2017 25th Mediterranean Conference on Control and Automation (MED)
July 3-6, 2017. Valletta, Malta

Lyapunov based Control Design for Cancer Gompertz-Logistic Generalized Model Therapy

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Abstract— **This article explores the structure of the Gompertz-Logistic generalized model, that describes several cancer types, to design drug administration profiles. The aim is to handle the nonlinear behaviour of the generalized model such that the tumor size follows a decreasing reference target. Since the Gompertz model can be transformed in a linear dynamical model by applying the $\ln(.)$ transformation, this transformation is applied to the Gompertz-Logistic generalized model to simplify the controller design formed by the $\ln(.)$ function and a PI controller (LnPI). The Lyapunov stability analysis is employed to evaluate the LnPI controller. The main conclusion is this appraoch provides a globally asymptotically stable closed-loop for the Gompertz-Logistic model family in the presence of model parameter uncertainty.**

Keywords: Cancer modeling, Gompertz-Logistic models, NonLinear control, Lyapunov stability analysis.

I. INTRODUCTION

Cancer is associated to an uncontrolled growth of cells that do not respond to the cellular regulation mechanisms of control division, differentiation and cell death. Powerful drugs are administrated to kill tumor cells, but these therapeutic drugs are toxic to healthy cells and may cause side-effects. Thus, the control of the tumor involves the killing of tumor cells and the control of drug side-effects that depend on the patient biology/reaction to drugs. Several models have been proposed to represent different tumor dynamics [1], [2], the Gompertz model and the Logistic model being the ones that are most frequently used. The Gompertz and the Logistic models are nonlinear models where the state growth rate is a nonlinear function of the state and of the manipulated input. These models do not take into account the drug pharmacokinetics (PK).

Early studies, [3], already show that the logarithmic growth rate embedded in the Gompertz model yields better fit to tumor growth data than other models such as the logistic model. However, from the perspective of modeling the dynamic of cancer progression, it is important to be able to select a model from a family of models the best describe real data. This motivates the use of a generalized model that provides a family of models, including the Gompertz and the Logistic models.

Although studies such as the ones referred in [4] provide a means to design a time profile of drug administration, that optimizes in a systematic way the compromise between tumor cells killing and drug toxicity, they do not consider feedback treatments that yield an asymptotically stable closed-loop. The use of a control Lyapunov function that is defined jointly for output regulation and parameter estimation allows to ensure global asymptotic stability. In this framework, in [5] a model reference adaptive controller is proposed. In [2] an adaptive controller for the chemotherapy process is presented.

The work described in this article explores the $\ln(.)$ transformation, that can be used to transform the Gompertz model in a linear dynamical model. This is applied to the Gompertz-Logistic generalized model to simplify the controller design formed by the $\ln(.)$ transformation and a PI controller. A reference that represents the desired tumor size is introduced to drive the tumor size close to zero. The rate at which this reference vanishes is an important knob that allows to manipulate the peak of drug delivery. The Lyapunov stability theorems are used to evaluated the properties of the proposed controller formed by the nonlinear function $(\ln(.))$ and a PI controller (LnPI). The global stability of the closed-loop dynamics is proved and, as an important conclusion, the proposed LnPI controller is shown to be robust in the presence of parameter uncertainty.

II. MATHEMATICAL MODELING

From observed clinical data there is a general consensus that a tumor, in its initial stage, has an exponential growth that slows and approaches a plateau value. In this work the following generalized model that has embedded the Gompertz and the Logistic models is used to address the design of drug administration procedures,

$$\frac{dx(t)}{dt} = \frac{\alpha}{\xi}\left(1 - (\frac{x(t)}{m})^{\xi}\right)x(t) - \beta x(t)u(t), \qquad (1)$$

where $x(t) \geq 0$ represents the total tumor volume, or the number of tumor cells ($1mm^3 \approx 10^5$ cells), $\alpha > 0$ is a parameter, m is a parameter that represents the plateau value, $u(t)$ quantifies the amount of therapeutic drug and $\beta > 0$ is a parameter that quantifies the intensity of drug. The parameter $\xi \in [0;\ 1]$ is used to fit data and to choose between the Gompertz model ($\xi = 0$) or the Logistic model ($\xi = 1$), thus the above dynamic model represent a family of Gompertz-Logistic models.

The generalized model has two equilibrium points, one unstable ($x = 0$), and the other stable ($x = m$).

*This work was supported by Fundação para a Ciência e Tecnologia under the research project PTDC/EM-SIS/0642/2014 and the program UID/CEC/50021/2013.

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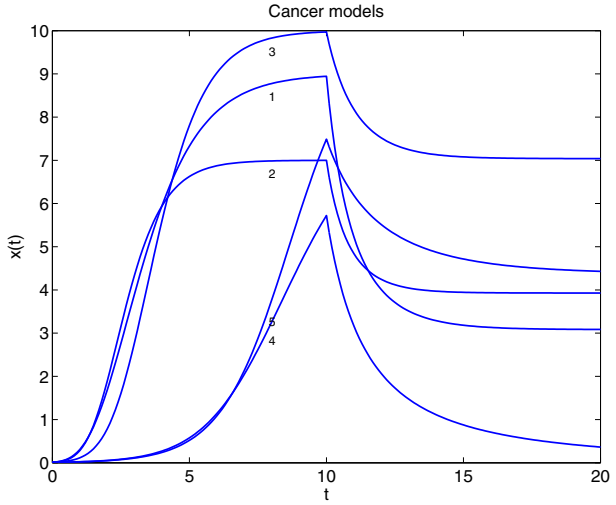


Fig. 1. Illustration of the temporal behaviour of tumors that are described by the Gompertz/Logistic generalized model with the parameters shown on Table I.

TABLE I

TUMOR MODELS: SET OF PARAMETERS TO ILLUSTRATE MODEL PARAMETER UNCERTAINTY

model	m	α	β	ξ
1	9	0.7	0.5	0.0
2	7	1.1	0.4	0.2
3	10	0.9	0.2	0.3
4	8	0.6	0.6	0.7
5	10	0.8	0.3	1.0

Figure 1 illustrates the temporal behaviour of the Gompertz-Logistic model family with different values for the parameters m, α, β and ξ presented in the Table I. Each time response is labeled with the model number presented in the first column of the Table I. These parameter values are hypothetical and used to illustrate the effect of model parameters. During the first 10 time units, the therapeutic regimen is not applied ($u(t) = 0$) and the tumor increases. After time $t = 10$ the manipulated variable $u(t)$ is set to $u(t) = 1.5$. The response of the tumors to the drug is not identical and thus it can be concluded that personalized therapeutic must be used. It is interesting to note that in the initial phase there are models with similar time response.

III. CONTROL PROBLEM FORMULATION

To define the control problem, a reference profile for tumor size is designed that takes in account the objective to decrease the tumor size and the undesired side-effects that are associated with the drug toxicity. The reference profile is represented by $r(t)$, and decays to a small final value $r^\star$ that represents a tumor size that does not cause a life threat condition to the patient. In the present work the reference profile $r(t)$ is selected as the solution of

$$\frac{dr(t)}{dt} = -\theta r(t) + \theta r^\star, \tag{2}$$

where $\theta > 0$ is an adjustable parameter. Given the reference, the tracking error $e(t)$ is defined as

$$e(t) = x(t) - r(t), \tag{3}$$

where $x(t)$ represents the tumor size. This tracking error can be used to describe the error dynamics as in [6], however in this work a nonlinear transformation, the $\ln(.)$ function, is first applied to equation (1). The motivation to apply the $\ln(.)$ function to the the Gompertz/Logistic generalized model (a class of nonlinear dynamical models) is that, it transforms the Gompertz model in a linear dynamical model and it simplifies the control design.

IV. NONLINEAR PI CONTROLLER

In order to apply the $\ln(.)$ transformation, the terms of equation (1) are rearranged,

$$\frac{1}{x(t)}\frac{dx(t)}{dt} = \frac{\alpha}{\xi}\left(1 - (\frac{x(t)}{m})^\xi\right) - \beta u(t), \tag{4}$$

where $\frac{1}{x(t)}\frac{dx(t)}{dt}$ is replaced by $\frac{dln(x(t))}{dt}$,

$$\frac{dln(x(t))}{dt} = \frac{\alpha}{\xi}\left(1 - (\frac{x(t)}{m})^\xi\right) - \beta u(t)\,. \tag{5}$$

Defining now a new variable $z(t) = ln(x(t))$, the tumor's dynamics can be written as

$$\frac{dz(t)}{dt} = \frac{\alpha}{\xi}(1 - \mathrm{e}^{\xi(z(t)-m_z)}) - \beta u(t), \tag{6}$$

where $m_z = ln(m)$. Note that the input $u(.)$ has now a linear contribution.

With this transformation a new tracking error is defined,

$$e_z(t) = z(t) - r_z(t), \tag{7}$$

where $r_z(t) = ln(r(t))$. The error dynamics after the nonlinear transformation is given by

$$\frac{de_z(t)}{dt} = \frac{\alpha}{\xi}(1 - \mathrm{e}^{\xi(e_z(t)+r_z(t)-m_z)}) - \beta u(t) + \theta(1 - \frac{r^\star}{r(t)})\,. \tag{8}$$

Given that the transformed Gompertz model is a linear model, a linear PI controller is proposed to control the transformed Gompertz/Logistic generalized model. The proposed PI controller is described by

$$u(t) = K_p e_z(t) + K_i s_z(t); \quad \text{with} \quad \frac{ds_z(t)}{dt} = e_z(t)\,, \tag{9}$$

where $s_z(t)$ represents the integral action that is computed from $e_z(t)$, and $K_p > 0$ and $K_i > 0$ are the controller gains.

From the definition of $e_z(t)$ and $e_{rz}(t) = r_z(t) - r_z^\star$, $z(t) = e_z(t) + r_z(t)$; $z(t) = e_z(t) + r_z(t) - r_z^\star + r_z^\star$; that yields $z(t) = e_z(t) + e_{rz}(t) + r_z^\star$. The closed-loop dynamics with the proposed controller is described by

$$\begin{aligned}\frac{de_z(t)}{dt} &= \frac{\alpha}{\xi}(1 - \mathrm{e}^{\xi(e_z(t)+e_{rz}(t)+r_z^\star-m_z)}) - \\ &- \beta K_p e_z(t) - \beta K_i s_z(t) + \theta(1 - \mathrm{e}^{-e_{rz}(t)}) \quad (10)\\ \frac{ds_z(t)}{dt} &= e_z(t) \quad (11)\\ \frac{de_r(t)}{dt} &= -\theta e_r(t) \;\; or \;\; \frac{de_{rz}(t)}{dt} = -\theta(1 - \mathrm{e}^{-e_{rz}(t)}) \quad (12)\end{aligned}$$

that has the equilibrium point

$$e_z(t) = 0;\;\; s_z(t) = s_z^\star = \frac{\alpha}{\beta K_i \xi}\left(1 - (\frac{r^\star}{m})^\xi\right);\;\; r(t) = r^\star\,.$$

This is used to describe the error dynamics in relation to the equilibrium point, where $e_{sz}(t) = s_z(t) - s^\star$.

A. Stability analysis

The stability of the closed-loop is now analysed using the Lyapunov stability analysis, where the Lyapunov candidate function is selected as

$$V(t) = \frac{1}{2}e_z^2(t) + \frac{1}{2}\beta K_i e_{sz}^2(t) + \frac{1}{2}\lambda e_{rz}^2(t)\,, \qquad (13)$$

with $\lambda > 0$.

Computing the time derivative of $V(t)$, substituting $\frac{de_z(t)}{dt}$, $\frac{de_{sz}(t)}{dt}$, $\frac{de_{rz}(t)}{dt}$ by (10), (11), (11) and completing the square terms, yields

$$\frac{dV(t)}{dt} = -h_1 e^2(t) - \frac{\theta}{2}h_2(e_{rz}(t)) - h_3(e_z(t), e_{rz}(t)) \quad (14)$$

where

$$h_1 = \beta K_p - \frac{\theta}{2}, \qquad (15)$$

$$h_2(e_{rz}(t)) = -(1 - \mathrm{e}^{-e_{rz}(t)})^2 + 2\lambda_a e_{rz}(t)(1 - \mathrm{e}^{-e_{rz}(t)}), \qquad (16)$$

$$h_3(e_z(t), e_{rz}(t)) = f(e_z(t), e_{rz}(t)) + \lambda_b \theta e_{rz}(t)(1 - \mathrm{e}^{-e_{rz}(t)}), \qquad (17)$$

and

$$f(e_z(t), e_{rz}(t)) = \frac{\alpha}{\beta}\,\mathrm{e}^{\xi(r_z^\star - m_z)}[\mathrm{e}^{\xi(e_z(t)+e_{rz}(t))} - 1]e_z(t)\,, \qquad (18)$$

with $\lambda = \lambda_a + \lambda_b > 0$, where $\lambda_a > 0$ and $\lambda_b > 0$.

Proposition: The closed-loop dynamics is asymptotically stable for $x(t) > 0$, if the controller parameters fulfill the conditions $K_p > \frac{1}{\beta}\frac{\theta}{2}$, $K_i > 0$ and $\theta > 0$. The controller parameters do not depend on the model parameters m, α, ξ and thus the controller is robust to model parameter uncertainty.

Proof: A sufficient condition that implies $\frac{dV(t)}{dt} \leq 0$, is obtained with $h_1 > 0$, $h_2(e_{rz}(t)) > 0$ and $h_3(e_z(t), e_{rz}(t)) > 0$. From the condition on h_1 the proportional gain of the controller, $K_p > \frac{1}{\beta}\frac{\theta}{2}$. The function $h_2(e_{rz}(t))$ is positive for $\lambda_a > \frac{1}{2}$, this can be concluded by putting in evidence the term $(1 - \mathrm{e}^{-e_{rz}(t)})$, that is positive, and comparing the remaining terms.

The function $h_3(e_z(t), e_{rz}(t))$ depends on the properties of $f(e_z(t), e_{rz}(t))$, that is

$$f(e_z(t), e_{rz}(t)) = \begin{cases} \geq 0 & e_z(t) \geq 0 \\ < 0 & -e_{rz}(t) < e_z(t) < 0 \\ \geq 0 & -e_r(t) > e_z(t) \end{cases} \qquad (19)$$

and the minimum of $f(e_z, e_{rz})$ occurs in the interval $-e_{rz} < e_z < 0$, note that $e_{rz} \geq 0$.

Computing $df(e_z, e_{rz})/de_z$ and equating to zero, a mathematical expression is obtained that gives the minimum value of $f(e_z, e_{rz})$, this is represented by $f_{min}(\bar{e}_z, e_{rz})$, where

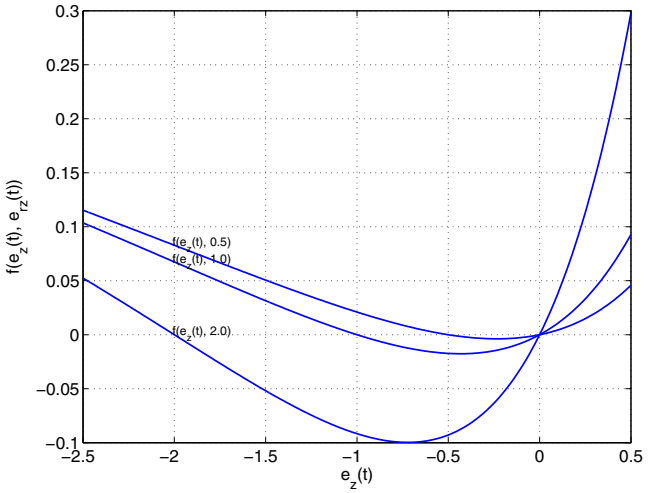


Fig. 2. Illustration of $f(e_z(t), e_{rz}(t))$ in the interval $-e_{rz}(t) < e_z(t) < 0$ for three values of $e_{rz}(t)$ and $\xi = 1$ that corresponds to the logistical model. The negative part of $f(e_z(t), e_{rz}(t))$ must be compensated using λ_b such that $h_3(e_z(t), e_{rz}(t)) > 0$.

$\bar{e}_z(t)$ is the value of e_z corresponding to the minimum of $f(e_z, e_{rz})$,

$$f_{min}(\bar{e}_z(t), e_{rz}(t)) = -(\bar{e}_z(t))^2 \alpha\,\mathrm{e}^{\xi(r_z^\star - m_z)}\,\mathrm{e}^{\xi(\bar{e}_z(t)+e_{rz(t)})}\,. \qquad (20)$$

As $e_{rz}(t)$ approaches to zero and because $\bar{e}_z(t) \in [-e_{rz}(t); 0]$, then $\bar{e}_z(t)$ tends to zero and from equation (20) the minimum value of $f(.,.)$ tends to zero.

Figure 2 illustrates the behaviour of $f(e_z(t), e_{rz}(t))$, in the interval $-e_r(t) < e(t) < 0$.

From the equation (20) a lower bound for $f_{min}(\bar{e}_z(t), e_{rz}(t))$ can be obtained,

$$f_{min}(\bar{e}_z(t), e_{rz}(t)) \geq -(\bar{e}_{rz}(t))^2 \alpha\,\mathrm{e}^{\xi(r_z^\star - m_z)}\,\mathrm{e}^{\xi(e_{rz(t)})}\,, \qquad (21)$$

that is used with equation (17) to compute a lower bound on λ_b,

$$\lambda_b \geq \frac{\alpha\,\mathrm{e}^{\xi(r_z^\star - m_z)}}{\xi\theta}\max\left(\xi e_{rz}(t)\frac{\mathrm{e}^{\xi e_{rz}(t)}}{1 - \mathrm{e}^{\xi e_{rz}(t)}}\right)\,, \qquad (22)$$

where the maximum value occurs at $t = 0$, when the value of $e_{rz}(t)$ is maximum.

It is remarked that λ, λ_a and λ_b are not used in the control law. They are used to demonstrate that $\frac{dV(t)}{dt} < 0$ for $e_z(t) \neq 0$ and $e_{rz}(t) \neq 0$.

In the particular case that $e_z(t) = 0$, $e_{rz}(t) = 0$, and $e_{sz}(t) \neq 0$, the time derivative of $V(t)$ is zero, $\frac{dV(t)}{dt} = 0$. But this state set does not correspond to equilibrium states of the closed-loop system. The time derivative of $[e_z(t) e_{sz}(t) e_{rz}(t)]'$ is not null for these states and the system will evolve to a state where $e_z(t) \neq 0$ that implies $\frac{dV(t)}{dt} < 0$. In the limit, the system converges to the equilibrium point $[0\ 0\ 0]'$ (LaSalle's invariant principle [7]).

Thus, it is concluded that the closed-system is asymptotically stable for $x(t) > 0$ and the controller parameters do not depend on the model parameters α, ξ and m.

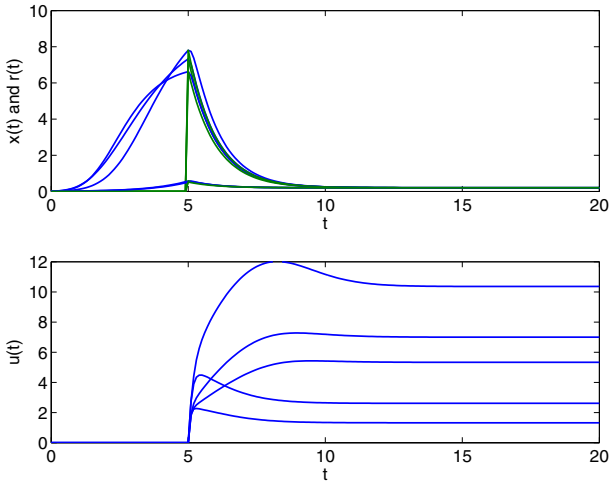


Fig. 3. Results obtained by applying the adaptive LnPI Controller ($K_p = 30$, $K_i = 30$) to the models described in Table I. The controller is operating for $t > 5$. The tumor models are controlled and track the reference but need different steady state drug levels.

Considering the bounds on β and using the previous results, the controller gains must be selected according to

$$K_p > \frac{1}{\beta_{min}} \frac{\theta}{2}; \text{ and } K_i > 0\,. \tag{23}$$

B. Local approximation

The selection of the control gains is an important practical issue. From the results obtained, there is no guideline on how to select the value for the controller parameter K_i. To overcome this issue, the local behaviour of the closed-loop system can used to select K_i. In the case the reference is selected as $r_z(t) = r_z^\star$ and $|e_z(t)| << r_z^\star$ the closed-loop dynamics is simplified

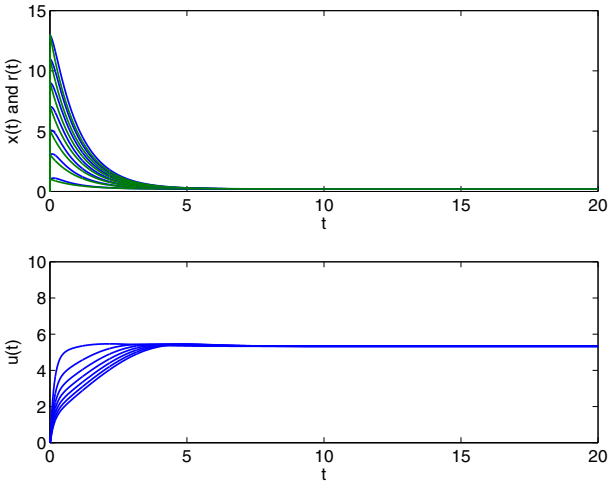
$$\begin{aligned} \frac{de_z(t)}{dt} &= \frac{\alpha}{\xi}\left(1 - \mathrm{e}^{\xi(r_z^\star - m_z)}\right) \\ &- \beta K_p e_z(t) + \beta K_i e_{sz}(t) + \beta K_i s_z^\star \\ \frac{de_{sz}(t)}{dt} &= e_z(t) \end{aligned}$$

where the gains can be computed by selecting the closed-loop poles.

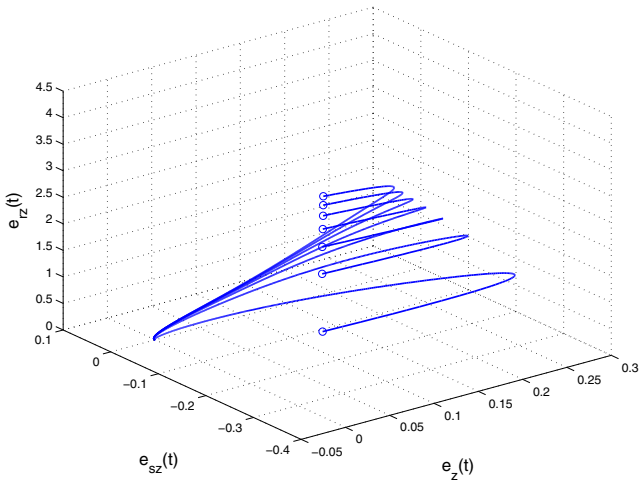
C. Simulation results

The controller robustness in the presence of model parameter uncertainty is illustrated with the results shown in figure 3. All models from Table I are controlled with the adaptive controller (nonlinear PI controller) with $K_p = 30$ and $K_i = 30$. During the first 5 time units the models are in open loop and the controller is connect at $t = 5$, where the reference signal $r(5)$ is chosen to be equal to $x(5)$. In all the cases the tumor sizes evolve according to the selected reference.

Figure 4(a) shows 7 simulations with the model (1) (that has the structure of the Gompertz model, that is $\xi = 0$) and with 7 initial tumor sizes $\{1,\ 3,\ 5,\ 7,\ 9,\ 11,\ 13\}$. The tumor size approaches the reference defined by the parameters $\theta =$



(a) Tracking the reference.



(b) Phase plane of the $(e_z(t), e_{sz}(t))$.

Fig. 4. Closed-loop control using the adaptive PI controller applied to model 1 (Gompertz model) with $K_p = 15$ and $K_i = 15$, for several initial tumor sizes, $\{1,\ 3,\ 5,\ 7,\ 9,\ 11,\ 13\}$.

1 and the target value $r^\star = 0.2$. The controller gains are $K_p = 15$ and $K_i = 15$. The initial value of the reference $r(0)$ is chosen to be near to $x(0)$. This avoids a sharp transition on $u(0)$. As $x(0)$ increases, the control signal tends to show a change on its behaviour, but in all the cases the tumor size follows the reference $r(t)$.

The behaviour of $e_z(t)$ and $e_{sz}(t)$, for the LnPI controller corresponding to the results shown in figure 4(a), are presented in the form of the phase plane the figure 4(b). The starting points are marked with the symbol 'o', that are near $e(0) \approx 0$. All trajectories converge to the equilibrium point (0,0). Note that the tracking error can be decreased by changing the controller gains.

For this tumor model, the stable equilibrium point is $x(t) = m = 9$. In the cases where $x(0)$ is set to 11 and to 13, $x(t)$ will decrease to m without the use of drug. The need to applied a drug amount depends on the reference decreasing rate.

The control action of the controller can be ad-

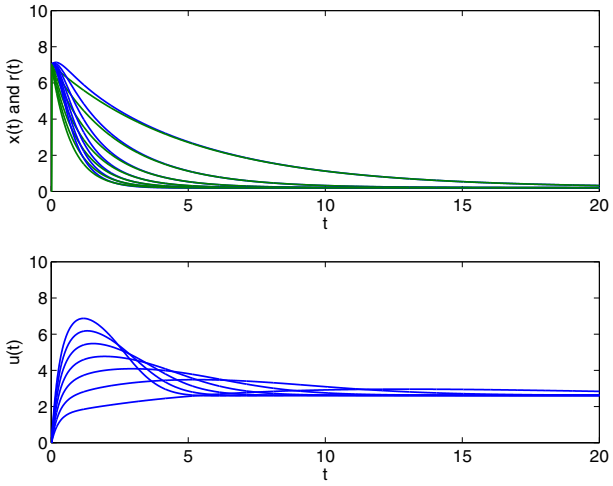


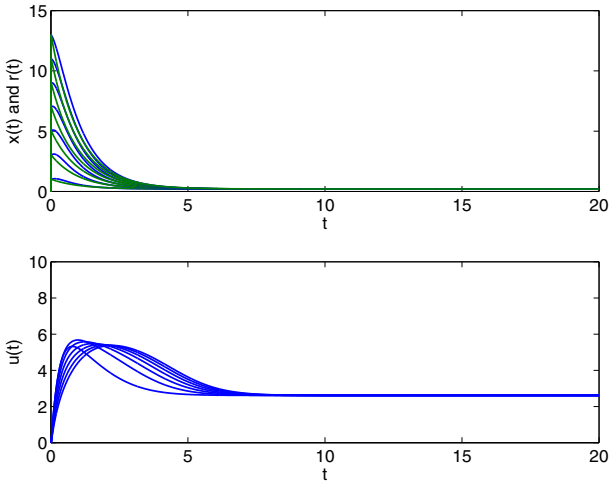
Fig. 5. Control behaviour as a function of reference parameter θ. As the reference has a faster decay (increasing the θ value) the control action becomes stronger to decrease the tracking error $e(t)$.

justed/smoothed by changing the decay rate of the reference, that depends on the parameter θ. This is illustrate in figure 5 where several references are specified using the parameter $\theta = \{0.2,\ 0.4,\ 0.6,\ 0.8,\ 1.0,\ 1.2,\ 1.4\}$ are used to control (model 5) Logistic model that starts with $x(0) = 7$. As the reference has a faster decay, the control action becomes stronger in order to decrease the tracking error $e(t)$.

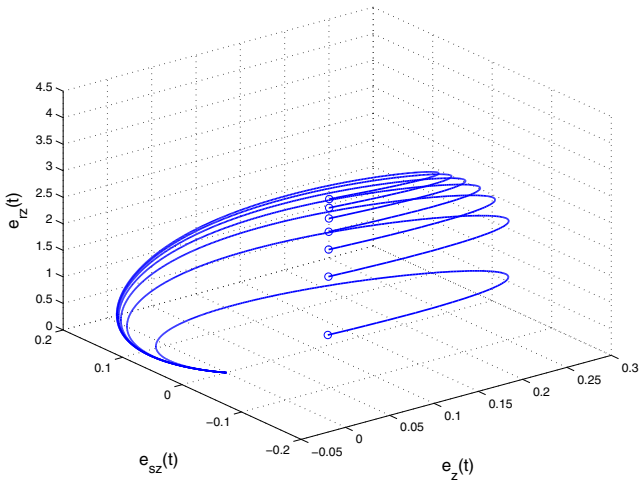
Figures 6(a) and 6(b) show 7 simulations but now the the model used has the structure of the Logistic model that is $\xi = 1.0$, (model 5). Seven initial tumor sizes $\{1, 3, 5, 7, 9, 11, 13\}$ are used to evaluate the controller behaviour. The simulation conditions are the same as the conditions used for the Gompertz model shown in figure 4(a).

V. CONCLUSIONS

This article addresses the design of controllers for the generalized Gompertz-Logistic model that is used to describe the kinetic of tumors such as in cancer diseases. The closed-loop stability is analysed using the Lyapunov stability method. It is concluded that the closed-loop system is global asymptotically stable and is robust to the presence of model parameter uncertainty.



(a) Tracking the reference.



(b) Phase plane of the $(e_z(t), e_{sz}(t))$.

Fig. 6. Closed-loop control using the adaptive PI controller applied to model 5 (Logistic model) with $K_p = 15$ and $K_i = 15$, for several initial tumor sizes, $\{1,\ 3,\ 5,\ 7,\ 9,\ 11,\ 13\}$.

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