

# Control of a prostate cancer model using intermittent androgen suppression\*

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**Abstract**—This article addresses the control of a prostate tumor model where androgen suppression is used to control the tumor and to avoid relapse. The model is non-linear and open loop unstable. The stabilization is investigated and a switching control strategy is proposed that renders the closed-loop model stable.

**Index Terms**—Prostate tumor, Exponential growth, Switched control.

## I. INTRODUCTION

Prostate cancer is the second most common cancer in men, being skin cancer in the first place. If detected early, when is confined to the prostate gland, it can be treated with success. However its behaviour is not deterministic, there are tumors that grow slowly and other that are extremely aggressive, invading other organs and causing metastasis. In early stages it does not cause symptoms. But in more advanced stages signs<sup>1</sup> appear such as, *blood present in the urine, pain in the hips, back (spine), chest (ribs), weakness in the legs or feet* and others symptoms. The treatment depends on the cancer staging and there are several possibilities, such as *active surveillance, surgery, radiation therapy, cryotherapy, hormone therapy and chemotherapy*. This paper is focused in hormone therapy, the androgen suppression therapy used to reduce male hormones that are helping prostate cancer cells to develop and grow. In clinical treatments there are two approaches, the Continuous Androgen Deprivation/Suppression Therapy (CAD or CAS ) and the Intermittent Androgen Deprivation/Suppression Therapy (IAD or IAS) [6] [5].

The aim of this paper is to address CAS and IAS treatments from a control point of view, where the drug administration is administrated based on the stability properties of the a prostate tumor dynamical model [2], [4], and [3]. With this objective, the model described in [3] is used because it is based on clinical data, and its structure includes nonlinear elements such as the Hill-function. This model describes the time evolution of androgen-dependent cell population (AD), the androgen-independent cell population (AI), their proliferation,

mutation, dead rates, and their relation with the serum prostate-specific antigen (PSA). In [3] a control mechanism based on a hysteresis is presented, but it is not clear how the parameters of the control system are selected. This model was extended in [8] to include competition between the two populations (AD e AI). It uses the same approach as described in [3] to control the prostate model. But additional information is necessary to justify the range of parameters of the competition sub-model. In [1] model predictive control is explored to control prostate tumor and bifurcation analysis [7] is applied to intermittent hormonal therapy for prostate cancer.

In this paper, the structure of the prostate tumor model is explored and it is viewed as a linear parameter-varying system (LPV). The stability properties are explored to devise a switched control strategy that renders the closed-loop model stable.

This article is organized as follows. Section II describes the model of the prostate tumor used. Section III addresses the stability properties of the model and describes the approach followed to design the controller. The control design and the results obtained with computer numerical simulations are presented in section IV. The conclusions are presented in the last section.

## II. MATHEMATICAL MODELING

The prostate tumor growth [3] is described by the following equations

$$\frac{da(t)}{dt} = -\gamma(a(t) - a_0) - \gamma a_0 u(t), \quad (1)$$

$$\frac{dx_1(t)}{dt} = [\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t)) - m(a(t))]x_1(t) \quad (2)$$

$$\frac{dx_2(t)}{dt} = m(a(t))x_1(t) + [\alpha_2 p_2(a(t)) - \beta_2 q_2(a(t))]x_2(t), \quad (3)$$

$$y(t) = c_1 x_1(t) + c_2 x_2(t), \quad (4)$$

where  $a(t) \geq 0$  represents the androgen concentration,  $a_0$  represents the normal androgen concentration level,  $x_1(t) > 0$  represents the population of AD cells,  $x_2(t) \geq 0$  represents the population of AI cells, and  $y(t) > 0$  represents the output to be controlled, that is, the PSA concentration level, where a large amount is produced by the cancer cells.

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<sup>1</sup><https://www.cancer.org/cancer/prostate-cancer/about/what-is-prostate-cancer.html>

The parameters  $c_1 > 0$  and  $c_2 > 0$  are constants that can be normalized as  $c_1 = 1$  and  $c_2 = 1$ , note that, for other values a transformation can be used to obtain a new representation such that  $y = z_1(t) + z_2(t)$ , and without loss of generality the input  $u(\cdot)$  is normalized to be in the interval  $[0; 1]$ .

The functions that depend on the androgen concentration  $a(t)$  are described by,

$$p_1(a(t)) = k_1 + (1 - k_1) \frac{a(t)}{a(t) + k_2}, \quad (6)$$

$$q_1(a(t)) = k_3 + (1 - k_3) \frac{a(t)}{a(t) + k_4}, \quad (7)$$

$$p_2(a(t)) = 1 - D \frac{a(t)}{a_0}, \quad (8)$$

$$q_2(a(t)) = 1, \quad (9)$$

$$m(a(t)) = m_1 \left(1 - \frac{a(t)}{a_0}\right), \quad (10)$$

and the parameter values are presented in the Table I

### III. STABILITY PROPERTIES OF THE MODEL

The prostate tumor model described, is a positive system where the state variables, the androgen-dependent functions, and the parameters are all positive. This implies that the time derivatives of the state variables, their signs, and the existence of stationary points depend on the relative magnitudes of the several terms present in the model. The time derivatives of  $x_1(t)$  and  $x_2(t)$  depend only on  $x_1(t)$ ,  $x_2(t)$  and on the level of  $a(t)$  through nonlinear functions. At this point it is important to find possible stationary points defined by the conditions  $\frac{da(t)}{dt} = 0$ ,  $\frac{dx_1(t)}{dt} = 0$ , and  $\frac{dx_2(t)}{dt} = 0$ . Note that the set of stationary points defined by  $x_1 = 0$  and  $x_2 = 0$  are not considered because they are trivial stationary points.

#### A. Stationary points

In order to find the stationary points, the model is represented as

$$\frac{da(t)}{dt} = -\gamma a(t) + \gamma a_0(1 - u(t)), \quad (11)$$

$$\frac{dx_1(t)}{dt} = w_{11}(a(t))x_1(t), \quad (12)$$

$$\frac{dx_2(t)}{dt} = w_{21}(a(t))x_1(t) + w_{22}(a(t))x_2(t), \quad (13)$$

$$y(t) = c_1 x_1(t) + c_2 x_2(t), \quad (14)$$

where

$$w_{11}(a(t)) = \alpha_1 p_1(a(t)) - \beta_1 q_1(a(t)) - m(a(t)), \quad (15)$$

$$w_{21}(a(t)) = m(a(t)), \quad (16)$$

$$w_{22}(a(t)) = \alpha_2 p_2(a(t)) - \beta_2 q_2(a(t)). \quad (17)$$

By inspecting the model, it can be concluded that the state variable  $a(t)$  is bounded to the interval  $[0, a_0]$  because  $u(t) \in [0, 1]$  and  $\gamma > 0$ . From the condition  $\frac{da(t)}{dt} = 0$ , a constant value for  $a$  is obtained as a function of the input value  $u$ ,  $a_u = a_0(1 - u)$ .

Considering that  $x_1(t) > 0$  and the expression that defines  $\frac{dx_1(t)}{dt}$ , and imposing the condition  $\frac{dx_1(t)}{dt} = 0$ , it implies that  $w_{11}(a)$  must be equal to zero. Using the data described in the table I, it can be concluded that, for  $a(t) = a_0$  (obtained by imposing  $u = 0$ ) the  $dx_1(t)/dt \approx \alpha_1 k_1 - \beta_1 k_3 - m_1$  is negative, and for  $a(t) = 0$  (obtained by imposing  $u = 1$ ) implies that  $dx_1(t)/dt \approx \alpha_1 - \beta_1$  is positive. Thus there exists a constant value  $a_c$  such that  $\frac{dx_1(t)}{dt} = 0$ . Since the function  $w_{11}(a)$  depends on several parameters and functions, it is not possible to obtain a closed form for  $a_c$ , the behavior of  $w_{11}(a)$  is shown in the figure 1, where  $w_{11}(a) > 0$  for  $a > a_c$  and  $w_{11}(a) < 0$  for  $a < a_c$ . It can be concluded that it is possible to use  $a(t)$  to control  $x_1(t)$ , and (non trivial) stationary points (if exist) must occur at  $a = a_c$ .

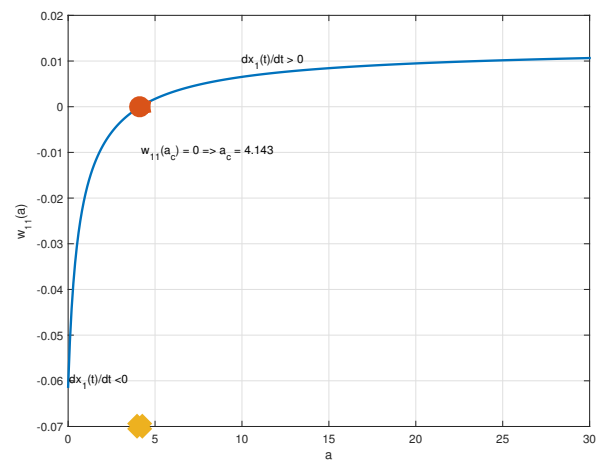


Fig. 1. Function  $w_{11}(a)$  that defines the decreasing or increasing behaviour of  $\frac{dx_1(t)}{dt}$ . The  $a_c$  point that yields  $\frac{dx_1(t)}{dt} = 0$  is marked with a red point.

In the case of  $dx_2(t)/dt$ , the functions  $w_{21}(a)$  and  $w_{22}(a)$  are evaluated around  $a = a_c$ . Note that  $w_{22}(a)$  depends on the parameter  $D \in [0, 1]$ ,  $w_{22}(a, D)$ . The behaviour of  $w_{21}(a)$  and  $w_{22}(a)$  around  $a = a_c$  are shown in the figure 2. At  $a = a_c$  the functions  $w_{21}(a_c) > 0$  and  $w_{22}(a_c) > 0$ , this implies that  $dx_2(t)/dt > 0$  and the conclusion is that the model has not stationary points, except the stationary points defined by  $a_u = a_0(1 - u)$ ,  $x_1 = 0$  and  $x_2 = 0$  that are trivial.

#### B. Strategy to stabilize the model

From the fact that the model has not stationary points, the aim is to devise a control strategy that force  $x_1(t)$  and  $x_2(t)$  to stay bounded. Considering the structure of the model and the fact that  $x_1(t)$  does not depend on  $x_2(t)$

$$x_1(t) = e^{\int_{t_0}^t w_{11}(a(\tau))d\tau} x_1(t_0),$$

it is possible to force the state variable  $x_1(t)$  to decrease exponentially to zero if  $\int_{t_0}^t w_{11}(a(\tau))d\tau < 0$ . This can be achieved by adjusting  $a(t)$  such that  $a(t) < a_c$ .

Parameter	Value	Unit	Note
$\gamma$	0.08	[1/day]	Androgen clearance and production rate
$a_0$	30	[nmol/l]	Normal androgen concentration level
$\alpha_1$	0.0204	[1/day]	Proliferation rate of AD cells at $a(t) = a_0$
$\beta_1$	0.0076	[1/day]	Apoptosis rate of AD cells at $a(t) = a_0$
$\alpha_2$	0.0242	[1/day]	Proliferation rate of AI cells at $a(t) = 0$
$\beta_2$	0.0168	[1/day]	Apoptosis rate of AI cells at $a(t) = 0$
$k_1$	0	[]	$\alpha_1 k_1$ is the proliferation rate of AD cells at $a = 0$
$k_2$	2	[]	Plausible value, see $p_1(a(t))$
$k_3$	8	[]	$\beta_1 k_3$ is the apoptosis rate of AD cells at $a = 0$
$k_4$	0.5	[]	Plausible value, see $q_1(a(t))$
$D$	[0, 1]	[]	Characterization of AI cells proliferation rate
$m_1$	0.00005	[1/day]	Mutation rate from AD cells at $a = 0$

TABLE I  
PARAMETER VALUES USED WITH THE MODEL [3] AND [8].

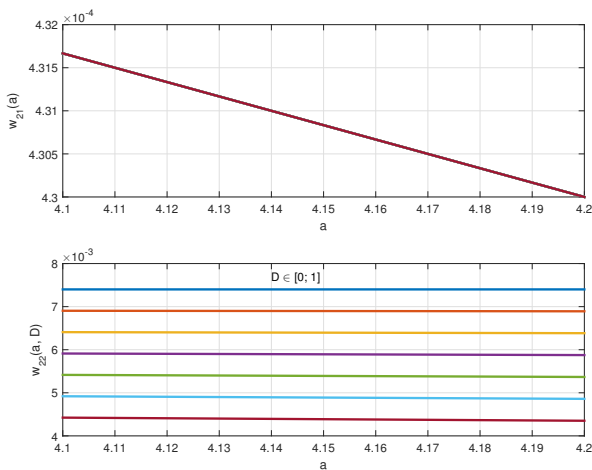


Fig. 2. Functions  $w_{21}(a)$  and  $w_{22}(a, D)$  evaluated around  $a = a_c$  with  $a_c = 4.143$ . This implies that  $w_{21}(a_c)x_1 + w_{22}(a_c)x_2 > 0$  and the model does not have stationary points.

Considering the expression of  $dx_2(t)/dt$  and if  $x_1(t)$  tends to zero, the term  $w_{21}(a(t))x_1(t) > 0$  will vanish and  $dx_2(t)/dt$  can be approximated by

$$dx_2(t)/dt \approx w_{22}(a(t))x_2(t).$$

It can be concluded that, in order to decrease  $x_2(t)$ ,  $w_{22}(a(t))$  must be negative ( $w_{22}(a(t)) < 0$ ). This is a necessary condition but it is not a sufficient condition.

It is interesting that, if the manipulated variable  $u(t)$  is kept constant, during a time interval (greater than  $2 \times \frac{1}{\gamma}$ ), it can impose a constant value on  $a(t)$ , and the subsystem formed by the state variables  $x_1(t)$  and  $x_2(t)$  can be viewed as a linear time varying system, where  $a(t)$  represents the switching variable,

$$\begin{bmatrix} \frac{dx_1(t)}{dt} \\ \frac{dx_2(t)}{dt} \end{bmatrix} = \begin{bmatrix} w_{11}(a) & 0 \\ w_{21}(a) & w_{22}(a, D) \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix}. \quad (18)$$

This approximation depends on the dynamics of  $a(t)$ ,  $x_1(t)$  and  $x_2(t)$ . The poles of this linear subsystem are  $p_1 = w_{11}(a)$  and  $p_2 = w_{22}(a, D)$ , where  $a \in [0, a_0]$  and  $D \in [0; 1]$ . Figure 3 shows the behaviour of  $w_{11}(a)$  and  $w_{22}(a, D)$ . By inspecting the behaviour of  $w_{22}(a, D)$ , there are regions where  $w_{22}(a, D)$  is positive and this depends only on the  $D$  parameter ( $D \in [0; 0.3]$ ). In this case,  $\frac{dx_2(t)}{dt} > 0$ , the model is uncontrollable. But for  $D \in ]0.3; 1.0]$ ,  $u(t)$  can be used to select  $a(t)$  to obtain  $\frac{dx_2(t)}{dt} < 0$ .

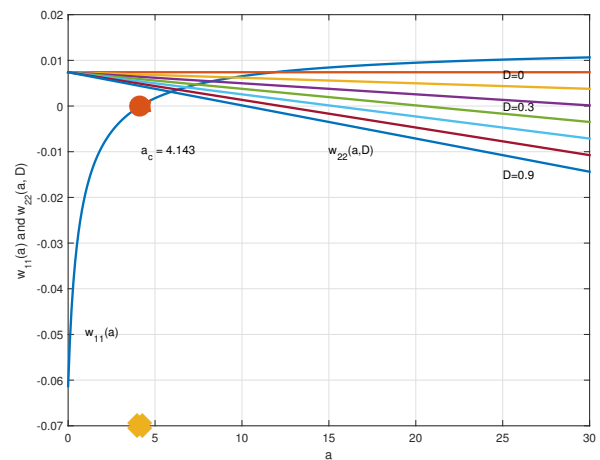


Fig. 3. Behaviour of the function  $w_{11}(a)$  and the function  $w_{22}(a, D)$ , where  $D \in [0; 1]$ . Both functions define the poles of the linear varying subsystem.

Considering now the behaviour of  $w_{11}(a(t))$  and  $w_{22}(a(t), D)$  for  $D \in ]0.3; 1.0]$ , (see figure 3), there are three cases that must be considered. As an example consider  $D = 0.6$ , in the figure 4, there are three zones where  $w_{11}(a(t))$  and  $w_{22}(a(t), D)$  evolve from negative ("stable") to positive ("unstable").

- Zone 1, for  $a < a_c$ ,  $x_1(t)$  decreases and  $x_2(t)$  increases because  $w_{11}(a(t)) < 0$  and  $w_{22}(a(t), D) > 0$ .
- Zone 2, for  $a \in ]a_c, 15.3]$ ,  $x_1(t)$  increases and  $x_2(t)$  increases because  $w_{11}(a(t)) > 0$  and  $w_{22}(a(t), D) > 0$ .

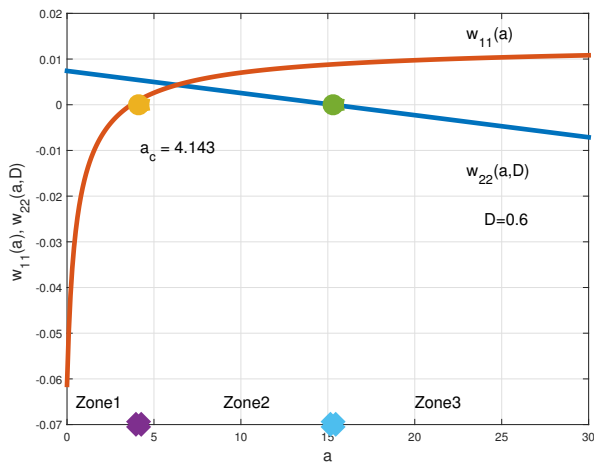


Fig. 4. Illustration of  $w_{11}(a)$  and  $w_{22}(a, D)$  for constant values of  $a(t)$  and with  $D = 0.6$ .

- Zone 3, for  $a > 15.3$ ,  $x_1(t)$  increases and  $x_2(t)$  decreases because  $w_{11}(a(t)) > 0$  and  $w_{22}(a(t), D) < 0$ .

This behavior of the functions  $w_{11}(a(t))$  and  $w_{22}(a(t), D)$  suggests a control law based on a switching mechanism to stabilize the model. The aim is to apply a value  $a_L$  from zone 1, a (long enough) finite time interval such that  $x_1(t)$  decreases and  $x_2(t)$  increases, and to switch to a value  $a_M$  from zone 3 with the purpose to increase  $x_1(t)$  and to decrease  $x_2(t)$ . In order to simplify the presentation of the analysis, the effect of transient of  $a(t)$  in the closed/loop stability associated to the switching of  $u(t)$ , is not included.

The values of  $a_L$  and  $a_M$  are selected to obtain high decreasing rates for  $dx_1(t)/dt < 0$  or  $dx_2(t)/dt < 0$  and low increasing rates for  $dx_1(t)/dt > 0$  and  $dx_2(t)/dt > 0$ . The selection is based on the data presented in the figures 3 and 4,  $a_L = 0$  and  $a_M = a_0$ .

The matrices with the coefficients  $w_{ij}$  are

$$W(a_L) = \begin{bmatrix} -0.0613 & 0 \\ 0.0005 & 0.0074 \end{bmatrix}, \quad (19)$$

$$W(a_M) = \begin{bmatrix} 0.0108 & 0 \\ 0.0000 & -0.0071 \end{bmatrix}. \quad (20)$$

The aim is to choose time intervals  $T_1$  and  $T_2$  such that the closed model is stable.

From a stability analysis the time intervals  $T_1$  and  $T_2$  must be such that, the transition matrix  $\Phi(T_2)\Phi(T_1)$  must have the eigenvalues  $0 < \lambda_i < 1$ , where  $\Phi(T_1) = e^{W(a_L)T_1}$  and  $\Phi(T_2) = e^{W(a_M)T_2}$ .

As a simplified numerical example, where  $W(a_L)$  is approximated by a diagonal matrix, the following inequalities are obtained,

$$-0.0613T_1 + 0.0108T_2 < 0, \quad (21)$$

$$0.0074T_1 - 0.0071T_2 < 0, \quad (22)$$

that yields

$$1.04T_1 < T_2 < 5.67T_1.$$

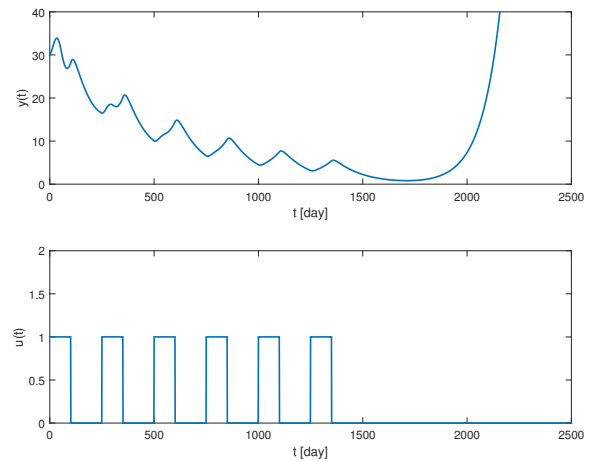


Fig. 5. Exp1: Control of the prostate model ( $D = 0.6$ ), switching period  $T_1 = 100$  and  $T_2 = 150$ . For  $t > 1500$  the control was suspended, causing the population of AD cells to grow exponentially.

Additional conditions can be obtained by choosing the maximum increasing factor for  $x_2(t)$  during the interval  $T_1$  ( $f_i > e^{0.0074T_1}$ ), and for  $x_1(t)$  during the time interval  $T_2$  ( $f_i > e^{0.0108T_2}$ ). The time period of the switching control is defined by  $T = T_1 + T_2$ .

It must be emphasized that  $a(t)$  can not be switched instantaneously, it depends on the parameter  $\gamma$ , the androgen clearance and production rate. For a detailed stability analysis this dependence must be taken in consideration because there is a finite time interval, corresponding to the crossing of zone 2 (figure 4), where  $x_1(t)$  and  $x_2(t)$  increase.

#### IV. PROPOSED CONTROL LAW

In practice the variable  $x_1(t)$  and  $x_2(t)$  are not measured. The variable that is measured and controlled is the PSA, that is represented by the variable  $y(t)$ . From the previous section it was concluded that it is possible to find a control mechanism to switch (periodically)  $u(t)$  between a lower value  $u_1 = 0$  and a higher value  $u_2 = 1$ , that forces  $a(t)$  to switch between  $a_L$  and  $a_M$  causing  $x_1(t)$ ,  $x_2(t)$  and  $y(t)$  to converge to zero.

The figure 5 shows the results obtained with the switching mechanism define by  $T_1 = 100$ ,  $T_2 = 150$ ,  $u_1 = 0$  and  $u_2 = 1$ . The initial values of the state variables are  $a(0) = a_0$ ,  $x_1(0) = 15$  and  $x_2(0) = 15$ . The control was suspended after  $t > 1500$  to visualize the uncontrolled increase of  $x_1(t)$ , that represents the population of AD cells. The state variables  $a(t)$ ,  $x_1(t)$  and  $x_2(t)$  are shown in the figure 6. The results that are shown in the figures 7 and 8 were obtained in the same conditions as used in experiment 1, figures 5 and 6, but the control input is set to its maximum value after  $t > 1500$ . In this case the population of AD cells decreases to zero but the AI cells increase exponentially.

With the application of the periodic control signal,  $x_1(t)$  and  $x_2(t)$  converge to zero. From a clinical point of view it is questionable to continue the administration of a drug when the PSA has a "very low" value, because that may cause

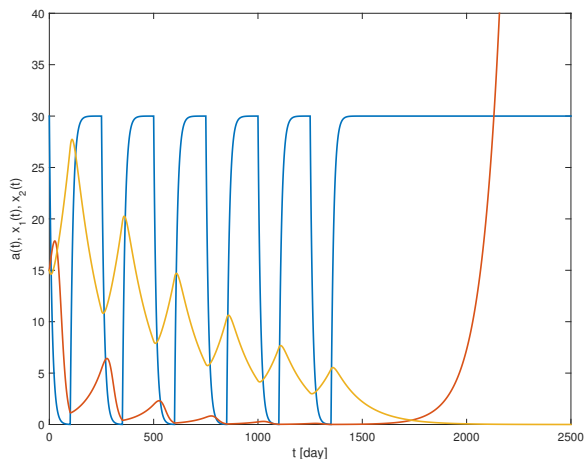


Fig. 6. Exp1: Evolution of the state variables of the prostate model ( $D = 0.6$ ), switching period  $T_1 = 100$  and  $T_2 = 150$ . For  $t > 1500$  the control was suspended, causing the population of AD cells to grow exponentially.

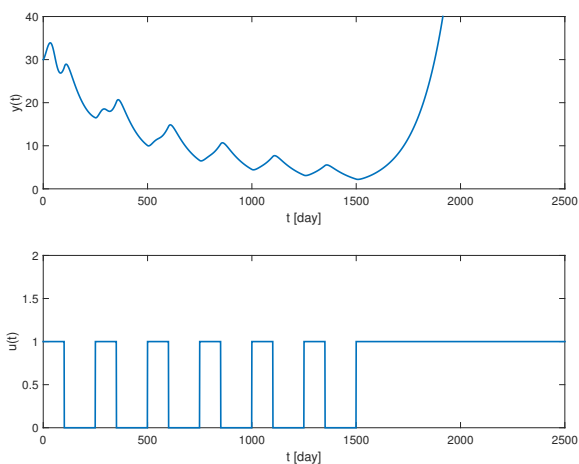


Fig. 7. Exp2: Control of the prostate model ( $D = 0.6$ ), switching period  $T_1 = 100$  and  $T_2 = 150$ . For  $t > 1500$  the control was set to 1 causing the population of AI cells to grow exponentially.

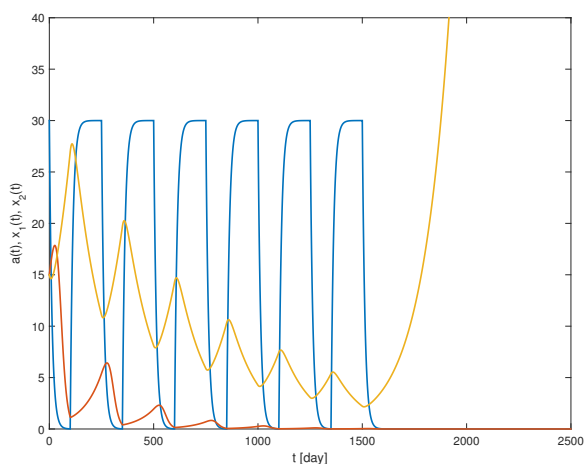


Fig. 8. Exp2: Evolution of the state variables of the prostate model ( $D = 0.6$ ), switching period  $T_1 = 100$  and  $T_2 = 150$ . For  $t > 1500$  the control was set to 1 causing the population of AI cells to grow exponentially.

side-effect in the patient without any relevant gains to him. A possible approach to reduce and to adjust the amount of drug is to use a trigger mechanism that start the periodic control signal when  $y(t) > y_{trig}$  and, stops the periodic control signal if  $y(t) < y_{stop}$ . This is illustrated in the figures 9 and 10. The initial state is  $a(0) = a_0$ ,  $x_1(0) = 15$  and  $x_2(0) = 15$ . With the use of the trigger mechanism, the pulse width for  $u = 1$  is reduced by 10%.

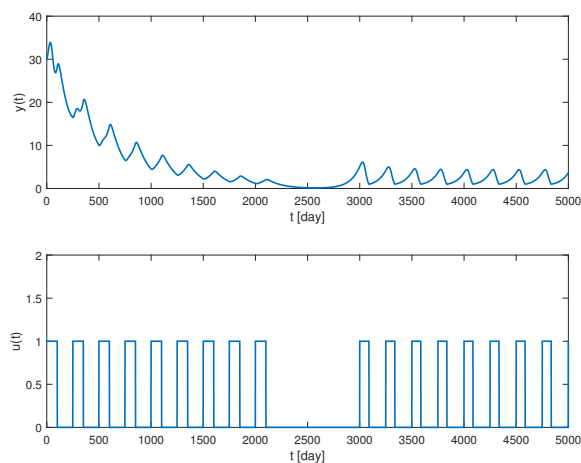


Fig. 9. Exp3: Control of the prostate model ( $D = 0.6$ ) using the periodic control signal that is filtered by a relay mechanism.

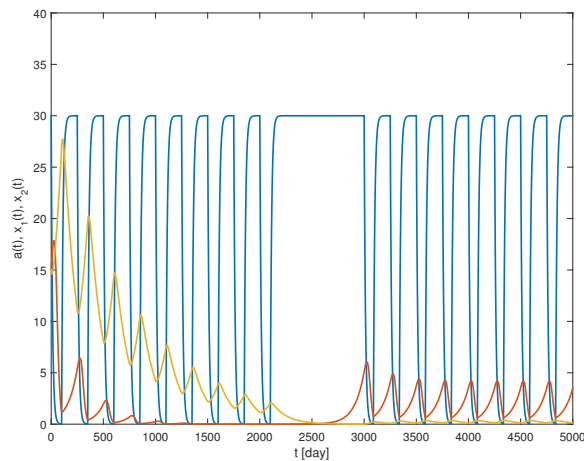


Fig. 10. Exp3: Evolution of the state variables of the prostate model ( $D = 0.6$ ) using the periodic control signal that is filtered by the relay mechanism.

The computer numerical simulations show that  $x_1(t)$  and  $x_2(t)$  are controlled. The implementation of the relay mechanism was simplified, the switched control signal is applied during  $y(t) > y_{trig}$  and it is blocked for  $y(t) < y_{stop}$ . The actuation of the relay mechanism is not synchronized with the time-based switched control signal and the relay mechanism does not trigger the start of the time-based switched control signal.



## V. CONCLUSIONS

This article addresses the control of a nonlinear model of prostate cancer. This model is open-loop unstable. To address the control design, the structure and the stability properties of the model are explored. A time based switched control is proposed that renders a stable closed-loop. From a clinical point of view it is questionable to continue the administration of drug when the PSA has a "very low" value, because that may cause side-effect in the patient without any relevant gains to the patient. A possible approach is to reduce and to adjust the amount of drug using a trigger mechanism that starts the periodic control signal when  $y(t) > y_{trig}$  and stops the periodic control signal if  $y(t) < y_{stop}$ .

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