Prostate Cancer Treatment Using Fixed-Time Synergetic Controller

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บทคัดย่อ การกำหนดการรักษาโรคมะเร็งต่อมลูกหมากสามารถดำเนินการได้บนพื้นฐานของการควบคุมป้อนกลับไม่เชิงเส้น ในการควบคุมป้อนกลับแบบเวลาบังคับ สามารถกำหนดขอบเขตของเวลาเข้าสู่ได้ล่วงหน้าโดยไม่ต้องคำนึงถึงเงื่อนไขเริ่มต้น วิธีการควบคุมนี้สามารถนำไปประยุกต์ใช้ได้อย่างหลากหลายดังจะเห็นได้จากการสำรวจวรรณกรรมก่อนหน้านี้ วิธีการควบคุมแบบซินเนอร์เจติกสามารถที่จะควบคุมระบบไม่เชิงเส้นโดยปราศจากสัญญาณความถี่สูงในสัญญาณควบคุม ดังนั้นการศึกษาการประยุกต์ใช้การควบคุมซินเนอร์เจติกเวลาบังคับเพื่อสังเคราะห์การรักษาสำหรับผู้ป่วยโรคมะเร็งต่อมลูกหมากจึงได้มีการค้นคว้าในการศึกษานี้ และได้จำลองสถานการณ์ของระบบควบคุมมะเร็งต่อมลูกหมากเพื่อแสดงให้เห็นถึงความสามารถของการรักษาที่ได้เสนอในการศึกษานี้ ผลการจำลองสถานการณ์แสดงให้เห็นว่าตัวแปรสภาวะของระบบควบคุมนี้ลู่เข้าสู่ระดับที่ต้องการภายในขอบเขตของเวลาที่ได้กำหนดล่วงหน้าของตัวแปรแมคโครที่สอดคล้องด้วยการรักษาที่ปราศจากสัญญาณความถี่สูง จากการควบคุมการรักษาที่ได้นำเสนอนี้ ระบบควบคุมมะเร็งต่อมลูกหมากมีเสถียรภาพแบบเวลาบังคับโดยปราศจากสัญญาณความถี่สูงในการรักษา

คำสำคัญ : มะเร็งต่อมลูกหมาก, การควบคุมป้อนกลับไม่เชิงเส้น, การควบคุมซินเนอร์เจติก, การลู่เข้าในเวลาบังคับ

Abstract Treatment for prostate cancer can be determined based on nonlinear feedback control. In fixed-time feedback control, the bound of settling time can be pre-specified regardless of an initial condition. This control method has been successfully employed in various applications as seen in past literature. The synergetic control method is capable of controlling nonlinear systems under chattering free control inputs. Thus, studying the application of fixed-time synergetic control to synthesize the treatment for a prostate cancer patient was investigated in this study. The controlled prostate cancer

treatment system was simulated to demonstrate the capability of the proposed treatment. Apparently, the state variables of the control system were driven to the required level within the pre-defined bound of the convergence time of the corresponding macro variables by the chattering-free control treatments. According to the proposed control treatment, the controlled prostate cancer treatment system has fixed-time stability without chattering in the control treatment.

Keywords: prostate cancer, nonlinear feedback control, synergetic control, fixed-time convergence

1. Introduction

Referring to information provided by WHO [1], cancer is one of the deadliest diseases. In 2018, the lives of approximately 9.6 million individuals around the world were taken away by the disease [2]. One of the common detected cancerous tumors in males is prostate cancer [1, 3]. In 2018, the prevalence of prostate cancer was approximately 1,280,000 cases; and the mortality rates were higher than 350,000 deaths [4 - 6]. The symptoms are, for example, anemia, renal failure, and paralysis caused by spinal metastases [6, 7]. The prostate cancer can be detected by using digital rectal examination (DRE), which measures the level of serum prostate-specific antigen (PSA), and MRI [5]. Androgen deprivation therapies (ADT) are normally used to suppress the prostate cancer during the metastatic stage. This approach can be achieved by using androgen-suppressing agents or castration [7]. Nowadays, more effective and safer androgen-suppressing agents such as gonadotropin-releasing-hormone (GnRH) analogues are commonly used for the treatment [7].

Like other types of cancer, during the last two decades, the mathematical models for prostate cancer were developed and presented in various forms [8 - 12]. These models represent the dynamic growth of prostate cancer as affected by the androgen hormones in the male reproductive system. They were constructed based on the populations of cancers, related antigens, and different regimens of therapies [10]. According to [8 - 12], androgen-dependent (AD) cells, androgen-independent (AI) cells, were commonly considered as state variables of the prostate cancer system. For the treatment, typical therapies such as continuous and intermittent ADT were generally considered as control variables or inputs. This mathematical representation is feasible for the designers to apply feedback control to determine the treatment for a prostate cancer patient [8, 11]. Iedata et al. [8] presented the mathematical model of prostate cancer with a control variable. In their model, the control variable represents the control androgen hormone. Also, the feedback control was applied to define the treatment for a patient. According to [11], sliding mode control was employed to define the prostate cancer treatment. The treatment given by the sliding mode control was robust to uncertainties or noises [13]. However, the chattering phenomena is the drawback and needs to be addressed. In [11], the chattering was solved by employing the super twisting sliding mode control to determine the cancer treatment.

The synergetic control is a suitable approach applicable for complex nonlinear high-order systems. This method was introduced by Kolesnikov et

al. [14 - 16]. If a proper selection of the macro variables of the synergetic controller is made, it is possible to obtain the desired characteristics of the control system, including parameter insensitivity, noise suppression, and global stability. Importantly, the control system with a set of chattering- free control inputs is attained [17].

Finite time convergence control can drive the state variables of a dynamical system to their equilibrium points in finite time. This finite time can be pre- determined by the designer based on the controller parameters and the initial condition of the control system [18, 19]. For synergetic control, this convergence characteristic can be achieved by using the terminal or finite time synergetic control as well. This type of synergetic control was also applied in various nonlinear high- order dynamical systems such as robotics [20], mechanical systems [21], electrical systems [22], and glucose regulation homeostasis [23].

However, when the information of the initial condition is lacking or unknown, the designer cannot determine the convergence time of the control system in advance. This drawback can be solved by using the concept of fixed-time control which is firstly introduced with sliding mode control by Polyakov et al. [24]. The key advantage of the fixed-time control is that the bound of convergence time or settling time can be pre- specified from the controller parameters without requiring the information relevant to the initial conditions. The concept of fixed-time convergence was also employed with the synergetic control by selecting the dynamic evolutions of macro variables that satisfy this characteristic. This control method is known as the fixed-time synergetic control [25 - 27]. Thus, two improvements regarding to convergence and chattering- free properties can be achieved. Several applications of fixed-time synergetic control which includes power systems [25] and hydraulic systems [26]. Also, this type of synergetic control has been utilized to control the biological systems such as glucose systems [27] and biological pest control systems [28]. Dubey and Chakraborty [11] have applied the super twisting sliding mode control in this application. However, the pre-specifying bound of the settling time has not been analyzed.

Given the advantages of the fixed-time synergetic control, this work is aimed to study the application of the fixed- time synergetic controller design procedure to synthesize the treatment of prostate cancer. To the best of the authors' knowledge, this control method has not been applied to the prostate cancer control.

This paper is organized in the following sections. The mathematical representation of the prostate cancer system is illustrated in Section 2. In Section 3, the fixed- time synergetic controller design for prostate cancer treatment is provided. Section 4 shows the simulation of the controlled prostate cancer treatment system. Section 5 is the study conclusion.

2. Materials and Methods

According to the advantages of hormone therapy, the model structure proposed by Ideta et al. [8] is appropriate for determining the treatment based on the feedback control. The model consists of three state variables including the concentration of AI cell, the concentration of AD cell, and the concentration of the androgen. The model has one control input affecting the androgen concentration. The further modified version of the model by Ideta et al. [8] is presented by Tanaka et al. [12] and Dubey and Chakraborty [11]. In [11], the three control inputs were added into

the model in [8] . These control inputs directly affect each concentration of the AD cell, the AI cell, and the androgen cell. According to [11] , the model can be presented as (1) [8, 11]:

$$\begin{aligned}\dot{x} &= \alpha_x(k_1+(1-k_1)\frac{z}{z+k_2})x \\ &\quad -\beta_x(k_3+(1-k_3)\frac{z}{z+k_4})x \\ &\quad -m_1(1-\frac{z}{z_0})+u_1, \\ \dot{y} &= \alpha_y(1-\frac{dz}{z_0})-\beta_y y+m_1(1-\frac{z}{z_0})+u_2, \\ \dot{z} &= -\frac{1}{\tau}z+u_3,\end{aligned} \tag{1}$$

where x and y denote the population of the AD cells and the AI cells, respectively; and z denotes the concentration of the androgen. The variables u_1 , u_2 , and u_3 represent the control inputs.

The model parameters in [8, 11] are defined as follows. Parameters referring to the rates of proliferation and apoptosis corresponding to the AD cells are denoted by α_x and β_x , respectively; when $z = z_0$. Likewise, the parameter α_y denotes the proliferation of AI cells at $z = 0$, and the parameter β_y denotes apoptosis rates of AI cells. The parameter k_1 is associated with the proliferation rate of the AD cells, $\alpha_x k_1$, at $z = 0$. The plausible rate of the AD cells is denoted by k_2. The parameter k_3 is associated with the apoptosis rate of the AD cells, $\beta_x k_3$, at $z = 0$. The parameter k_4 represents the plausible rate of the apoptosis rate corresponding to the AD cells. The rate of mutation from AD to AI cells when $z = 0$ is represented by m_1. The parameter d refers to the slope of the proliferation rate curve corresponding to the AI cells. The normal androgen level is z_0. The time constant of the androgen dynamic is denoted by τ. The parameters r_1 and r_2 represent the upper and lower thresholds corresponding to the serum PSA level, respectively. The time of the model is denoted by t in the unit of day.

Let $x_1 = x$, $x_2 = y$ and $x_3 = z$, the model equation (1) can be expressed as equation (2):

$$\dot{x}_i = f_i(x)+u_i, \tag{2}$$

for $i = 1, 2, 3$ where

$$\begin{aligned}f_1(x) &= \alpha_x(k_1+(1-k_1)\frac{x_3}{x_3+k_2})x_1 \\ &\quad -\beta_x(k_3+(1-k_3)\frac{x_3}{x_3+k_4})x_1 \\ &\quad -m_1(1-\frac{x_3}{x_{30}}), \\ f_2(x) &= \alpha_y(1-\frac{dx_3}{x_{30}})-\beta_y x_2 \\ &\quad +m_1(1-\frac{x_3}{x_{30}}),\end{aligned}$$

and $f_3(x) = -\frac{1}{\tau}x_3$.

In the fixed-time synergetic control design, some mathematical preliminaries are collected below.

Lemma 1 [29] If $\sigma_1, \sigma_2, ..., \sigma_n$ and q are real with $\sigma_1, \sigma_2, ..., \sigma_n > 0$ and $q > 0$, then

$$\begin{aligned}&(\sigma_1+\sigma_2+,...,+\sigma_n)^q \\ &\le \max(n^{q-1},1)(\sigma_1{}^q+\sigma_2{}^q+,...,+\sigma_n{}^q).\end{aligned} \tag{3}$$

Corollary 2 [30] Consider the dynamical system of state vector $x(t) \in \mathbb{R}^n$ represented by a nonlinear function vector $f : \mathbb{R}^n \to \mathbb{R}^n$ as equation (4):

$$\dot{x}(t) = f(x(t)), \quad x(0) = x_0. \tag{4}$$

If there exists a positive definite function, $V(x): \mathbb{R}^n \to \mathbb{R}$ and $V(x)$ is a regular and radially unbounded function such that the inequality equation (5) is satisfied by any solution of the system equation (4).

$$\dot{V}(x) \le -\alpha V^{\nu} - \beta V^{\mu}, x(t) \in \mathbb{R}^n \setminus \{0\}, \tag{5}$$

where $\alpha, \beta, \nu > 0$ and $\nu > 1$, $0 < \mu < 1$, then the system equation (4) is fixed-time stable at the zero equilibrium, and the bound of the settling time is obtained by

$$T(x_0) \le T_{\max} \triangleq \frac{1}{\beta}\left(\frac{\beta}{\alpha}\right)^{\frac{1-\mu}{\nu-\mu}}\left(\frac{1}{1-\mu}+\frac{1}{\nu-1}\right) \tag{6}$$

According to [11] , the control objective is to determine the prostate cancer treatment so that concentration of AD cells (x_1), AI cells (x_2), and androgen (x_3) concentrations are driven to the corresponding desired levels, x_{1r} , x_{2r} , and x_{3r}. The dynamic errors are defined as equation (7):

$$e_i = x_i - x_{ir} \quad \text{for } i = 1,2,3. \tag{7}$$

The fixed-time synergetic controller design process can be utilized to determine the treatment for a prostate cancer patient. In accordance with [14, 17, 20, 27, 28] , the design procedure is shown below:

1) The macro variables are selected based on the control objective and control inputs as equation (8):

$$\psi_i = e_i + k_{Ii}\int_0^t e_i(\tau)d\tau. \tag{8}$$

For $i = 1, 2, 3$. At $\psi_i = 0$, the dynamic errors, $e_i(t)$, converges to zero for $i = 1, 2, 3$.

2) The dynamic evolution of each macro variable is selected as [31, 32]:

$$\dot{\psi}_i = -a_i\psi_i^{g/h} - b_i\psi_i^{l/m}, \tag{9}$$

where the coefficient a_i and b_i are real numbers and denoted as $a_i > 0$ and $b_i > 0$ for $i = 1, 2, 3$. The exponent terms in, g , h , l , and m , are odd numbers with $1 < g/h < 2$ and $0 < l/m < 1$.

3) The control inputs are determined by solving u_1, u_2 , and u_3 from equation (9). Substituting the prostate cancer model equation (2) into equation (9) yields

$$f_i(x) + u_i - \dot{x}_{ir} + k_{Ii}e_i = -a_i\psi_i^{g/h} - b_i\psi_i^{l/m} \tag{10}$$

for $i = 1, 2, 3$. Solving equation (10) gives

$$u_i = a_i\psi_i^{g/h} + b_i\psi_i^{l/m} - f_i + \dot{x}_{ir} - k_{Ii}e_i. \tag{11}$$

The control system stability can be proved below. The Lyapunov function is selected as equation (12):

$$V = 0.5\psi_1^{\,2} + 0.5\psi_2^{\,2} + 0.5\psi_3^{\,2}. \tag{12}$$

Derivative of equation)12 (is obtained as

$$\begin{aligned}\dot{V} &= \psi_1\dot{\psi}_1 + \psi_2\dot{\psi}_2 + \psi_3\dot{\psi}_3 \\ &= \psi_1[\dot{x}_1 - \dot{x}_{1r} + k_{I1}e_1] \\ &\quad +\psi_2[\dot{x}_2 - \dot{x}_{2r} + k_{I2}e_2] \\ &\quad +\psi_3[\dot{x}_3 - \dot{x}_{3r} + k_{I3}e_3] \\ &= \psi_1[f_1(x) + u_1 - \dot{x}_{1r} + k_{I1}e_1] \\ &\quad +\psi_2[f_2(x) + u_2 - \dot{x}_{2r} + k_{I2}e_2] \\ &\quad +\psi_3[f_3(x) + u_3 - \dot{x}_{3r} + k_{I3}e_3].\end{aligned} \tag{13}$$

Substituting u_1, u_2 , and u_3 into equation (13) gives

$$\begin{aligned}\dot{V} &= \psi_1[-a_1\psi_1^{g/h} - b_1\psi_1^{l/m}] \\ &\quad +\psi_2[-a_2\psi_2^{g/h} - b_2\psi_2^{l/m}] \\ &\quad +\psi_3[-a_3\psi_3^{g/h} - b_3\psi_3^{l/m}], \\ \dot{V} &= -\sum_{i=1}^{3} a_i\left(\psi_i^{\,2}\right)^{(g+h)/(2h)} \\ &\quad -\sum_{i=1}^{3} b_i\left(\psi_i^{\,2}\right)^{(l+m)/(2m)}.\end{aligned} \tag{14}$$

Based on Lemma 1, equation (14) can be obtained as equation (15):

$$\dot{V} \le -\frac{1}{S_a}[a_1\psi_1^{\,2} + a_2\psi_2^{\,2} + a_3\psi^3]^{(g+h)/(2h)} \frac{1}{S_b}[b_1\psi_1^{\,2} + b_2\psi_2^{\,2} + b_3\psi_3^{\,2}]^{(l+m)/(2m)}, \quad (15)$$

wher $S_a = \max(3^{(g+h)/(2h)-1},1)$ and $S_b = \max(3^{(l+m)/(2m)-1},1)$. Then, we manipulated equation (15) as

$$\begin{aligned}\dot{V} &\le -\left(\frac{1}{S_a}a_{\min}2^{\frac{(g+h)}{(2h)}}\right)\left(\frac{1}{2}\sum_{i=1}^{3}\psi_i^{\,2}\right)^{\frac{(g+h)}{(2h)}} \\ &\quad -\left(\frac{1}{S_b}b_{\min}2^{\frac{(l+m)}{(2m)}}\right)\left(\frac{1}{2}\sum_{i=1}^{3}\psi_i^{\,2}\right)^{\frac{(l+m)}{(2m)}} \\ \dot{V} &\le -\left(\frac{1}{S_a}a_{\min}2^{\frac{(g+h)}{(2h)}}\right)V^{\frac{(g+h)}{(2h)}} \\ &\quad -\left(\frac{1}{S_b}b_{\min}2^{\frac{(l+m)}{(2m)}}\right)V^{\frac{(l+m)}{(2m)}}.\end{aligned} \quad (16)$$

According to Corollary 2 and equation (16), the controlled prostate cancer treatment system satisfies the fixed- time stability condition in (5). Thus, the bound of the settling time of the control system is defined by equation (17):

$$T(\psi_0) \le \frac{1}{\beta}\left(\frac{\beta}{\alpha}\right)^{\frac{1-\mu}{\nu-\mu}}\left(\frac{1}{1-\mu}+\frac{1}{\nu-1}\right), \quad (17)$$

where $\alpha = \dfrac{a_{\min}2^{\nu}}{\max(3^{\nu-1},1)}$, $\beta = \dfrac{b_{\min}2^{\mu}}{\max(3^{\mu-1},1)}$, $\nu = \dfrac{(g+h)}{(2h)}$, and $\mu = \dfrac{(l+m)}{(2m)}$.

3. Results and Discussion

The prostate cancer system presented by Dubey and Chakraborty [11] was used as a simulation example. The treatment based on fixed- time synergetic control in equation (11) was applied to the system. The system parameters from [11] and [12] were used for simulation. These parameters are defined as follows : (i) $\alpha_x = 2.04\times10^{-2}\,\mathrm{d}^{-1}$, $\beta_x = 7.60\times10^{-3}\,\mathrm{d}^{-1}$, $\alpha_y = 2.42\times10^{-2}\,\mathrm{d}^{-1}$, and $\beta_y = 1.68\times10^{-2}\,\mathrm{d}^{-1}$, (ii) $k_1 = 0$, $k_2 = 2$, $k_3 = 8$, and $k_4 = 0.5$, (iii) $d = 1$ ($0 \le d \le 1$) , (iv) $m_1 = 5.00\times10^{-5}\,\mathrm{d}^{-1}$,(v) $z_0 = x_{30} = 20.00\,\mathrm{nmoll}^{-1}$, (vi) 62.50 days, $r_1 = 10.00\,\mathrm{ng\,ml}^{-1}$, and $r_0 = 4.00\,\mathrm{ng\,ml}^{-1}$. The controller parameters are selected so that the pre-determined bound of the settling time is 120 days. First, we selected the exponent terms as $g = 5$, $h = 3$, $l = 3$, and $m = 5$; and the coefficient α is specified as $\alpha = 5.00\times10^{-3}$. The value of $a_{\min}$ and $b_{\min}$ were calculated from equation (17). Finally, we set as $a_1 = a_2 = a_3 = a_{\min}$ and $b_1 = b_2 = b_3 = b_{\min}$. The value of k_{Ii} for $i = 1, 2, 3$ were selected as $k_{I1} = k_{I2} = k_{I3} = 1.01\times10^{-5}$. The control system was simulated in MATLAB software. The Runge Kutta method was applied for numerical simulation from the initial time $t_0 = 0$ to the final time $t_f = 400$ days. The incremental time used in the numerical integration is 0.01 day. To demonstrate the fixed- time convergence property of the proposed prostate cancer treatment, three different initial conditions were used for simulation: (i) $x(0) = [15.00, 0.10, 12.00]^T$ IC$_1$) from [8, 11]. (ii) $x(0) = [20.00\ 0.50\ 32.00]^T$ (IC$_2$), and (iii) $x(0) = [25.00\ 1.10\ 22.00]^T$ (IC$_3$) . The simulation results of the controlled

prostate cancer treatment system under the fixed-time synergetic treatment are shown here. The plots of the state variables of the three initial conditions are in Fig. 1, and the corresponding control inputs are in Fig. 2. The simulation results showed that the fixed-time synergetic control treatment can manipulate all state variables. These variables, including the AD cell population, AI cell population, and androgen concentrations from different initial conditions converge to zero. The macro variables converge to zero within the pre-specified convergence time of 120 days as shown in Fig.3. Also, the convergence times of the state variables corresponding to different initial conditions are not greater than 120 days. Moreover, the control input representing the treatment are free of chattering. Compared to the simulation results presented in [11] , our proposed treatment could manipulate the cancer populations and androgen concentration to zero as the treatment presented in [11] did. However, the bound of the settling time could be pre- specified according to the controller parameters independently from the initial condition.

Apparently, the treatment based on the fixed-time synergetic control is useful in practical situation since the bound of the settling time can be pre-specified despite the absence of information about the initial condition. Without the chattering in the control inputs, the treatment is feasible in practical implementation.

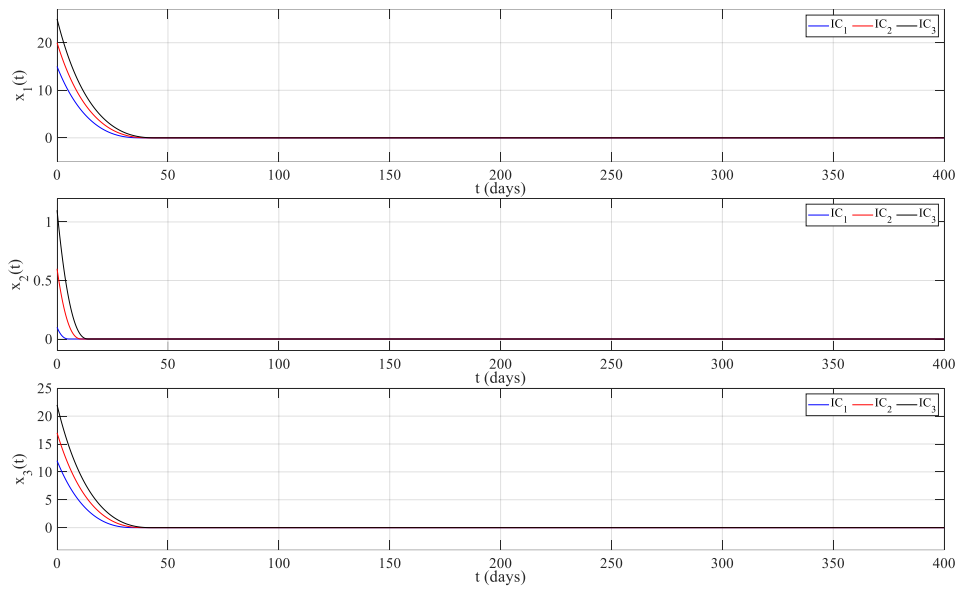

Fig. 1 The time responses of the control prostate system for three different initial conditions.

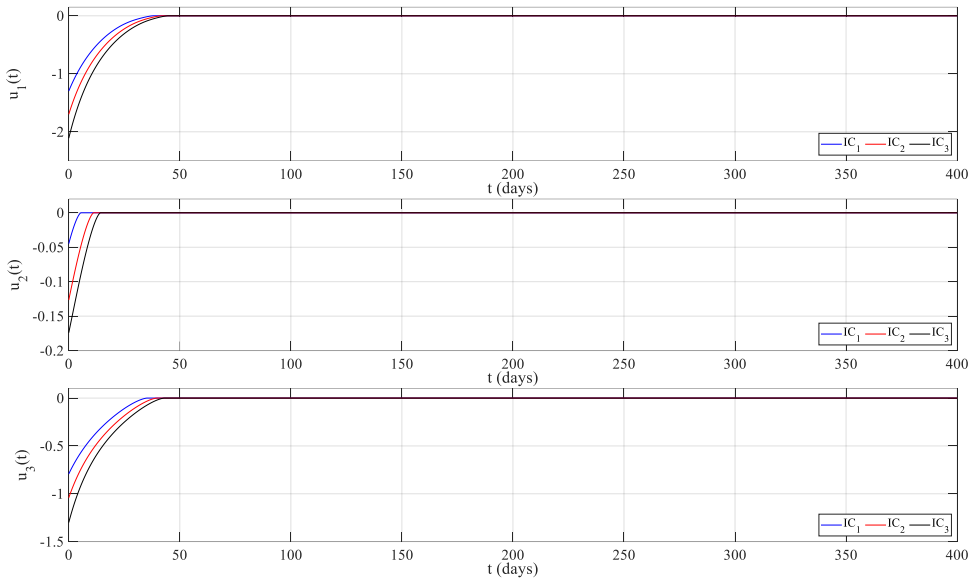

Fig. 2 The control inputs of the control prostate system for three different initial conditions.

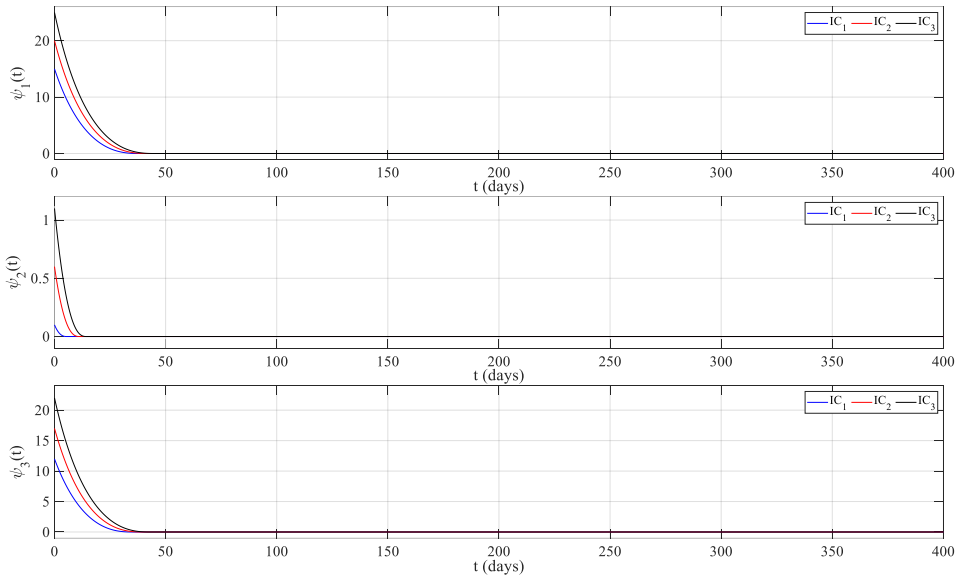

Fig. 3 The plot of the macro variables for three different initial conditions.

4. Conclusion

The fixed-time synergetic control was applied to synthesize the treatment for a prostate cancer patient. The controller design procedure was conducted based on the selected fixed-time dynamic evolution. The proposed control treatment provided the fixed-time stability property for the control prostate system. Simulation results showed that all state variables were driven to the specified value within the pre-defined

bound of settling time of the corresponding macro variables under the chattering free control inputs. Using the fixed-time synergetic control to determine the treatment for a prostate cancer patient is an alternative approach that satisfies two preferable characteristics of the convergence and chattering phenomena. Therefore, the proposed control treatment is suitable in practical situations.

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