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ARTICLE

Control and Treatment of Bone Cancer: A Novel Theoretical Study

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ABSTRACT

The human body has symmetric bones. This paper uses control engineering concepts to design a suitable controller to synchronize two symmetric bones of the human body to control and treat bone cancer. A Nonsingular Terminal Sliding Mode Control (NTSMC) method will be employed to design the proposed control inputs. The control inputs can be the chemical drugs that can be used to treat bone cancer. The dynamical equations of bone cancer will be used to apply the designed control method and test it. For testing the designed controller, Simulink/MATLAB software will be used. The proposed controller is chattering-free, robust against uncertainties and external disturbances, and finite-time stable in the control engineering view. Bone cancer will be treated for almost one year using the proposed control method.

Keywords: Bone cancer; Synchronization; Finite-time stability; Biomedical engineering

1. Introduction

The human bones are composed of two types of cells: Osteoblast (OB) and Osteoclast (OC). This collection is called a Basic Multicellular Unit (BMU) [1,2]. Bone diseases are diverse, one of them is

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bone cancer. Bone cancer happens when the growth rate order of the bone cells (OB or OC) is disrupted, which grows into cancer cells (CCs) [1-3]. Osteosarcoma (OS) is a type of bone disease. When the OS happens in the bone, the discipline of the growth of the bone cells disorganizes. OS is more likely to happen at 13-16 years old and after 55 years old. This sickness more occurs in boy children [3,4]. OB cells are responsible for the remodeling of bone, and OC cells are for bone growth. If the order of growth and reproduction of these cells is lost, OB cells will grow more and cause CCs [5,6]. In the healthy bone (bone without cancer), OB and OC cells multiply clearly and periodically. However, in sick bone (cancerous bone), there is no systematic growth and reproduction [1].

Bones are the skeleton of the human body, and almost all of them are symmetrical. If one of the human bones becomes cancerous, the closest value of the parameters is its symmetric bone. Therefore, symmetric bone parameters can be used for the reconstruction and treatment of cancerous bone. This fact can be used to model, design, and control cancerous bones. This concept in control engineering is called "synchronization". In the synchronization problem, the variables and parameters of the "slave" system will be the same as the variables and parameters of the "master" system [7]. In the synchronization of two human bones, the cancerous bone (slave) will be the same as the healthy bone (master). For synchronization, the systems need to apply control inputs to the system. These control inputs in the synchronization of the human bones can be considered as the effect of the dose of the chemical drugs. Recently, many control efforts have been made using the synchronization concept in different fields, such as synchronizing communication systems [8,9], chaotic systems [10,11], and chemical systems [12,13].

The Nonsingular Terminal Sliding Mode Control (NTSMC) method is a robust finite-time control strategy that guarantees that the system states reach zero at a finite time. The NTSMC is an extended version of Finite-time Sliding Mode Control methods that have been used in controlling different applications. This method has been used to solve the stability and tracking problems of rigid manipulators, high-order nonlinear systems, and robotic surgery [14-16]. It is used for controlling some practical systems such as manipulator robots [17], perturbed nonlinear systems [18], DC-DC buck converters [19], Quadrotor unmanned aerial vehicles [20], underactuated underwater robots [21], acute Leukemia therapy [22]. Recently control engineering methods have been used to increase biomedical applications such as drug delivery in cancerous tumors [23], tumor treatment immunity [24], cancer chemotherapy [25], control the tumor growth [26], and angiogenic inhibition therapy [27]. An extended adaptive NTSMC using fractional disturbance observer has been presented to accelerate system response without resulting in chattering [28]. Also, the NTSMC has been used to deal with the time delay for controlling the integrating processes [29].

One of the challenges in the designed controller by NTSMC is the chattering phenomenon. The chattering phenomenon is because of the high frequency switching gain in the controller. Chattering is a very harmful phenomenon in control applications. It can reduce the actuators' age and add unwanted noise to the system. In biomedical applications, especially cancer treatment, the chattering causes to control inputs will be uncreatable. It means that the chattered control inputs cannot be created in the practical tests. Some types of control methods are developed to remove, eliminate or reduce the chattering from the control input signals [30-33].

This paper proposes three control signals to synchronize two symmetrical human bones to control bone cancer. It is assumed that one of the human bones (arm or leg bones) is cancerous with cancer, and it will be treated by applying the proposed control inputs, which are the effect of the chemical drugs. The proposed control inputs will be designed by the NTSMC control method. The control inputs are designed using the chattering-free concepts. Below are the most important features of the proposed control method:

- Robustness against model uncertainties and external disturbances,

- Chattering-free control of the bone cancer,
- Accurate tracking of the healthy cells,
- Smooth control of the system,
- Fast tracking of the master states,
- Implementable results in control signals.

2. Mathematics

Definition 1. Function $sig^a(x)$ with the relation between absolute function $|x|$ and symbol-function for $sig^a(x) = |x|^a sign(x)$ is defined. Function $sign(x)$ is defined as follows [34,35]:

$$sign(x) = \begin{cases} 1 \ ; \ x > 0 \\ 0 \ ; \ x = 0 \\ -1 \ ; \ x < 0 \end{cases} \quad (1)$$

Definition 2. The relation between absolute and signum function is as $|x| = xsign(x)$ [34].

Lemma 1. For a nonlinear system $\dot{x} = f(x), f(0) = 0, x \in D \subseteq \Re^n, x(0) = x_0$ by assuming the constants ρ_1 to ρ_4 as $\rho_1 > 0, \rho_2 > 0, \rho_3 > 1, \rho_4 = 1 - \frac{1}{2\rho_3}, \rho_5 = 1 + \frac{1}{2\rho_3}$ and Lyapunov function $V(x): \Re^n \to \Re^+ \cup \{0\}$, as a scalar continuous radially unbounded function therefore if $\dot{V}(x) \leq -\rho_1 V^{p4}(x) - \rho_2 V^{p5}(x)$ so the equilibrium $x = 0$ of this system will be globally finite-time stable, and state variables of this system converge from each initial condition to zero, and the upper bound of its settling time is for $T \leq \pi\rho_3(\sqrt{\rho_1\rho_2})^{-1}$ [36].

Lemma 2. Considering scalars $a_1, a_2, ..., a_n \in \Re$ and choosing $0 < q < 2$ then will have $|a_1|^q + |a_2|^q + ... + |a_n|^q \geq \left(a_1^2 + a_2^2 + ... + a_n^2\right)^{\frac{q}{2}}$ [37].

3. Explanation of the purpose

This paper aims to synchronize the OBs and OCs cells of the cancerous bone to OBs and OCs cells of the symmetrical healthy bone and destroy the CCs. The model of bone OBs, OCs cells, and CCs for cancerous and healthy bones are the same, and only the parameter values are different [1]. The provided bone model and the values of its parameters for healthy and cancerous bone are published [1,2,38] for Mixed Lesion and Osteolytic Lesion diseases. These are the most common cancerous bone diseases. This model is called the Komarova model, which is presented in Equation (2).

$$\begin{cases} \dot{u} = \alpha_1 u v^{\gamma_1} - \beta_1 u + \sigma_1 u\omega \\ \dot{v} = \alpha_2 v u^{\gamma_2} - \beta_2 v + \sigma_2 v\omega \\ \dot{\omega} = \alpha_3 \left(1 - \frac{\omega}{K}\right)\omega + (\sigma_3 u^{\gamma_2} + \sigma_4 v^{\gamma_1})\omega - \beta_3\omega \end{cases} \quad (2)$$

where u, v and ω are the density of OC, OB and CC cells, respectively. α_i, β_i, $i = (1, 2, 3)$ multiplication rate of OC, OB and CCs and are fixed parameters and positive. σ_j, $j = (1, 2, 3, 4)$ coefficients constant for the relationship between OC, OB and CCs that σ_1, σ_3 are positive and σ_2, σ_4 are negative or positive. γ_1, γ_2 are the rate of signaling between OBs and OCs that are coefficient and $\gamma_1 < 0$, $\gamma_2 > 0$ and K is the ability to carry CCs. As well as the model of bone mass is as follows [2]:

$$\dot{z} = -k_1\sqrt{\max\{u - \overline{u}, 0\}} + k_2\sqrt{\max\{v - \overline{v}, 0\}} \quad (3)$$

where z is the bone mass and k_1, k_2 are normalized activities of bone formation that are constant and positive. $\overline{v}$, $\overline{u}$ are steady-state of the OB and OC cells that are presented as follows:

$$\begin{aligned} \overline{u} &= \left(\frac{\beta_2}{\alpha_2}\right)^{\frac{1}{\gamma_2}} \\ \overline{v} &= \left(\frac{\beta_1}{\alpha_1}\right)^{\frac{1}{\gamma_1}} \end{aligned} \quad (4)$$

For healthy bone, the values of parameters are presented as follows:

$$\begin{aligned} &\alpha_{1m} = 0.3, \alpha_{1m} = 0.1, \beta_{1m} = 0.2, \beta_{2m} = 0.02, \\ &\gamma_{1m} = -0.3, \gamma_{2m} = 0.5, k_{1m} = 0.07, k_{2m} = 0.0022, \\ &\alpha_{3m} = 0.045, \beta_{3m} = 0.05, \sigma_{1m} = 0.001, \sigma_{2m} = -0.00005, \\ &\sigma_{3m} = 0.005, \sigma_{4m} = 0.005, \sigma_{4m} = 0, K_m = 300 \end{aligned} \quad (5)$$

In addition, for the Fixed Lesion disease, these parameters have values as follows:

$$\begin{aligned} &\alpha_{1s} = 0.3, \alpha_{2s} = 0.1, \beta_{1s} = 0.2, \beta_{2s} = 0.02, \gamma_{1s} = -0.3, \\ &\gamma_{2s} = 0.5, k_{1s} = 0.023, k_{2s} = 0.0023, \alpha_{3s} = 0.055, \\ &\beta_{3s} = 0.05, \sigma_{1s} = \sigma_{2s} = -0.005, \sigma_{3s} = 0.001, \sigma_{4s} = 0, K_s = 3 \end{aligned} \quad (6)$$

For the synchronization of two healthy and cancerous bones, the synchronization errors are defined as $e_1 = u_s - u_m$, $e_2 = v_s - v_m$, $e_3 = \omega_s - \omega_m$ where m is the abbreviation of the master system (healthy bone), also s is the abbreviation of the slave system (cancerous bone). This paper aims to reach these errors to zero at a finite time.

The error dynamic will be as follows:

$$\begin{cases} \dot{e_1} = f_{1s} - f_{1m} + D_1 + U_1 \\ \dot{e_2} = f_{2s} - f_{2m} + D_2 + U_2 \\ \dot{e_3} = f_{3s} - f_{3m} + D_3 + U_3 \end{cases} \quad (7)$$

where

$$\begin{cases} f_{1m} = \alpha_{1m} u_m v_m^{\gamma_{1m}} - \beta_{1m} u_m + \sigma_{1m} u_m \omega_m \\ f_{2m} = \alpha_{2m} v_m u_m^{\gamma_{2m}} - \beta_{2m} v_m + \sigma_{2m} v_m \omega_m \\ f_{3m} = \alpha_{3m} \left(1 - \frac{\omega_m}{K_m}\right) \omega_m + \left(\sigma_{3m} u_m^{\gamma_{2m}} + \sigma_{4m} v_m^{\gamma_{1m}}\right) \omega_m - \beta_{3m} \omega_m \end{cases} \quad (8)$$

and

$$\begin{cases} f_{1s} = \alpha_{1s} u_s v_s^{\gamma_{1s}} - \beta_{1s} u_s + \sigma_{1s} u_s \omega_s \\ f_{2s} = \alpha_{2s} v_s u_s^{\gamma_{2s}} - \beta_{2s} v_s + \sigma_{2s} v_s \omega_s \\ f_{3s} = \alpha_{3s} \left(1 - \frac{\omega_s}{K_s}\right) \omega_s + \left(\sigma_{3s} u_s^{\gamma_{2s}} + \sigma_{4s} v_s^{\gamma_{1s}}\right) \omega_s - \beta_{3s} \omega_s \end{cases} \quad (9)$$

U_i, i = (1, 2, 3) are the models of the control inputs that will be designed in the next section and D_i are the models of unknowns and uncertainties. Assuming that the upper bounds for D_i are available as follows:

$$\begin{aligned} |D_i| &\le \eta_{i1} \\ |\dot{D}_i| &\le \eta_{i2} \end{aligned} \quad (10)$$

4. Designing the control inputs

Designing the controller using the NTSMC method consists of two parts. The first part is designing the sliding surfaces and proof of their stability, and the second part is proof of reaching the sliding surface. Since this paper aims for finite-time stability, must both these parts prove at a finite time to ensure the finite-time stability.

Theorem 1: Consider system Equation (7), defined sliding surfaces Equation (11), and control inputs Equation (12). So the states of this system reach zero in a finite time.

$$\begin{cases} s_1 = \dot{e}_1 + c_{11} sig^{\alpha_{11}}(e_1) + c_{12} sig^{\alpha_{12}}(e_1) \\ s_2 = \dot{e}_2 + c_{21} sig^{\alpha_{21}}(e_2) + c_{22} sig^{\alpha_{22}}(e_2) \\ s_3 = \dot{e}_3 + c_{31} sig^{\alpha_{31}}(e_3) + c_{32} sig^{\alpha_{32}}(e_3) \end{cases} \quad (11)$$

where c_{i1}, c_{i2} are positive control parameters and α_{i1}, α_{i2} are positive constants as $\begin{cases} \alpha_{i1} = N \\ \alpha_{i2} = \frac{N}{2-N} \end{cases}$ and $N \in (1, 2)$.

$$\begin{cases} U_i = U_{eq_i} + U_{r_i} \\ U_{eq_i} = f_{im} - f_{is} - c_{i1} sig^{\alpha_{i1}}(e_i) - c_{i2} sig^{\alpha_{i2}}(e_i) \\ \dot{U}_{r_i} = -k_{i1} sig^{\beta_{i1}}(s_i) - k_{i2} sig^{\beta_{i2}}(s_i) - \eta_{i2} sign(s_i) \end{cases} \quad (12)$$

In these control inputs k_{i1}, k_{i2} are positive constants and β_{i1}, β_{i2} are positive and smaller than one constant.

Proof: It has been shown that sliding surfaces Equation (11) have finite-time stability, provided that c_{i1}, c_{i2} are chosen so polynomial of $p^2 + c_{i2}p + c_{i1} = 0$ is Hurwitz [39]. For prooving the reaching phase (second part), consider the Lyapunov function $V = \sum_{i=1}^{3} \frac{1}{2} s_i$ which has conditions of the Lyapunov function of Lemma 1. Then will have $\dot{V} = \sum_{i=1}^{3} s_i \dot{s}_i$ and with applying the control inputs to the system also putting up $\dot{s}_i$ in $\dot{V}$ so can be written $\dot{V} = \sum_{i=1}^{3} s_i (\dot{U}_{r_i} + \dot{D}_i)$ as follows:

$$\dot{V} = \sum_{i=1}^{3} s_i \left(-k_{i1} sig^{\beta_{i1}}(s_i) - k_{i2} sig^{\beta_{i2}}(s_i) - \eta_{i2} sign(s_i) + \dot{D}_i\right) \quad (13)$$

by simplifying:

$$\dot{V} = \sum_{i=1}^{3} -k_{i1} |s_i|^{1+\beta_{i1}} - k_{i2} |s_i|^{1+\beta_{i2}} - \eta_{i2} |s_i| + \dot{D}_i s_i \quad (14)$$

since the $\dot{D}_i s_i \le |\dot{D}_i| |s_i|$ also $|\dot{D}_i| \le \eta_{i2}$ so:

$$\dot{V} \le \sum_{i=1}^{3} -k_{i1} |s_i|^{1+\beta_{i1}} - k_{i2} |s_i|^{1+\beta_{i2}} \quad (15)$$

due to the Lemma 2:

$$\dot{V}(x) \le \sum_{i=1}^{3} -\left(\sqrt{2}\right)^{\beta_{i1}+1} k_{i1} s_i^{\frac{\beta_{i1}+1}{2}} - \left(\sqrt{2}\right)^{\beta_{i2}+1} k_{i2} s_i^{\frac{\beta_{i2}+1}{2}} \quad (16)$$

with the selection of parameters values as follows:

$$r_1 = \left(\sqrt{2}\right)^{\beta_{i1}+1} k_{i1} > 0, r_2 = \left(\sqrt{2}\right)^{\beta_{i2}+1} k_{i2} > 0, r_4 = \beta_{i1} = 1 - \frac{1}{r_3}, r_5 = \beta_{i2} = 1 + \frac{1}{r_3} \quad (17)$$

where $r_3 > 1$:

$$\dot{V}(x) \le -r_1 V^{r_4} - r_2 V^{r_5} \quad (18)$$

due to the Lemma 1, the system Equation (2) is stable for a finite time, and the settling time is $T \le \pi r_3 \left(\sqrt{(r_1 r_2)}\right)^{-1}$. Theorem 1 is proved.

5. Simulation

The aim of this paper was to show that OB and OC cells of cancerous bone track the OB and OC cells of healthy bone as well as eliminate the CCs of the cancerous bone. The simulation was conducted in MATLAB software. The control parameters are selected as follows:

$$c_{i1} = 0.02, c_{i2} = 0.0001, k_{i1} = 0.01,$$
$$k_{i2} = 0.01, N = 0.9, r_3 = 0.5 \quad (19)$$

Figure 1 shows the curves of the OC cells, and **Figure 2** shows the OB cells of the healthy and cancerous bones. **Figure 3** shows the curve of the CCs for cancerous bone. As well as **Figure 4** illustrates the curves of the designed control inputs. In this simulation, the initial conditions of healthy bone are (u_0, v_0, ω_0) = (10, 5, 1). Since the cancerousness happens, the distances of the OC and CCs cells are more than a healthy bone, and the distance of the OB cells is less than, so the initial conditions of cancerous bone are selected as (u_0, v_0, ω_0) = (40, 1, 5).

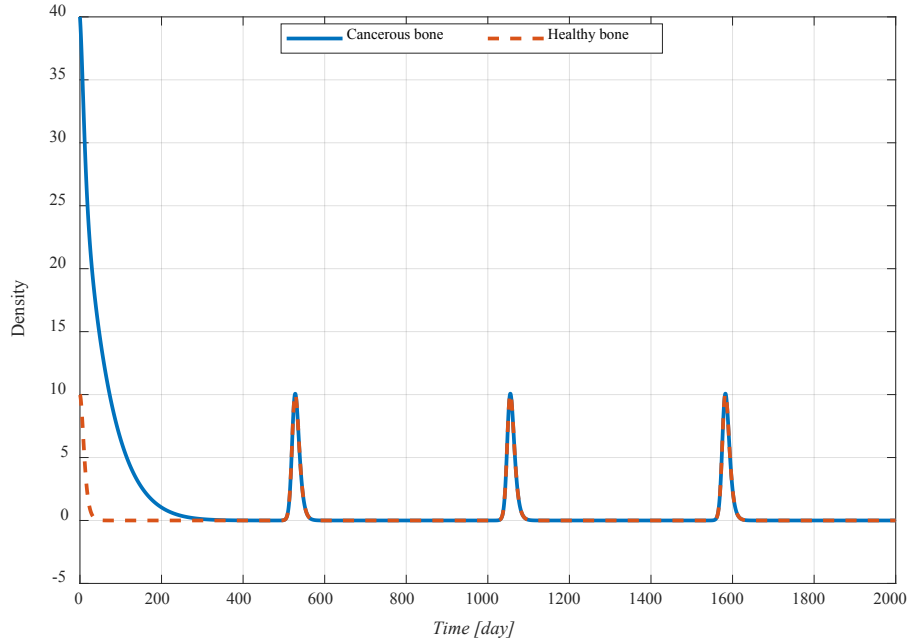

Figure 1. The curves of the OC cells of cancerous and healthy bone.

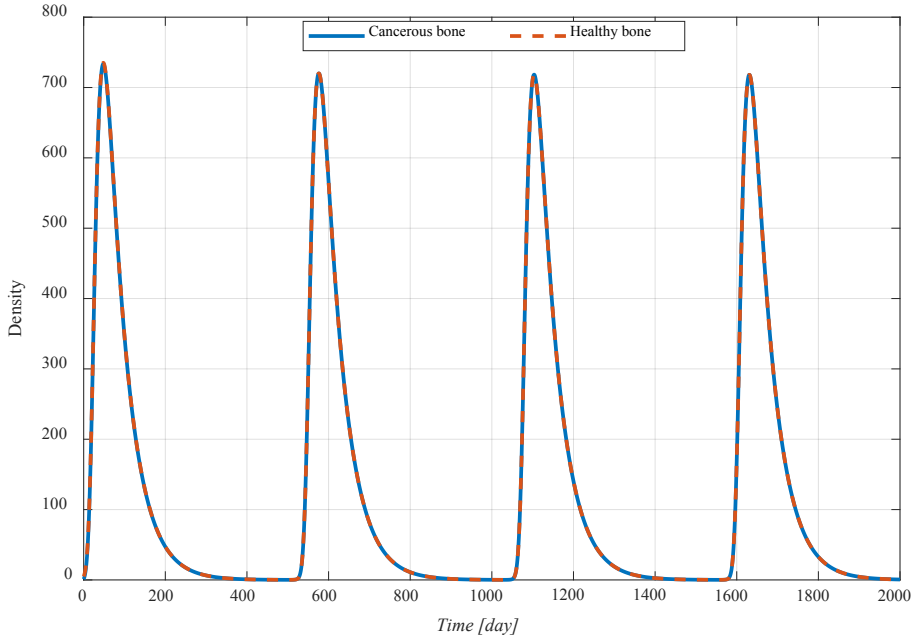

Figure 2. The curves of the OB cells of cancerous and healthy bone.

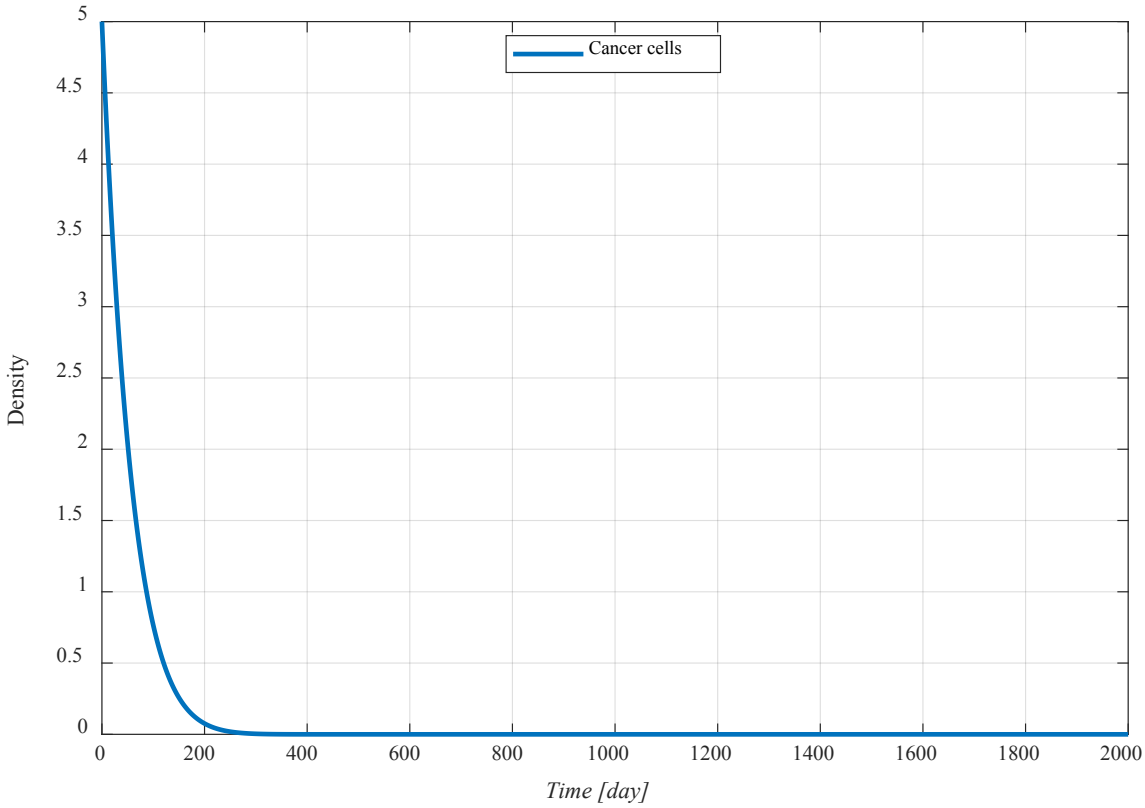

Figure 3. The curves of the CCs of cancerous bone.

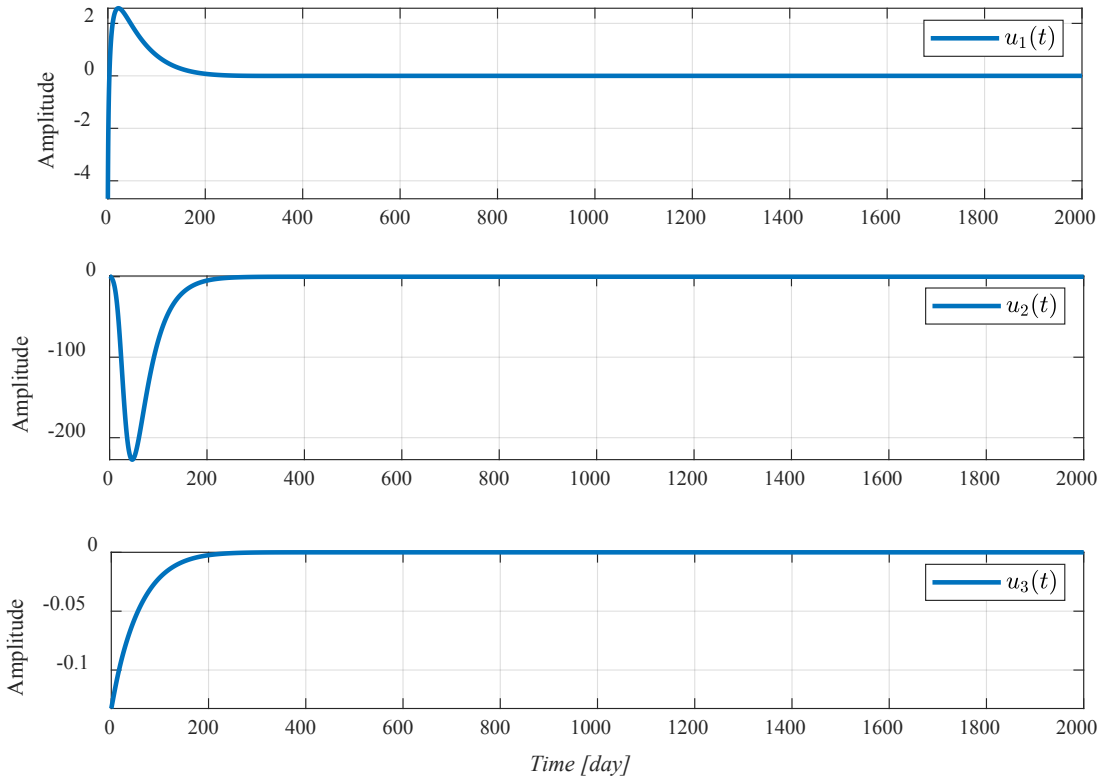

Figure 4. The curves of the control inputs.

6. Discussion

As the figures are precise, after about 300 days (almost one year), the OC cells of cancerous bone have tracked the OC cells of healthy bone until the CCs have disappeared. In the OB cells, because the initial conditions of cancerous bone and healthy bone are close and the amplitude of the figure is big, the result is not clear correctly. **Figure 5** shows the curve of the OB cells in 30 days (zoomed in). The period of OS treatment is almost five years in the real world. This is the reason for selecting the final time of the simulation as 2000 days. The control inputs are smooth. They are possible to implement in real tests. The smoothness happened because of the chattering-free design.

In brief, all the required features of a controller for controlling bone cancer have been considered in designing the proposed controller. The controller is robust, chatter-free, accurate, smooth, fast, and implementable. The results presented in **Figures 1-5** show the power of the proposed controller.

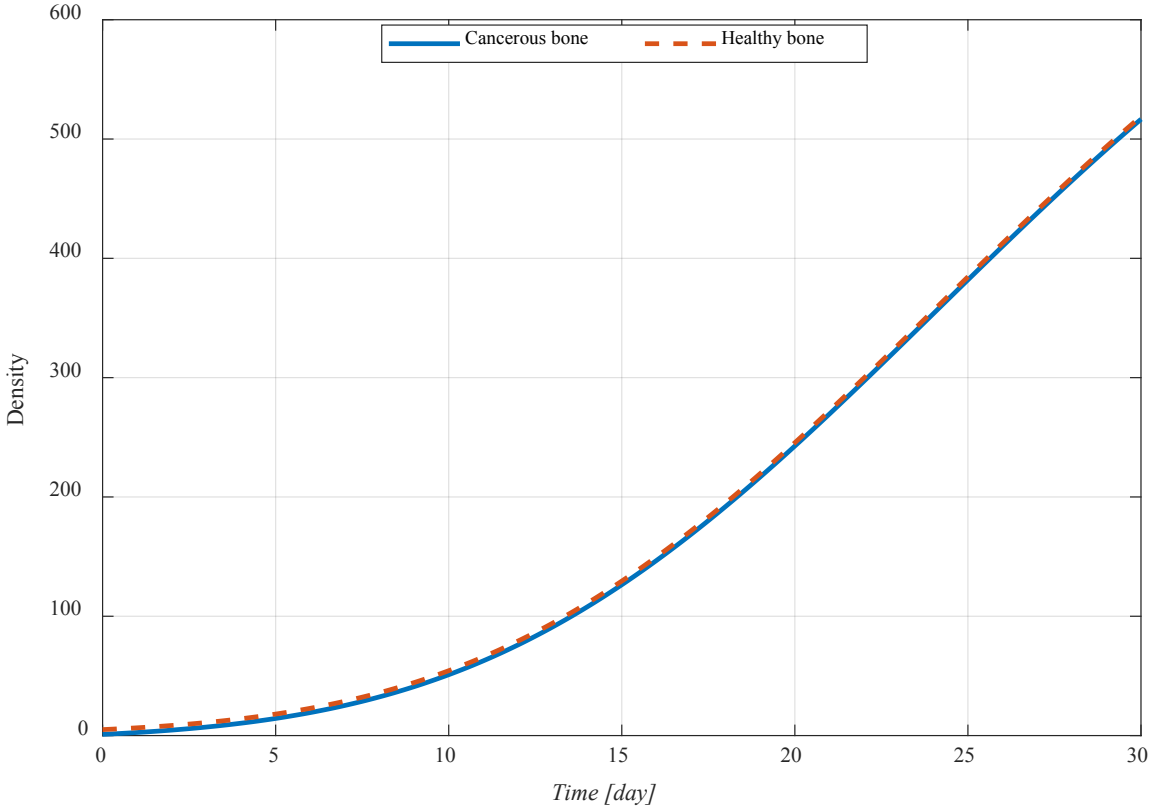

Figure 5. The curve of the OB cells of cancerous and healthy bone in 30 days.

7. Conclusions

In this paper, the NTSMC control method is employed to synchronize two human body bones. One of these bones was cancerous bone, and the other bone was healthy. This paper was a theoretical study that controlled and treated bone cancer with a theoretical method. Three designed control inputs have the features of chattering-free, finite-time stability and robustness against unknowns and uncertainties, which can be used in practical tests. These control inputs can be the effects of doses of medicines or the power of X-rays. After about a year, it was shown that the CCs had disappeared, and the cancerous bone looked like symmetrical healthy bone. For the subsequent studies, it is suggested to work on implementing these types of studies in real tests for the treatment of some animals' bone cancer.

Authors' Contributions

Ali Soltani Sharif Abadi: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, review and editing, visualization, and funding.

Mansour Rafeeyan: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing, review and editing, visualization, supervision.

Vahid Abootalebi: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing, review and editing, visualization, supervision.

Conflict of Interest

There is no conflict of interest.

Data Availability Statement

Not applicable.

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