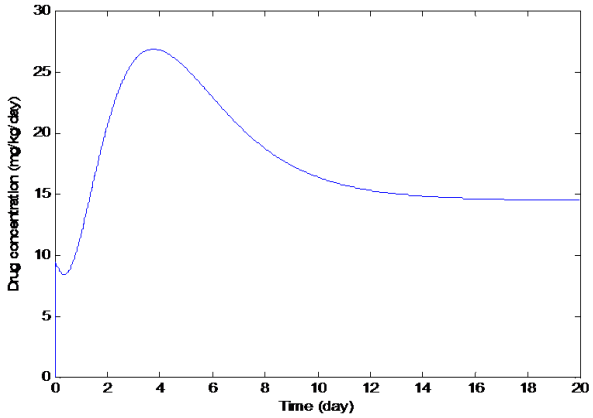

Figure 4.8: Time behavior of the administered drug concentration(in the case of delayed measure of output=0.5 day)

	-40	-20	0	50	100	200
-40	138.4106	138.6609	138.8843	139.3644	139.7707	140.4498
-20	138.0575	138.2901	138.4975	138.9423	139.3180	139.9448
0	137.8722	138.0980	138.2991	138.7302	139.0940	139.7007
50	137.6483	137.8695	138.0665	138.4887	138.8450	139.4391
100	137.5325	137.7534	137.9502	138.3720	138.7282	139.3224
200	137.3805	137.6020	137.7994	138.2228	138.5806	139.1779

Table 4.3: Final value of tumor volume x1 (13Δ), At the end of the treatment(in the case of delayed measure of output=0.5 day)

	-40	-20	0	50	100	200
-40	245.8465	248.3188	250.4788	254.9837	258.6596	264.5513
-20	244.5529	246.9222	248.9905	253.3006	256.8156	262.4480
0	244.1626	246.4903	248.5216	252.7536	256.2041	261.7327
50	244.2331	246.5297	248.5337	252.7087	256.1132	261.5694
100	244.6186	246.9087	248.9072	253.0718	256.4687	261.9148
200	245.3655	247.6492	249.6426	253.7983	257.1897	262.6302

Table 4.4: Total amount of the administered anti-angiogenic drug(in the case of delayed measure of output=0.5 day)

	-40	-20	0	50	100	200
-40	26.1311	26.4923	26.8012	27.4256	27.9153	28.6639
-20	25.7020	26.0628	26.3716	26.9965	27.4876	28.2404
0	25.7699	25.9521	26.2305	26.8573	27.3502	28.1063
50	26.1493	26.3284	26.4777	26.9017	27.3978	28.1587
100	26.5400	26.7136	26.8582	27.1399	27.5815	28.3440
200	27.2108	27.3734	27.5084	27.7703	27.9655	28.7172

Table 4.5: Maximum average daily amount of anti-angiogenic drug(in the case of delayed measure of output=0.5 day)

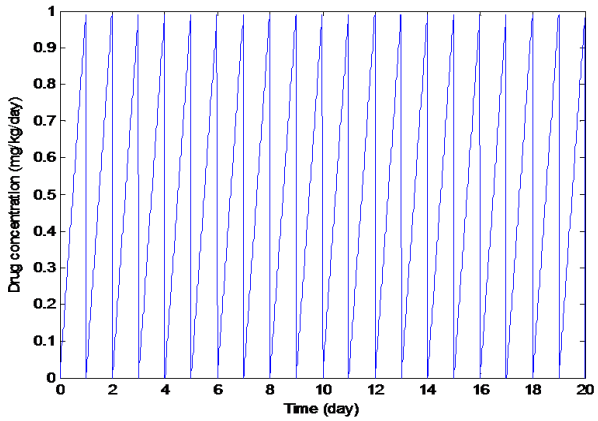

Figure 4.9: Discontinuous delay function represent the delay of the measured output (Delay=1 day)

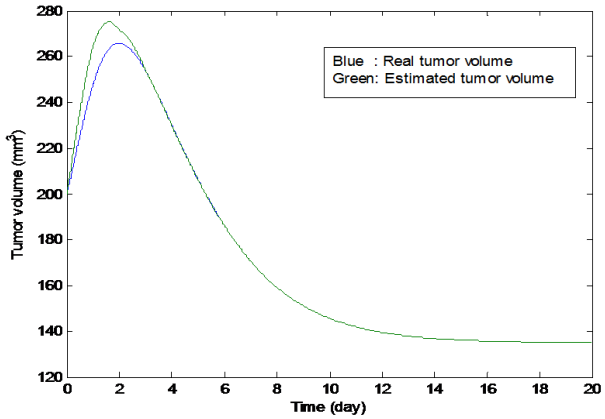

Figure 4.10: Graphical comparison of the real and estimated tumor volume under the action of the closed loop control law (in the case of delayed measure of output=1 day)

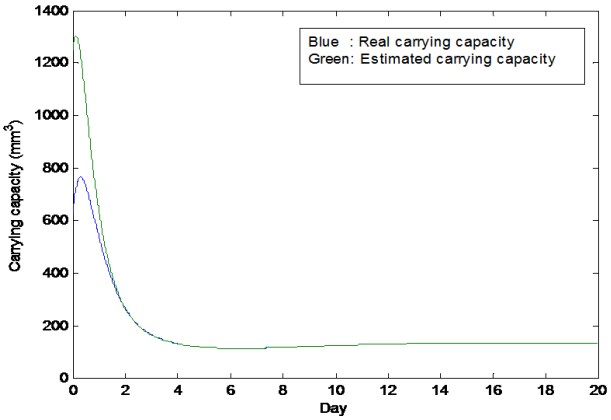

Figure 4.11: Graphical comparison of the real and estimated carrying capacity under the action of the closed loop control law (in the case of delayed measure of output=1 day)

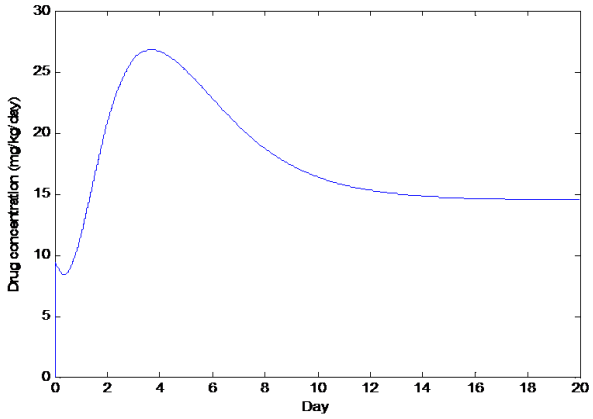

Figure 4.12: Time behavior of the administered drug concentration (in the case of delayed measure of output=1 day)

	-40	-20	0	50	100	200
-40	138.4106	138.6534	138.8699	139.3351	139.7287	140.3866
-20	138.0649	138.2901	138.4907	138.9208	139.2839	139.8897
0	137.8865	138.1048	138.2991	138.7154	139.0666	139.6521
50	137.6783	137.8917	138.0817	138.4887	138.8321	139.4046
100	137.5762	137.7892	137.9788	138.3852	138.7282	139.3005
200	137.4471	137.6605	137.8505	138.2582	138.6027	139.1779

Table 4.6: Final value of tumor volume x1 (13Δ), At the end of the treatment (in the case of delayed measure of output=1 day)

	-40	-20	0	50	100	200
-40	245.8465	248.3482	250.5363	255.1068	258.8422	264.8388
-20	244.5307	246.9222	249.0124	253.3754	256.9398	262.6613
0	244.1260	246.4718	248.5216	252.7994	256.2939	261.9036
50	244.1694	246.4788	248.4967	252.7087	256.1504	261.6777
100	244.5322	246.8318	248.8417	253.0382	256.4687	261.9808
200	245.2403	247.5291	249.5303	253.7110	257.1308	262.6302

Table 4.7: Total amount of the administered anti-angiogenic drug(in the case of delayed measure of output=1 day)

	-40	-20	0	50	100	200
-40	26.1311	26.5413	26.8917	27.5987	28.1520	28.9946
-20	25.6839	26.0628	26.4137	27.1228	27.6791	28.5294
0	25.7811	25.9576	26.2305	26.9431	27.5025	28.3585
50	26.1722	26.3463	26.4905	26.9017	27.4672	28.3328
100	26.5777	26.7460	26.8852	27.1533	27.5815	28.4523
200	27.2849	27.4409	27.5693	27.8151	27.9948	28.7172

Table 4.8: Maximum average daily amount of anti-angiogenic drug (in the case of delayed measure of output=1 day)

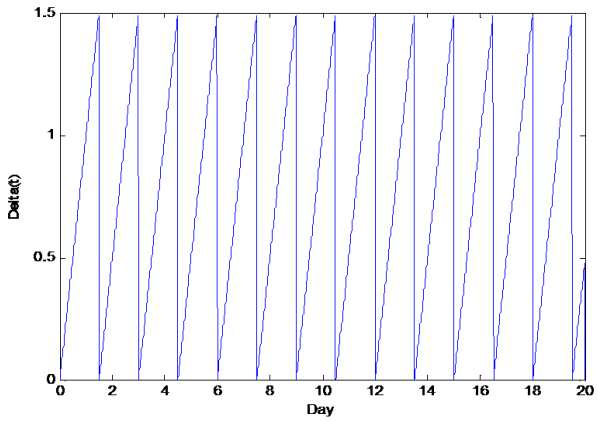

Figure 4.13: Discontinuous delay function represent the delay of the measured output (Delay=1.5 day)

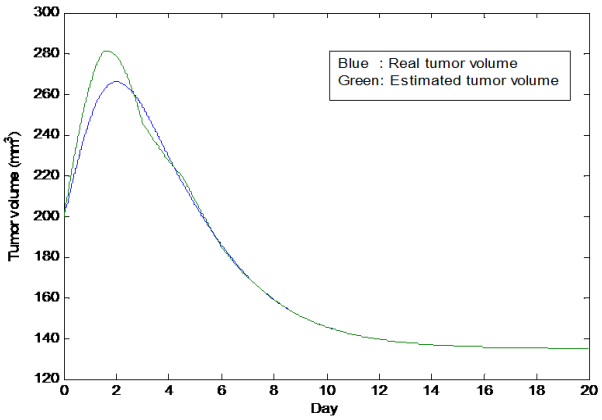

Figure 4.14: Graphical comparison of the real and estimated tumor volume under the action of the closed loop control law (in the case of delayed measure of output=1.5 day)

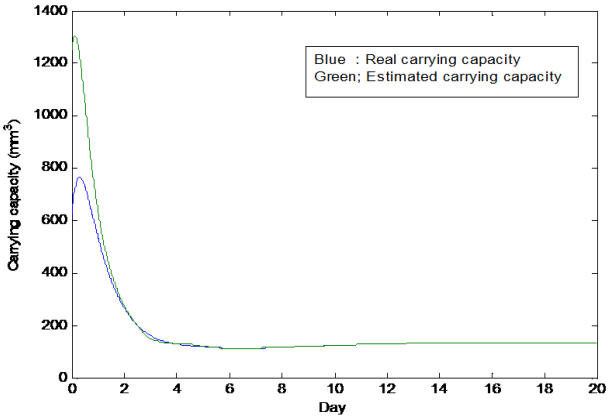

Figure 4.15: Graphical comparison of the real and estimated carrying capacity under the action of the closed loop control law (in the case of delayed measure of output=1.5 day)

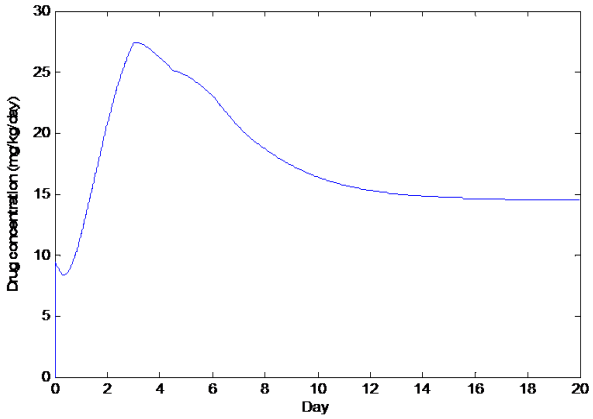

Figure 4.16: Time behavior of the administered drug concentration (in the case of delayed measure of output=1.5 day)

	-40	-20	0	50	100	200
-40	138.4106	138.6556	138.8733	139.3390	139.7310	140.3825
-20	138.0623	138.2901	138.4923	138.9238	139.2862	139.8872
0	137.8817	138.1029	138.2991	138.7174	139.0683	139.6499
50	137.6687	137.8858	138.0783	138.4887	138.8329	139.4030
100	137.5626	137.7797	137.9724	138.3834	138.7282	139.2997
200	137.4271	137.6452	137.8389	138.2529	138.6008	139.1779

Table 4.9: Final value of tumor volume x1 (13Δ), At the end of the treatment (in the case of delayed measure of output=1.5 day)

	-40	-20	0	50	100	200
-40	245.8465	248.3520	250.5499	255.1593	258.9435	265.0460
-20	244.5390	246.9222	249.0119	253.3925	256.9886	262.7900
0	244.1504	246.4796	248.5216	252.8027	256.3179	261.9911
50	244.2460	246.5226	248.5194	252.7087	256.1519	261.7154
100	244.6665	246.9206	248.8987	253.0519	256.4687	261.9958
200	245.4935	247.7162	249.6681	253.7711	257.1518	262.6302

Table 4.10: Total amount of the administered anti-angiogenic drug (in the case of delayed measure of output=1.5 day)

	-40	-20	0	50	100	200
-40	26.1311	26.7470	27.2772	28.3587	29.2160	30.5413
-20	25.7967	26.0628	26.5909	27.6699	28.5277	29.8589
0	25.9947	26.0566	26.2305	27.3137	28.1756	29.5150
50	26.6086	26.6627	26.7030	26.9017	27.7758	29.1350
100	27.2089	27.2529	27.2837	27.3292	27.5815	28.9559
200	28.2476	28.2740	28.2880	28.2957	28.2854	28.7172

Table 4.11: Maximum average daily amount of anti-angiogenic drug (in the case of delayed measure of output=1.5 day)

4.3 Non-continuous input

As a forward step towards understanding of the realistic model, different simulations have been carried out in the case of the non continuous inputs, firstly impulses considered which could be representation for the physical situation where the drug is given to the patient as shot Injections for instantaneous times, secondly steps were considered as input, which could be the case if the drug is given to the patient as continuous injection for certain amount of time. These kind of simulations can be done for different values of the injection time, for example in the case of Impulses, it can be done for different frequencies of the drug shots, here only considered the case where the frequency is one shot/day. and for the case of steps, we considered the case of continuous injection for every second day. Simulations can be done for different values of frequency and step period, to get a general overview on the convergence in each case and then these results can be generalized. The values of K_c and K_o are kept the same for all the cases of inputs for better comparison. Figs. (4.17) and (4.18) represent the case of Impulses input, where Figs. (4.19) and (4.20) represent the case of steps input.

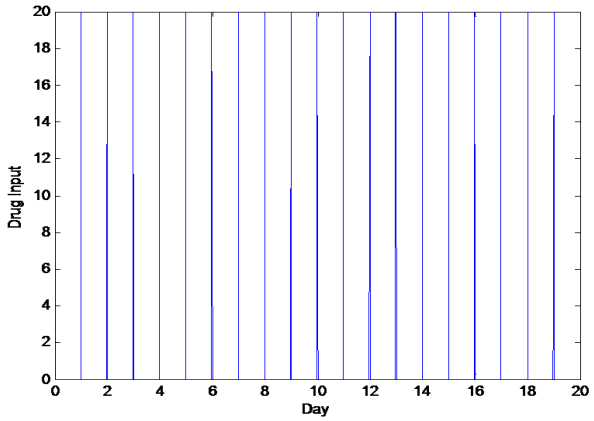

Figure 4.17: Time behavior of the administered drug concentration in case of impulses

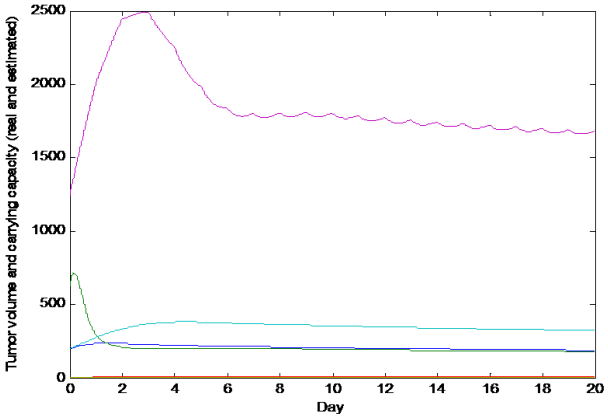

Figure 4.18: Real tumor volume(blue), and real carrying capacity(green) and their estimated values

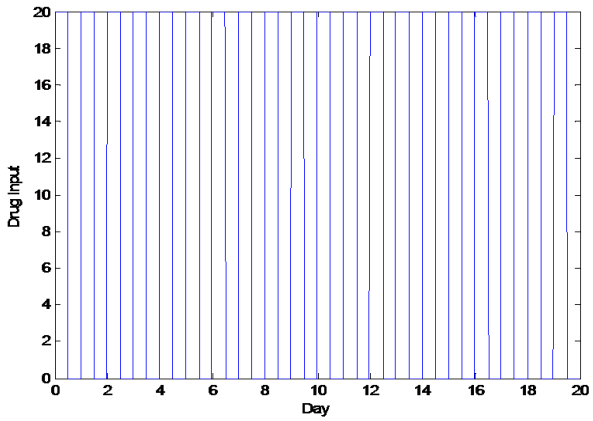

Figure 4.19: Time behavior of the administered drug concentration in case of steps

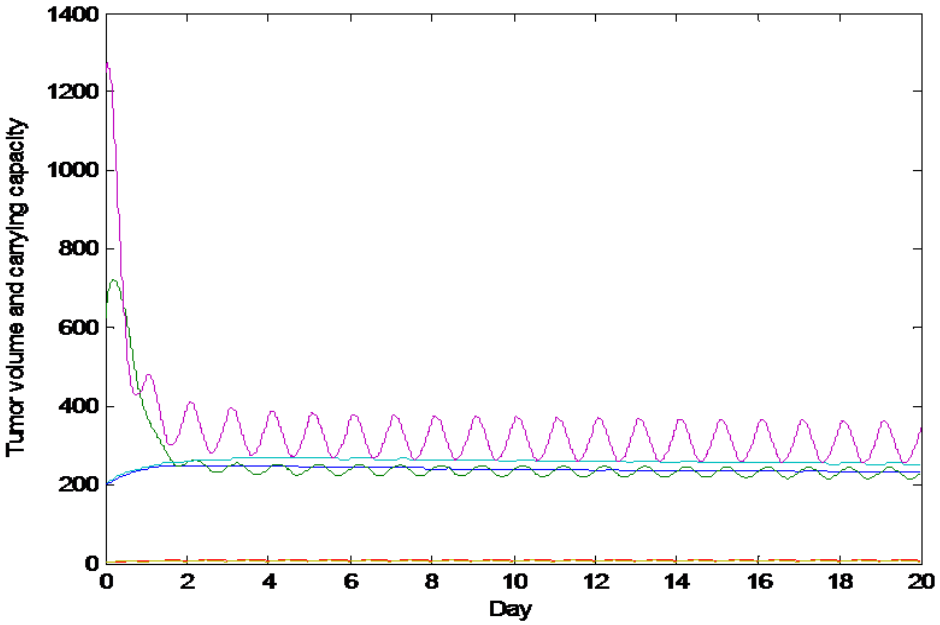

Figure 4.20: Real tumor volume(blue), and real carrying capacity(green) and their estimated values

Chapter 5

Conclusion

The work done in this thesis exploited a mathematical model of the tumor growth. The model accounts for the angiogenic inhibition and stimulation, additionally it has been used many times to simulate and predict the effects of antiangiogenic drug delivery. Based on the feedback linearization theory, the control law makes use of an observer for nonlinear systems with delay output measurements in order to design the model-based control by means of only available measurements. This work presents a control law with the aim to reduce the tumor volume.

The thesis deals with the problem of time-varying measurements delay of the output feedback control of nonlinear systems. A control law is formulated and discussed , that control law is made of an observer-controller cascade, where the observer is a high gain observer of the chain type, and the controller is the classic state linearizing scheme. It has been shown in the literature that under suitable conditions on the system, the observer is globally exponentially convergent, additionally replacing the true state with the observer one in the control law leads to an exponentially stabilizing feedback scheme. We discussed as well the main limitation of the single observer which is the existence of a delay bound that depends on the nonlinear system Lipschitz constant. In the particular case of our thesis, this limitations didn't affect us since we just focused our attention on the known and constant delay and this is the type of observer required for the thesis. The design of such observer in the case of constant and known delay, as it happens frequently in the applications is straightforward, not like the time-varying case which requires special attention. Therefore a classification of the delay functions with respect to the available output data is discussed and the design of the cascade of the elementary observers is presented to solve the reconstruction problem.

Theoretical results from the literature ensure that the control gain of the regulator can be set independently of the observer gain due to the special structural properties of the tumor growth model and this has been facilitated the control design. Numerical simulations showed the robustness of the control law, despite of the delayed measurements and the wide range of variation of the es-

timated carrying capacity. For better understanding of the practical treatment, different simulations have been carried out in the case of the non continuous inputs. This includes impulses which physically represents the situation where the drug is given to the patient as shot injections for instantaneous times. As well steps were considered as input, which could be the case if the drug is given to the patient as continuous injection for certain amount of time. In the case of impulses, we considered the situation where the frequency is one shot/day and in the case of steps, simulations can be done for different values of frequency and step period, to get a general overview on the convergence in each case and then these results can be generalized.

Bibliography

[1] Wadih Arap, Renata Pasqualini, and Erkki Ruoslahti. Chemotherapy targeted to tumor vasculature. *Current opinion in oncology*, 10(6):560–565, 1998.

[2] D Balding and DLS McElwain. A mathematical model of tumour-induced capillary growth. *Journal of theoretical biology*, 114(1):53–73, 1985.

[3] Filippo Cacace, Alfredo Germani, and Costanzo Manes. An observer for a class of nonlinear systems with time varying observation delay. *Systems & Control Letters*, 59(5):305–312, 2010.

[4] Filippo Cacace, Alfredo Germani, and Costanzo Manes. An exponential observer with delay-dependent gain for a class of nonlinear systems with time-varying measurement delay. In *CDC*, pages 2364–2369, 2012.

[5] Filippo Cacace, Alfredo Germani, and Costanzo Manes. A chain approach for state observation of a class of mimo nonlinear systems with time-varying output delays. In *Proceedings of 11th IFAC Workshop on Time-Delay Systems, Grenoble*, 2013.

[6] Filippo Cacace, Alfredo Germani, and Costanzo Manes. A chain observer for nonlinear systems with multiple time-varying measurement delays. *SIAM Journal on Control and Optimization*, 52(3):1862–1885, 2014.

[7] Filippo Cacace, Alfredo Germani, and Costanzo Manes. State estimation and control of nonlinear systems with large and variable measurement delays. In Michael Malisoff, Pierdomenico Pepe, Frederic Mazenc, and Iasson Karafyllis, editors, *Recent Results on Nonlinear Delay Control Systems*, volume 4 of *Advances in Delays and Dynamics*, pages 95–112. Springer International Publishing, 2016.

[8] G. CICCARELLA, M. DALLA MORA, and A. GERMANI. A luenberger-like observer for nonlinear systems. *International Journal of Control*, 57(3):537–556, 1993.

[9] Valerio Cusimano, Pasquale Palumbo, and Federico Papa. Closed-loop control of tumor growth by means of anti-angiogenic administration. In

accepted for presentation to IEEE Conference on Decision and Control, Dec 2015, Osaka, Japan, 2015.

[10] Juliana Denekamp. Vascular attack as a therapeutic strategy for cancer. *Cancer and Metastasis Reviews*, 9(3):267–282, 1990.

[11] Juliana Denekamp. Vascular attack as a therapeutic strategy for cancer. *Cancer and metastasis reviews*, 9(3):267–282, 1990.

[12] Dániel A Drexler, Levente Kovács, Johanna Sápi, István Harmati, and Zoltán Benyó. Model-based analysis and synthesis of tumor growth under angiogenic inhibition: a case study. In *Proc. of the 18th World Congress of the International Federation of Automatic Control, Milano, Italy*, pages 3753–3758, 2011.

[13] Ayla Ergun, Kevin Camphausen, and Lawrence M Wein. Optimal scheduling of radiotherapy and angiogenic inhibitors. *Bulletin of mathematical biology*, 65(3):407–424, 2003.

[14] Jeffrey S Flier, Lisa H Underhill, and Judah Folkman. Clinical applications of research on angiogenesis. *New England Journal of Medicine*, 333(26):1757–1763, 1995.

[15] J Folkman. Anti-angiogenesis: new concept for therapy of solid tumors. 175(3), 1972.

[16] Judah Folkman, Philip Hahnfeldt, and Lynn Hlatky. The logic of anti-angiogenic gene therapy. *Cold Spring Harbor Monograph Archive*, 36:527–543, 1999.

[17] Alfredo Germani, Costanzo Manes, and Pierdomenico Pepe. A new approach to state observation of nonlinear systems with delayed output. *Automatic Control, IEEE Transactions on*, 47(1):96–101, 2002.

[18] Philip Hahnfeldt, Dipak Panigrahy, Judah Folkman, and Lynn Hlatky. Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response, and postvascular dormancy. *Cancer Research*, 59(19):4770–4775, 1999.

[19] A. Isidori. *Nonlinear Control Systems*. Springer, 1995.

[20] Nikolaos Kazantzis and Raymond A Wright. Nonlinear observer design in the presence of delayed output measurements. *Systems & Control Letters*, 54(9):877–886, 2005.

[21] Robert S Kerbel. Inhibition of tumor angiogenesis as a strategy to circumvent acquired resistance to anti-cancer therapeutic agents. *Bioessays*, 13(1):31–36, 1991.

[22] Robert S Kerbel. A cancer therapy resistant to resistance. 390(6658), 1997.

[23] Robert S Kerbel and Barton A Kamen. The anti-angiogenic basis of metronomic chemotherapy. *Nature Reviews Cancer*, 4(6):423–436, 2004.

[24] RS Kerbel, G Klement, KI Pritchard, and B Kamen. Continuous low-dose anti-angiogenic/metronomic chemotherapy: from the research laboratory into the oncology clinic. *Annals of Oncology*, 13(1):12–15, 2002.

[25] Michael Klagsbrun and Shay Soker. VEGF/VPF: the angiogenesis factor found? 3(10):699–702, 1993.

[26] Costas Kravaris and Raymond A Wright. Deadtime compensation for nonlinear processes. 1989.

[27] Lance A Liotta, Gerald M Saidel, and Jerome Kleinerman. Diffusion model of tumor vascularization and growth. *Bulletin of mathematical biology*, 39(1):117–128, 1977.

[28] Luis Alejandro Márquez-Martínez, Claude H Moog, and Martín Velasco-Villa. Observability and observers for nonlinear systems with time delays. *Kybernetika*, 38(4):445–456, 2002.

[29] Seth Michelson and John T Leith. Positive feedback and angiogenesis in tumor growth control. *Bulletin of mathematical biology*, 59(2):233–254, 1997.

[30] Yu V Mikheev, VA Sobolev, and EM Fridman. Asymptotic analysis of digital control systems. *Automation and remote control*, 49(9):1175–1180, 1988.

[31] M.D. Mora, A. Germani, and C. Manes. Design of state observers from a drift-observability property. *Automatic Control, IEEE Transactions on*, 45(8):1536–1540, Aug 2000.

[32] P Skehan. On the normality of growth dynamics of neoplasms in vivo: a data base analysis. *Growth*, 50(4):496–515, 1985.

[33] Howard E Skipper. On mathematical modeling of critical variables in cancer treatment (goals: better understanding of the past and better planning in the future). *Bulletin of mathematical biology*, 48(3-4):253–278, 1986.

[34] Otto Smith. Closer control of loops with dead time. 1957.

[35] John S Spratt, John S Meyer, and John A Spratt. Rates of growth of human neoplasms: Part ii. *Journal of surgical oncology*, 61(1):68–83, 1996.

[36] Annamária Szeles, Johanna Sápi, Dániel András Drexler, Istvan Harmati, Zoltán Sápi, and Levente Kovacs. Model-based angiogenic inhibition of tumor growth using modern robust control method. In *Biological and Medical Systems*, volume 8, pages 113–118, 2012.

[37] Srinivas Tatiraju, Masoud Soroush, and Babatunde A Ogunnaike. Multi-rate nonlinear state estimation with application to a polymerization reactor. *AIChE Journal*, 45(4):769–780, 1999.

[38] Vincent Van Assche, Tarek Ahmed-Ali, Cheikh Hann, and Françoise Lamnabhi-Lagarrigue. High gain observer design for nonlinear systems with time varying delayed measurements. In *18th IFAC World congress*, pages 692–696, 2011.