Drug Administration Design for Cancer Gompertz Model Based on the Lyapunov Method

B. Andrade Costa and J. M. Lemos

Abstract This article addresses the design of therapeutic procedures for cancer using a control based on the Gompertz model, that describes the nonlinear dynamics of tumor growth. The aim is to reduce the tumor size according to a decreasing target reference. The approach presented on this work uses a control Lyapunov function and yields an adaptive PI strategy that results from the exact linearization. It is concluded that the closed-loop system is globally asymptotically stable and is robust with respect to the presence of model parameter uncertainty.

Keywords Cancer modeling · Gompertz model · Exact linearization · Adaptive control · Lyapunov stability analysis

1 Introduction

During the process of drug administration to control the progression of tumor cells it is necessary to adjust the drug amount in order to kill the tumor cells while, at the same time, avoiding the side-effects due to drug toxicity. The tumor dynamics and the effect of drug toxicity change from patient to patient suggesting the use od adaptive methods.

Several models have been proposed to represent different tumor dynamics [2, 4], the Gompertz model and the Logistic model being the ones that are most frequently used. Early studies [3] already show that the log growth rate embedded in the Gompertz model yields better fit to tumor growth data than other models such as the logistic model. These models do not take in account the drug pharmacokinetics (PK). The

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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. Although studies such as the ones referred in [5] 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 [1] a model reference adaptive controller is proposed. In [4] an adaptive controller for the chemotherapy process is presented.

The work described in this article also relies on an approach that uses Lyapunov stability theorems to obtain an adaptive nonlinear controllers, but has the following distinctive features. First a reference that represents the desired tumor size is introduced driving it close to zero. The rate at which this reference vanishes is an important knob that allows to manipulate the peak of drug delivery. Another major difference is the use of feedback linearization. In a first stage, the structure and the parameter values of the Gompertz model are assumed to be known. By exploring the structure of the model and by imposing a reference profile for the tumor growth, that decays exponentially, a nonlinear control law is designed using exact linearisation to cancel the effects of nonlinear terms. By analysing the structure of the exact linearization control law, a nonlinear adaptive PI controller with one adaptive element is proposed. It is assumed that bounds on the parameter values of the model are known. The global stability of the closed-loop dynamics is demonstrated and, as an important conclusion, the proposed adaptive PI controller is shown to be robust in the presence of parameter uncertainty. It is possible to explores the structure of the Gompertz model by applying the log() transformation to yield a new state representation that results in a linear model. From this point, a PI controller can be applied. However due to lack of space this approach is not presented.

2 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.

The tumor growth described by the Gompertz model is given by

$$\frac{dx(t)}{dt} = \alpha x(t) \log(\frac{m}{x(t)}) - \beta x(t) u(t), \tag{1}$$

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.

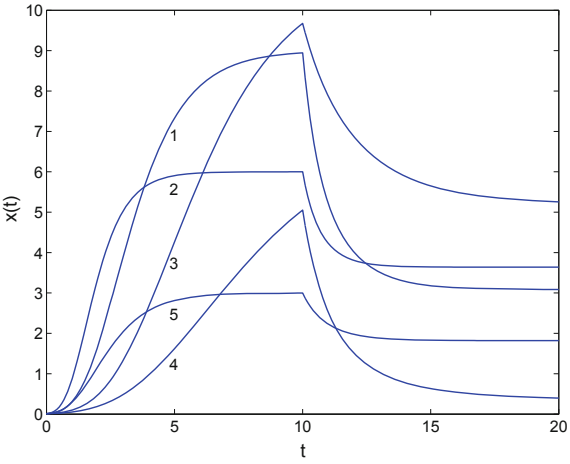

Fig. 1 Illustration of the temporal behaviour of tumors that are described by the Gompertz model with the parameters shown on Table 1

Table 1 Set of parameters for the Gompertz model to illustrate parameter uncertainty

Model	m	α	β
1	9	0.7	0.5
2	6	1.2	0.4
3	11	0.4	0.2
4	7	0.3	0.6
5	3	0.9	0.3

The models has two equilibrium points, one unstable (x = 0), and the other stable ($x = m$). The results obtained for the Gompertz model can be extended to the logistic model.

Figure 1 illustrates the temporal behaviour of the Gompertz model with different values for the parameters m, α and β presented in Table 1. Each time response is labeled with the model number presented in the first column of the Table 1. 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.

3 Design With Full Model Knowledge

The aim is to design a drug administration profile that decreases the tumor size but at the same time minimizes the undesired drug side-effects. To address this 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 along time t 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.

The control design is formulated by defining the tracking error $e(t)$ as

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

where $x(t)$ represents the tumor size. The error dynamics is

$$\frac{de(t)}{dt} = x(t)\alpha \log(\frac{m}{x(t)}) - \beta x(t)u(t) + \theta e_r(t) \tag{4}$$

where $e_r(t) = r(t) - r^\star$. By selecting the $\frac{de(t)}{dt} = -\gamma e(t)$, where $\gamma > 0$ is an adjustable parameter, the error $e(t)$ decays exponentially to zero. To obtain this result, $u(t)$ is selected as

$$u(t) = \frac{\gamma}{\beta}\frac{e(t)}{x(t)} + \frac{\theta}{\beta}\frac{e_r(t)}{x(t)} + \frac{\alpha}{\beta}\log(\frac{m}{x(t)}). \tag{5}$$

This nonlinear control law implements the exact feedback linearization strategy, and as such, it cancels the nonlinear terms on the right side of equation (4). The application of this nonlinear control law implies a perfect knowledge of the parameter values of the model α , β , m.

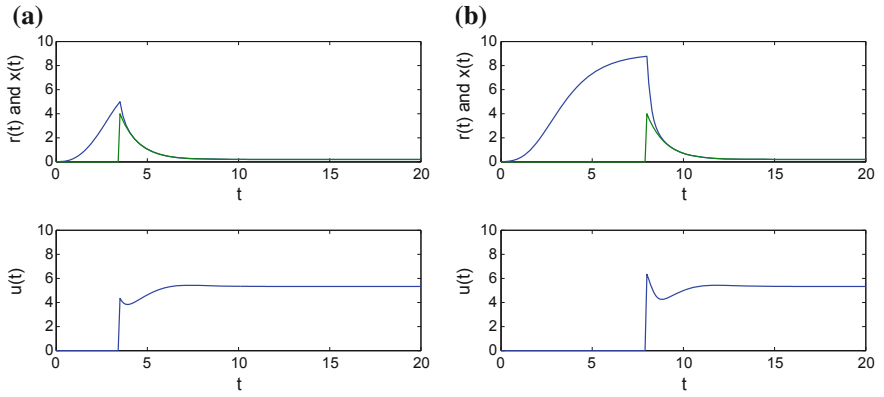

Fig. 2 Closed-loop control using the exact linearization controller and the Gompertz model 1 from Table 1. **a** Closed loop control $t \geq 3.5$. **b** Control is applied later, $t \geq 8$

Figure 2a, b illustrate the results obtained with the Gompertz model ($m = 9$, $\alpha = 0.7$, $b = 0.5$ and $x(0) = 0.01$) when the controller is applied at two different time instants corresponding to two different tumor level stages.

4 Adaptive PI Controller

Under the assumption that bounds on the model parameters are known, $\alpha_{min} \leq \alpha \leq \alpha_{max}$, $\beta_{min} \leq \beta \leq \beta_{max}$ and $m_{min} \leq m \leq m_{max}$ a modification of the above control law is proposed formed by

$$u(t) = K_p \frac{e(t)}{x(t)} + K_i s(t); \quad \text{with} \quad \frac{ds(t)}{dt} = w(t)e(t)\,, \tag{6}$$

where $s(t)$ represents an integral action that is computed from $e(t)$ using the weighting function $w(t)$. The controller gains $K_p > 0$ and $K_i > 0$ substitute the constant gains $\frac{\gamma}{\beta}$ and $\frac{\alpha}{\beta}$ in Eq. (5). The nonlinear integral action $s(t)$ is adapted to compensate the term $log(\frac{m}{x(t)})$, in particular during the steady state, when $x(t) \approx r(t) = r^\star$, corresponding to the value $log(\frac{m}{r^\star})$. The function $w(t)$ is selected based on the application of the Lyapunov stability method, that yields $w(t) = x(t)$. To simplify the control law the term on $e_r(t)$ is not included.

The closed-loop dynamics with the proposed controller is described by

$$\begin{aligned}
\frac{de(t)}{dt} &= -\beta K_p e(t) + \theta e_r(t) + x(t)[\alpha \log(\frac{m}{x(t)}) - \beta K_i s(t)] \\
\frac{ds(t)}{dt} &= x(t)e(t) \\
\frac{de_r(t)}{dt} &= -\theta e_r(t)\,,
\end{aligned}$$

where $e_r(t) = r(t) - r^\star$, and it has the equilibrium point

$$e(t) = 0; \;\; s(t) = s^\star = \frac{\alpha}{\beta K_i} \log(\frac{m}{r^\star}); \;\; r(t) = r^\star\,.$$

The error dynamics, defined in relation to the equilibrium point, is given by

$$\begin{aligned}
\frac{de(t)}{dt} &= -\beta K_p e(t) + \theta e_r(t) + x(t)[-\beta K_i s(t) + \alpha\,, \log(\frac{r^\star}{x(t)})]\,, \\
\frac{de_s(t)}{dt} &= x(t)e(t)\,, \\
\frac{de_r(t)}{dt} &= -\theta e_r(t)\,,
\end{aligned}$$

where $e_s(t) = s(t) - s^\star$. Note that from the definition of $e(t)$, $x(t) = e(t) + r(t)$; $x(t) = e(t) + r(t) - r^\star + r^\star$; that yields $x(t) = e(t) + e_r(t) + r^\star$.

4.1 Stability Analysis

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

$$V(t) = \frac{1}{2}e^2(t) + \frac{1}{2}\beta K_i e_s^2(t) + \frac{1}{2}\lambda e_r^2(t)\,, \tag{7}$$

with $\lambda > 0$.

Computing the time derivative of $V(t)$ and substituting $\frac{de(t)}{dt}$, $\frac{de_s(t)}{dt}$ and $\frac{de_r(t)}{dt}$ yields

$$\frac{dV(t)}{dt} = -\beta K_p e^2(t) - \alpha e(t)x(t)\log(\frac{x(t)}{r^\star}) + \tag{8}$$

$$+\theta e(t)e_r(t) - \lambda\theta e_r^2(t)\,,$$

that, after completing the square terms, can be rewritten as

$$\frac{dV(t)}{dt} = -p_1 e^2(t) - p_2(e(t), e_r(t)) - p_3(e(t), e_r(t)) \tag{9}$$

where

$$p_1 = \beta K_p - \frac{\theta}{2}, \tag{10}$$

$$p_2(e(t), e_r(t)) = \alpha e(t)x(t)\log(\frac{x(t)}{r^\star}), \tag{11}$$

$$p_3(e(t), e_r(t)) = \frac{\theta}{2}[(e(t) - e_r^2(t))^2 + (\lambda - \frac{1}{2})e_r^2(t)]\,. \tag{12}$$

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 parameter m and α, and thus the controller is robust to model parameter uncertainty. It is remarked that for $x(t) \leq 0$ the dynamic model does not have a real solution because of the term $\log(\frac{m}{x(t)})$, and thus $x(t) > 0$.

Proof: A sufficient condition that implies $\frac{V(t)}{dt} \leq 0$, is obtained with $p_1 > 0$ and $p_2(e(t), e_r(t)) + p_3(e(t), e_r(t)) > 0$. From the condition on $p1$ results $K_p > \frac{1}{\beta}\frac{\theta}{2}$. The function $p_3(e(t), e_r(t))$ is non-negative and has the minimum at $e(t) = e_r(t)$. Inspecting $p_2(e(t), e_r(t))$, where $x(t) = e(t) + e_r(t) + r^\star$ it is concluded that

$$p_2((e(t), e_r(t))) = \begin{cases} \geq 0 & e(t) \geq 0 \\ < 0 & -e_r(t) < e(t) < 0 \\ \geq 0 & -e_r(t) - r^* < e(t) < -e_r(t) \end{cases} \tag{13}$$

i.e., p_2 is negative in the interval $-e_r(t) < e(t) < 0$, where it has a minimum (that is represented by $-p_{2m} < 0$) and it is positive outside this interval. The minimum $-p_{2m}$ can be compensated with the function $p_3(e(t), e_r(t))$ such that $p_2(e(t), e_r(t)) + p_3(e(t), e_r(t)) > 0$.

In the interval $-e_r(t) < e(t) < 0$, the function $p_3(e(t), e_r(t))$ has the minimum at $e(t) = 0$, that is equal to $\frac{\theta}{2}(\lambda + \frac{\theta}{2})e_r^2(t)$.

In order to obtain $-p_{2m} + \frac{\theta}{2}(\lambda + \frac{\theta}{2})e_r^2(t) > 0$ at time t, it is necessary that

$$\lambda \geq \frac{2}{\theta} \frac{\Delta(e_r(t))}{e_r^2(t)} - \frac{1}{2}\,. \tag{14}$$

But, because $\frac{de_r(t)}{dt} = -\theta e_r(t)$, the above relation can be extended to $t = 0$, where $e_r(0) > 0$ is the maximum value. The parameter λ can now be selected according to

$$\lambda > \frac{2}{\theta} \frac{\Delta(e_r(0))}{e_r^2(0)} - \frac{1}{2}\,, \tag{15}$$

and it can be concluded that $p_2(e(t), e_r(t)) + p_3(e(t), e_r(t)) > 0$.

Figure 3 illustrates the behaviour of $p_2(e(t), e_r(t))$, and $p_3(e(t), e_r(t))$ in the interval $-e_r(t) < e(t) < 0$. As $e_r(t)$ tends to zero, the interval $-e_r(t) < e(t) < 0$ shrinks to zero and the minimum of $p_2(e(t), e_r(t))$ tends to zero.

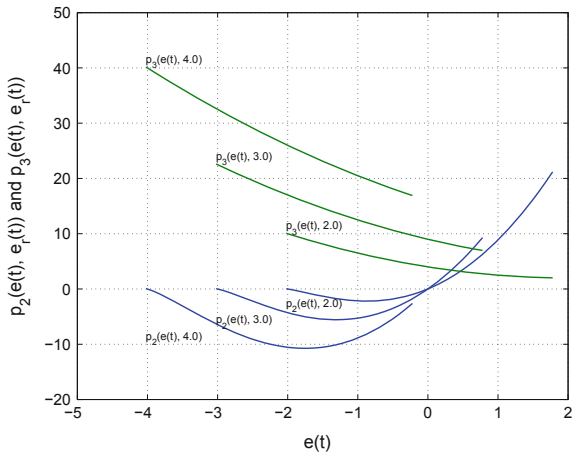

Fig. 3 Illustration of functions $p_2(e(t), e_r(t))$ and $p_3(e(t), e_r(t))$ in the interval $-e_r(t) < e(t) < 0$ for three values of $e_r(t)$, 2, 3 and 4. The condition $p_2(e(t), e_r(t)) + p_3(e(t), e_r(t)) > 0$ is fulfil by choosing the parameter $\lambda > 0$.

It is remarked that λ does not enter in the control law, being used just to demonstrate that $\frac{V(t)}{dt} < 0$ for $e(t) \neq 0$ and $e_r(t) \neq 0$.

In the particular case when $e(t) = 0$, $e_r(t) = 0$, and $e_s(t) \neq 0$, it follows that $\frac{V(t)}{dt} = 0$. But the state set defined by $e(t) = 0$, $e_r(t) = 0$ and $e_s(t) \neq 0$ does not correspond to equilibrium states of the closed-loop system. The time derivative of $[e(t)\ e_s(t)\ e_r(t)]'$ is not null for these states and the system will evolve to a state where $e(t) \neq 0$ that implies $\frac{V(t)}{dt} < 0$. In the limit, the system converges to the equilibrium point $[0\ 0\ 0]'$ (LaSalle's invariant principle [6]).

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 m and α.

4.2 Model Parameter Uncertainty

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

$$0 < \beta_{min} K_p - \frac{\theta}{2} \leq \beta K_p - \frac{\theta}{2} \leq \beta_{max} K_p - \frac{\theta}{2}$$

that yields,

$$K_p > \frac{1}{\beta_{min}} \frac{\theta}{2};\ \text{and}\ K_i > 0\,. \tag{16}$$

4.3 Local Approximation

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 is considered. In the case that $r(t) = r^\star$ and $|e(t)| \ll r^\star$ the closed-loop dynamics is simplified

$$\begin{aligned}
\frac{de(t)}{dt} &= -\beta K_p e(t) + (e(t) + r^\star)[-\beta K_i s(t) + \alpha \log(\frac{r^\star}{e(t) + r^\star})] \\
\frac{de_s(t)}{dt} &= (e(t) + r^\star) e(t)
\end{aligned}$$

and can be approximated to

$$\begin{aligned}
\frac{de(t)}{dt} &= -\beta K_p e(t) - r^\star \beta K_i s(t) \\
\frac{de_s(t)}{dt} &= r^\star e(t)\,.
\end{aligned}$$

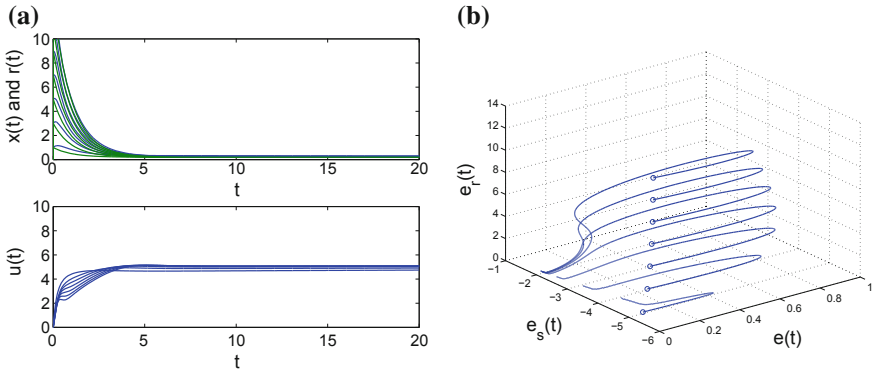

Fig. 4 Closed-loop control using the adaptive PI controller applied to model 1 with $K_p = 10$ and $K_i = 1$, for several initial tumor sizes, {1, 3, 5, 7, 9, 11, 13} **a** Tracking the reference. **b** Phase plane of the $(e(t), e_s(t))$

The proposed controller becomes a standard PI controller $u(t) = (K_p/r^\star)e(t) + (K_i r^\star)\int e(\tau)d\tau$ and the closed-loop poles are computed from

$$p_{1,2} = -\frac{\beta K_p}{2}(1 \pm \sqrt{(1 - \frac{4K_i(r^\star)^2}{\beta K_p^2}})$$

that can be used to select the value of K_i as a function of K_p.

4.4 Simulation Results

Figure 4a shows 7 simulations with the model (1) and with 7 initial tumor sizes {1, 3, 5, 7, 9, 11, 13}. The tumor size approaches the reference defined by the parameters $\theta = 1$ and the target value $r^\star = 0.2$. The controller gains are $K_p = 10$ and $K_i = 1$. 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 $e(t)$ and $e_s(t)$, for the adaptive controller corresponding to the results shown in the Fig. 4a, are presented in the form of the phase plane in the Fig. 4b. The starting points are marked with the symbol 'o', that are near $e(0) \approx 0$. As the reference changes there is an initial increase in the error $e(t)$ but $e_s(t)$ decreases. 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 $x(t) = m = 9$ and the maximum value of $e(t)$ tends to decrease if the initial value of $x(0) > m$. Because in the

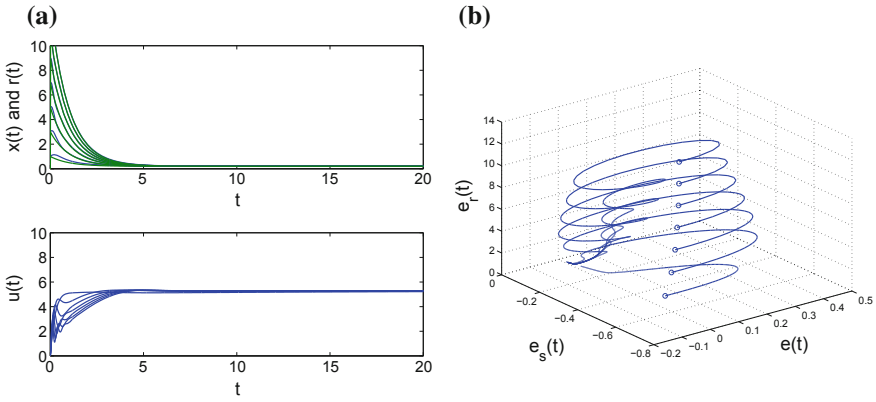

Fig. 5 Closed-loop control using the adaptive PI controller applied to model 1 with $K_p = 10$ and $K_i = 10$, for several initial tumor sizes, as in the Fig. 4a. **a** Tracking the reference. **b** Phase plane of the $(e(t), e_s(t))$

early working phase of the controller the reference decreases more rapidly than $x(t)$, then $e(t)$ is positive and increases.

The controller gain K_i is increased to $K_i = 10$ to obtain a faster decrease of the tracking error. The results are shown in Fig. 5a, b that illustrate the behaviour of the controller with $K_p = 10$ and $K_i = 10$ in the same conditions as the results shown in Fig. 4a, b. The control action of the controller can be adjusted/smoothed by changing the decay rate of the reference, that depends on the parameter θ. This is illustrate in the Fig. 6a where several references are specified using the parameter $\theta = \{0.2,\ 0.4,\ 0.6,\ 0.8,\ 1.0,\ 1.2,\ 1.4\}$ and the model starts with $x(0) = 7$ and is controlled with the adaptive controller ($K_p = 10$, $K_i = 10$). As the reference has a faster decay, the control action becomes stronger in order to decrease the tracking error $e(t)$.

Controller robustness in the presence of model parameter uncertainty is illustrated with the results shown in Fig. 6b. All models from Table 1 are controlled with the adaptive controller with $K_p = 10$ and $K_i = 10$. 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 with the reference used.

5 Conclusions

This article addresses the design of controllers for the Gompertz model that is used to describe the kinetic of tumors such in cancer diseases. The closed-loop stability is analysed using the Lyapunov stability method. It is concluded that the closed-

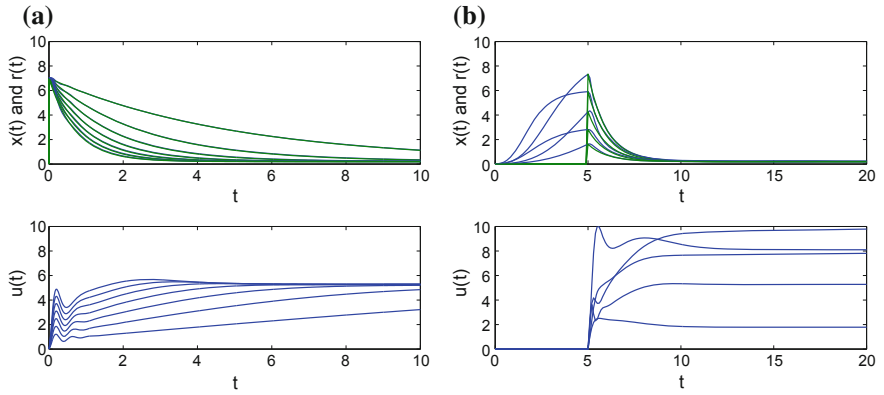

Fig. 6 Adaptive PI Controller with $K_p = 10$, $K_i = 10$. On the left, control behaviour as a function of reference parameter θ. As the reference has a faster decay (increasing the θ value) the control action becomes stronger to decrease the tracking error $e(t)$. On the right, closed-loop control of the Gompertz models of Table 1 with the adaptive PI controller applied after $t > 5$. All models are controlled and track the reference but need different steady state drug levels. **a** Control behaviour as a function of reference parameter θ. **b** Closed-loop control of the Gompertz models

loop system is global asymptotically stable and is robust to the presence of model parameter uncertainty.

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