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CHAOS AND STABILIZATION OF SELF-REMISSION TUMOR SYSTEM BY SLIDING MODE

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Abstract. *In this paper a pray-predator system that called self-remission tumor is considered, and a new approach in order to stabilizing the unstable equilibrium points of self-remission tumor system with sliding mode control is introduced.*

The stability analysis of the biologically feasible equilibrium points is presented by using the Lyapunov function.

A Lyapunov function is supposed for designing a sliding surface (SS).

Lyapunov function is constructed to establish the global asymptotic stability of the uninfected and infected steady states by describing sliding surface (SS), after that by considering the derivation of SS as zero, someone can achieve the equivalent control that inbreed system stays on SS and tends to equilibrium point in infinite horizon.

In addition, numerical examples are presented to illustrate the effectiveness of the proposed method.

Keywords: Chaos, Tumor, Equivalent control, Sliding surface

1. Introduction

Cancer is one of the greatest killers in the world and the control of tumor growth requires special attention [9].

The mathematical modeling of cancer self-remission and tumor has been approached by a few numbers of researchers under using a variety of models over the past decades [8, 9, 13, 18].

Many authors have discussed the problem of the chaotic behavior and stability analysis of some biological models such as cancer and tumor model, genital herpes epidemic, stochastic lattice gas prey-predator modes [7, 8, 13] and many other models.

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Optimal treatment scheduling of prey-predator system using a control theoretic approach is the subject of substantial research activity. In [1,2,6,14,16], open-loop type of optimal controllers is designed by using the Pontryagins Maximum Principle (PMC). A major drawback of open-loop optimal controllers is their lack of robustness against disturbances or model uncertainties. In fact, tumor dynamics are poorly known, this leads to model inaccuracies and parameter uncertainties. Also, another source of disturbances may arise from immune system fluctuating or immune effect of a co-infection, in addition to the measurements errors and estimation errors when using an observer to estimate the unmeasured states. Therefore, the design of optimal treatment schedules based on open-loop optimal controller, may lead to undesired results. To overcome this problem, we have to design a feedback controller, which inherits certain robustness to disturbances.

Feedback control for prey-predator has been studied by [3-5]. A common method for using feedback control is sliding mode control that introduced by Emelyanov [10] in the late 1960s based on the conceptions of variable structure control (VSC). However, Flgge-Lotz [11] was the first to present the concept of sliding motion, and Filippov [11] was the first to consider the solution of differential equations with a discontinuous right-hand side. Filippovs pioneering work still serves as the basis for work in sliding mode control which was essentially developed by Utkin [11,12,19,20] and Emelyanov [10], Draenovie and their co-workers.

The present paper is concerned with the problem of design equivalent control of the unstable equilibrium points of cancer self-remission and tumor system. Mathematical model of spontaneous tumor regression and progression as a deterministic prey-predator model have been constructed. Chaos and stability analysis of equilibrium points of the system and their biologically existence conditions are perused and inputs control that stabilizes these unstable equilibrium points by using sliding mode control are derived. Eventually, the results of this paper complement and extend recently published results by El-Gohary [9] and Sarkar [18].

This paper is organized as follows: Section 2 briefly introduces self remission tumor and its mathematical model. Section 3 addresses the equilibrium points and their stability

analysis. In Section 4, equivalent control is designed, and examples are presented in section 5 to illustrate the procedure and its validity of the proposed control design. Finally, conclusions are given in Section 6.

2 The mathematical model

In this section we start to construct the spontaneous tumor regression and progression system using a prey-predator system [9]. We consider the predator is T-lymphocytes and cytotoxic macrophages/ natural killer cells of immune system, which attacks, destroys or ingests the tumor cell. The prey is the tumor cells which are attacked and destroyed by the immune cells. The predator has two states, hunting and resting, and destroys the prey. The tumor cells are caught by macrophages which can be found in all tissues in the body and circulate round in the blood system [9,18]. Macrophages absorb tumor cells, eat them and release series of cytokines which activates the resting T-lymphocytes that coordinates the counter attack. The resting predator cells can also be directly simulated to interact with antigens. These resting cells cannot kill tumor cells, but they are converted to a special type of T-lymphocyte cells called natural killer or hunting cells and begin to multiply and release other cytokines that moreover simulate more resting cells. This conversion between hunting and resting cells result in a degradation of the resting cells undergoing natural growth and an activation of hunting cells. To introduce the mathematical model we assume that the tumor cells are being destroyed at a rate proportional to the tumor cells densities according to the law of mass action. Next we also assume that the resting predator cells are converted to the hunting cells either by direct contact with them or by contact with a fast diffusing substance produced by hunting cells. We consider that once a cell has converted, it will never return to the resting stage and active cells die at a constant probability per unit time. Finally we assume that all of resting predator and tumor cells are nutrient rich under going mitosis and the tumor cells have a proliferative advantage over the normal cells [9]. If $M(t)$, $N(t)$, and $Z(t)$ denote thedensities of tumor cells, hunting predator cells and resting predator cells at time t, respectively, the resulting system dynamical system can be described the following set of nonlinear ordinary differential

equations:

$$\begin{aligned}\frac{dM}{dt} &= q + rM(1 - k_1^{-1}M) - \alpha MN, \\ \frac{dN}{dt} &= \beta NZ - d_1 N, \\ \frac{dZ}{dt} &= sZ(1 - k_2^{-1}Z) - \beta NZ - d_2 Z,\end{aligned} \tag{1}$$

where q is the conversion of normal cells to malignant ones, r is the growth rate of the tumor cells, k_1 is the maximum carrying capacity of tumor cells, k_2 is the maximum carrying capacity of resting cells (also, $k_1 > k_2$), β is the conversion rate of resting cells to hunting cells, d_1 is the natural death of hunting cells, d_2 is the natural death rate of resting cells, s is the growth rate of resting predator cells, α is the rate of predation/destruction of tumor cells by the hunting cells. Cancer self-remission and tumor system have to be analyzed with the initial positivity conditions $M(0) > 0$, $N(0) > 0$, $Z(0) > 0$ [1,2].

2.1 Parameters reduction

We reduce the system parameters (1) by using new variables and new parameters. Now consider the following new variables:

$$\tau = qk_1^{-1}t, \quad x_1 = k_1^{-1}M, \quad x_2 = \alpha k_1 q^{-1}N, \quad x_3 = k_2^{-1}Z. \tag{2}$$

So we have:

$$\tau = qk_1^{-1}t \quad \Longrightarrow t = k_1 q^{-1}\tau \Longrightarrow \frac{dt}{d\tau} = k_1 q^{-1}.$$

Now consider the following constants $a_i, i = 1, \cdots, 6$

$$\begin{aligned} a_1 &= rk_1 q^{-1} \quad a_2 = \beta k_1 k_2 q^{-1} \quad a_3 = k_1 d_1 q^{-1} \\ a_4 &= sk_1 q^{-1} \quad a_5 = \beta\alpha^{-1} \quad a_6 = d_2 k_1 q^{-1} \end{aligned} \tag{3}$$

Substituting (2) and (3) into (1) we get the following system [9]:

$$\begin{aligned}\dot{x}_1 &= 1 + a_1 x_1(1 - x_1) - x_1 x_2, \\ \dot{x}_2 &= a_2 x_2 x_3 - a_3 x_2, \\ \dot{x}_3 &= a_4 x_3(1 - x_3) - a_5 x_2 x_3 - a_6 x_3,\end{aligned} \tag{4}$$

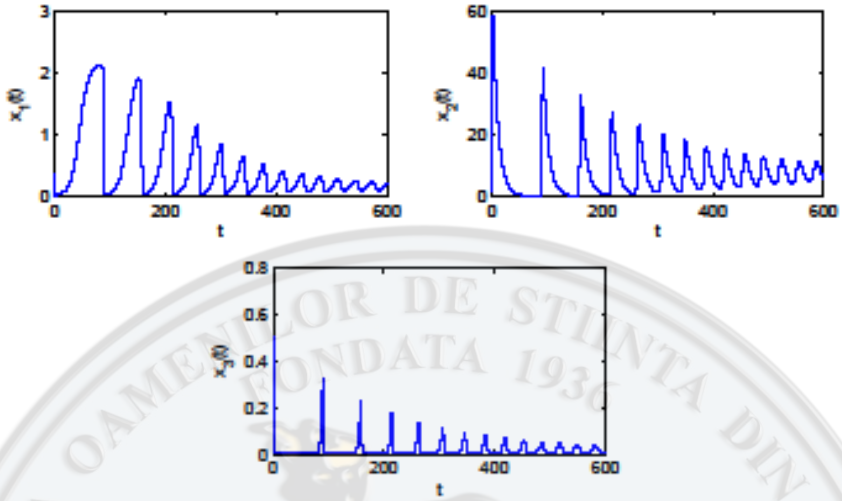

Fig. 1. The densities of tumor cells, hunting predator cells, resting predator cells for the parameters $a_1 = 0.4, a_2 = 5.9, a_3 = 0.1, a_4 = 0.5, a_5 = 0.06$ and $a_6 = 0.05$ and the initial densities are $x_1(0) = 0.3, x_2(0) = 1.5$ and $x_3(0) = 0.5$.

3 Equilibrium points, stability analysis

In this section will be discussed about all of the positive equilibrium points of nonlinear system (4) and analyse their local stability by Lyapunov linearization approach.
The positive equilibrium points of the nonlinear system 4 are as follow:

$$E_1 = [\frac{1}{2}(1 + \sqrt{1 + \frac{4}{a_1}}), 0, 0], \tag{5}$$
$$E_2 = [\frac{1}{2}(1 + \sqrt{1 + \frac{4}{a_1}}), 0, 1 - \frac{a_6}{a_4}],$$
$$E_3 = \{\frac{1}{2a_1}[(a_1 - x_2) + \sqrt{(x_2 - a_1)^2 + 4a_1}], [a_4(a_2 - a_3) - a_2a_6]/a_2a_5, \frac{a_3}{a_2}\},$$

The positive equilibrium points are biologically feasible. Therefore E_2 is feasible if $a_6 < a_4$. This means that E_2 exists and biologically admissible if the natural death rate of resting cells is less than the growth rate of the resting predator cells. E_3 is feasible if

$$[a_4(a_2 - a_3) - a_2a_6]/a_2a_5 > 0 \Longrightarrow \frac{a_3}{a_2} + \frac{a_6}{a_4} < 2. \tag{6}$$

Therefore the equilibrium points E_1, E_2, E_3 under the following conditions are positive and biologically admissible [9]:

$$\begin{aligned} &\frac{a_3}{a_2}+\frac{a_6}{a_4}<2, \\ &a_6<a_4, \end{aligned} \tag{7}$$

3.1 The local stability analysis the equilibrium points

To investigate the local stability positive equilibrium points under the conditions (7) by Lyapunov linearization approach, we obtain the Jacobian matrix J and its eigenvalues at these points.

The Jacobian matrix of the system (4) at the equilibrium state E_1 is given by

$$J|_{E_1}=\begin{bmatrix} -\sqrt{a_1^2+4a_1} & -(1+\sqrt{1+\frac{4}{a_1}})/2 & 0 \\ 0 & -a_3 & 0 \\ 0 & 0 & a_4-a_6 \end{bmatrix}. \tag{8}$$

The eigenvalues of the Jacobian matrix J_1 are given by

$$\begin{aligned} &\lambda_{11}=-\sqrt{a_1^2+4a_1}, \\ &\lambda_{12}=-a_3, \\ &\lambda_{13}=a_4-a_6, \end{aligned} \tag{9}$$

From the condition of the (7) we observe that the eigenvalue λ_{13} is positive and hence the E_1 equilibrium point is absolutely unstable [15,17].

The Jacobian matrix of the system (4) at the equilibrium state E_2 is given by

$$J|_{E_2}=\begin{bmatrix} -\sqrt{a_1^2+4a_1} & -(1+\sqrt{1+\frac{4}{a_1}})/2 & 0 \\ 0 & (a_2a_4-a_3a_4-a_2a_6)/a_4 & 0 \\ 0 & -a_5(a_4-a_6)/a_4 & a_4-a_6 \end{bmatrix}. \tag{10}$$

The eigenvalues of the Jacobian matrix J_2 are given by

$$\begin{aligned} &\lambda_{21}=-\sqrt{a_1^2+4a_1}, \\ &\lambda_{22}=(a_2a_4-a_3a_4-a_2a_6)/a_4, \\ &\lambda_{23}=a_6-a_4, \end{aligned} \tag{11}$$

From the condition of the (7) we observe that the eigenvalue λ_{22} is positive and hence the E_2 equilibrium point is absolutely unstable [15,17].

The Jacobian matrix of the system (4) at the equilibrium state E_3 is given by

$$J|_{E_3} = \begin{bmatrix} \overline{x}_2 - k & (a_1 - \overline{x}_2 + k)/2a_1 & 0 \\ 0 & 0 & a_2\overline{x}_2 \\ 0 & -(a_3a_5)/a_2 & -(a_3a_4)/a_2 \end{bmatrix}. \tag{12}$$

where $k = \sqrt{(a_1 - \overline{x}_2)^2 + 4a_1}$ and $\overline{x}_2 = [a_4(a_2 - a_3) - a_2a_6]/a_2a_5$. The eigenvalues of the Jacobian matrix J_3 are given by

$$\begin{aligned} \lambda_{31} &= \overline{x}_2 - k, \\ \lambda_{32} &= [-a_3a_4 + \sqrt{a_3^2a_4^2 - 4a_2^2a_3a_5\overline{x}_2}]/2a_2, \\ \lambda_{33} &= [-a_3a_4 - \sqrt{a_3^2a_4^2 - 4a_2^2a_3a_5\overline{x}_2}]/2a_2, \end{aligned} \tag{13}$$

From the condition of the (7) we observe that the eigenvalues λ_{31}, λ_{32} and λ_{33} have negative real parts therefore the equilibrium point E_3 is asymptotic stable [16,17].

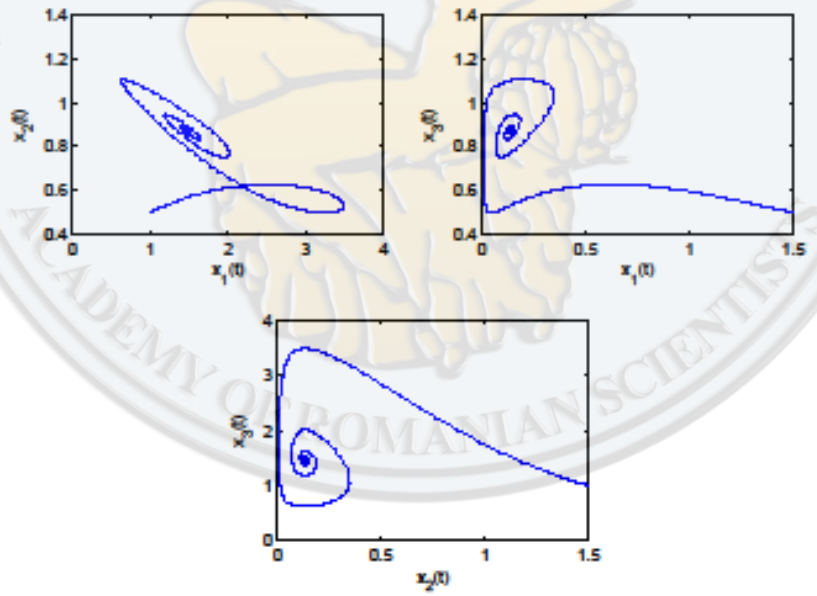

Fig. 2. The cancer self-remission and tumor system converges to stable inside limit cycles for the parameters $a_1 = 2.5, a_2 = 4.5, a_3 = 0.6, a_4 = 3.5, a_5 = 2$ and $a_6 = 0.1$ and the initial densities are $x_1(0) = 0.5, x_2(0) = 1, x_3(0) = 1.5$.

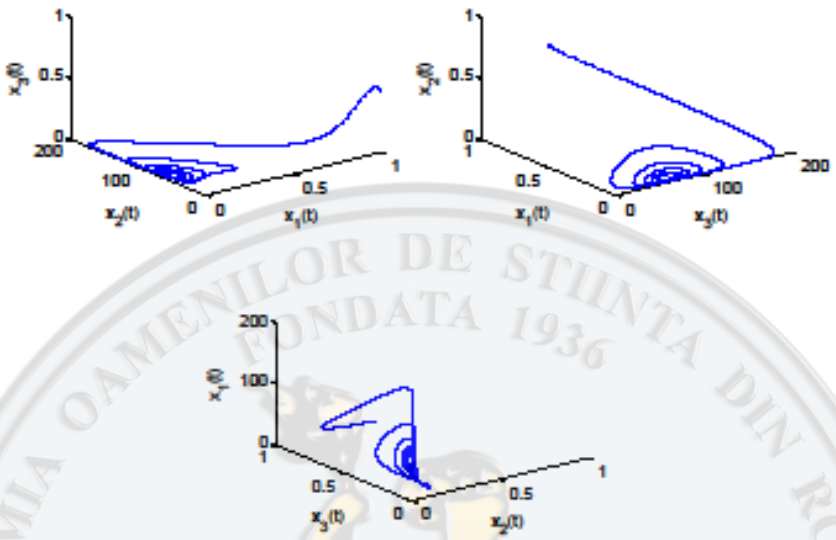

Fig. 3. The cancer self remission and tumor three dimensional phase plot which represent three different attractors for the values of the system parameters and initial densities $a_1 = 5, a_2 = 15, a_3 = 0.5, a_4 = 6.5, a_5 = 0.1$ and $a_6 = 0.21$ and the initial densities are $x_1(0) = 0.5, x_2(0) = 2, x_3(0) = 1$.

4 Designing equivalent control

In this section we will study the problem of design equivalent control of the cancer self-remission and tumor model about its equilibrium points. For this purpose of in this system as both Z and N cells are from T lymphocyte, we add the control u to system (4) in order to reinforce the immune system of body against the tumor cells. Then we will use sliding mode approach. Therefore let us consider the coupled system of the cancer self-remission and tumor has the form

$$\begin{aligned} \dot{x}_1 &= 1 + a_1 x_1(1 - x_1) - x_1 x_2, \\ \dot{x}_2 &= a_2 x_2 x_3 - a_3 x_2 + \alpha_1 u, \\ \dot{x}_3 &= a_4 x_3(1 - x_3) - a_5 x_2 x_3 - a_6 x_3 + \alpha_2 u, \end{aligned} \tag{14}$$

To study the problem of design equivalent control of the system (14) about the equilibrium points E_1 and E_2 we will obtained the equations of perturbed states about these

equilibrium points by introducing the following new variables

$$\eta_1 = x_1 - \overline{x}_1, \quad \eta_2 = x_2 - \overline{x}_2, \quad \eta_3 = x_3 - \overline{x}_3. \tag{15}$$

where $\overline{x}_i, i = 1,2,3$ denote the coordinates of the equilibrium points E_1 and E_2. Substituting (15) into (14) taking into account the identities that satisfy by the equilibrium points, we get the following system:

$$\begin{aligned}
\dot{\eta}_1 &= (a_1 - 2a_1\overline{x}_1 - \overline{x}_2)\eta_1 - a_1\eta_1^2 - \overline{x}_1\eta_2 - \eta_1\eta_2, \\
\dot{\eta}_2 &= (a_2\overline{x}_3 - a_3)\eta_2 + a_2\overline{x}_2\eta_3 + a_2\eta_2\eta_3 + \alpha_1 u, \\
\dot{\eta}_3 &= -a_5\overline{x}_3\eta_2 + (a_4 - a_6 - a_5\overline{x}_2 - 2a_4\overline{x}_3)\eta_3 - a_4\eta_3^2 - a_5\eta_2\eta_3 + \alpha_2 u,
\end{aligned} \tag{16}$$

In this phase we delete the control $\alpha_2 u$ than third equation.

$$y_1 = \eta_1, \quad y_2 = \eta_2, \quad y_3 = \eta_3 - (\frac{\alpha_2}{\alpha_1})\eta_2. \tag{17}$$

Therefore we get the following system:

$$\begin{aligned}
\dot{y}_1 &= (a_1 - 2a_1\overline{x}_1 - \overline{x}_2)y_1 - a_1y_1^2 - \overline{x}_1y_2 - y_1y_2, \\
\dot{y}_2 &= ((\frac{\alpha_2}{\alpha_1})a_2\overline{x}_2 + a_2\overline{x}_3 - a_3)y_2 + (\frac{\alpha_2}{\alpha_1})a_2y_2^2 + a_2\overline{x}_2y_3 + a_2y_2y_3 + \alpha_1 u, \\
\dot{y}_3 &= C_1y_2 + C_2y_2^2 + C_3y_3 + C_4y_2y_3 - a_4y_3^2,
\end{aligned} \tag{18}$$

where

$$\begin{aligned}
C_1 &= (\frac{\alpha_2}{\alpha_1})[a_3 + a_4 - a_6 - ((\frac{\alpha_2}{\alpha_1})a_2 + a_5)\overline{x}_2 - (a_2 + 2a_4 + (\frac{\alpha_2}{\alpha_1})a_5)\overline{x}_3], \\
C_2 &= -(\frac{\alpha_2}{\alpha_1})^2[a_2 + a_4 + (\frac{\alpha_1}{\alpha_2})a_5], \\
C_3 &= [a_4 - a_6 - ((\frac{\alpha_2}{\alpha_1})a_2 + a_5)\overline{x}_2 - 2a_4\overline{x}_3], \\
C_4 &= -(\frac{\alpha_2}{\alpha_1})[(a_2 + 2a_4 + (\frac{\alpha_1}{\alpha_2})a_5)],
\end{aligned} \tag{19}$$

Consider $V(y_1, y_2, y_3) = \frac{1}{2}(y_1^2 + y_2^2 + y_3^2)$ as the candidate Lyapunov function of the system (18). The time derivation of V along the trajectories of the system (18) is

$$\begin{aligned}
\dot{V} &= y_1\dot{y}_1 + y_2\dot{y}_2 + y_3\dot{y}_3 \\
&= (a_1 - 2a_1\overline{x}_1 - \overline{x}_2)y_1^2 - a_1y_1^3 - \overline{x}_1y_1y_2 - y_1^2y_2 \\
&\quad + ((\frac{\alpha_2}{\alpha_1})a_2\overline{x}_2 + a_2\overline{x}_3 - a_3)y_2^2 + (\frac{\alpha_2}{\alpha_1})a_2y_2^3 + a_2\overline{x}_2y_2y_3 + a_2y_2^2y_3 + y_2\alpha_1 u \\
&\quad + C_1y_2y_3 + C_2y_2^2y_3 + C_3y_3^2 + C_4y_2y_3^2 - a_4y_3^3.
\end{aligned} \tag{20}$$

First by factorization from linear coefficients of the y and then by factorization from nonlinear coefficients of the y, $\dot{V}$ convert to the following equation:

$$\begin{aligned}\dot{V} = & y_2(-\overline{x}_1 y_1 - y_1^2 + D_1 y_3 + D_2 y_3^2) \\ & + y_2(D_3 y_2 + D_4 y_2 y_3 + D_5 y_2^2 + \alpha_1 u) \\ & + f(y_1, y_3).\end{aligned} \tag{21}$$

where

$$f(y_1, y_3) = (a_1 - 2a_1\overline{x}_1 - \overline{x}_2)y_1^2 - (\frac{\alpha_2}{\alpha_1})^2(a_2 + a_4 + (\frac{\alpha_1}{\alpha_2})a_5)y_3^2 - a_4 y_3^3, \tag{22}$$

$$D_1 = (\frac{\alpha_2}{\alpha_1})[a_3 + a_4 - a_6 - (-(\frac{\alpha_1}{\alpha_2})a_2 + (\frac{\alpha_2}{\alpha_1})a_2 + a_5)\overline{x}_2 - (a_2 + 2a_4 + (\frac{\alpha_2}{\alpha_1})a_5)\overline{x}_3],$$

$$D_2 = -(\frac{\alpha_2}{\alpha_1})(a_2 + 2a_4 + (\frac{\alpha_1}{\alpha_2})a_5),$$

$$D_3 = a_2\overline{x}_3 - a_3 + (\frac{\alpha_2}{\alpha_1})a_2\overline{x}_2,$$

$$D_4 = -a_4 - (\frac{\alpha_1}{\alpha_2})a_5,$$

$$D_5 = (\frac{\alpha_2}{\alpha_1})a_2,$$

The sliding surface can be described as:

$$y_2 = -K(-\overline{x}_1 y_1 - y_1^2 + D_1 y_3 + D_2 y_3^2). \tag{23}$$

where $K > 0$. To get the equivalent control we can equal the nonlinear coefficient of the y to zero.

$$u_{eq} = -\alpha_1^{-1}(D_3 y_2 + D_4 y_2 y_3 + D_5 y_2^2). \tag{24}$$

So $\dot{V}$ can be written as:

$$\dot{V} = -K y_2^2 + f(y_1, y_3). \tag{25}$$

Now, we should assign K in a way that $\dot{V} < 0$, therefore the following inequality is obtained. For its numerical calculate, we use matlab software.

$$K > y_2^{-2} f(y_1, y_3). \tag{26}$$

By substituting sliding surface (23) in system (18), the dimension of this system decrease into two, and system trajectories approach to the origin by sliding surface (23). So system (16) is asymptotically stable in Lyapunov sense.

5 Analysis and numerical simulation

In this section the problem of the numerical solution of controlled nonlinear cancer self-remission and tumor system is considered, to exhibit the control of this system by using SMC. Numerical examples for controlled cancer self-remission and tumor system were carried out for various parameters values and different initial densities. The following figures display the stabilized behavior of the cancer self remission system about the unstable equilibrium points and its equivalent control input (See Figs. 4 and 5). We conclude that all of the unstable equilibrium points of the cancer self-remission and tumor system can be optimally asymptotically stabilized with nonlinear equivalent control inputs $\alpha_1 u_{eq}$ and $\alpha_2 u_{eq}$ under the conditions $a_4 > a_6$ and $\frac{a_1}{a_2} + \frac{a_6}{a_4} < 2$.

In Figure. 4, x_1, x_2 and x_3 the densities of tumor cells, predator hunting cells and resting predator cells respectively and equivalent control u_{eq} in equilibrium point E_1, are displayed against time for the system parameters and initial densities $a_1 = 0.4$, $a_2 = 5.9$, $a_3 = 0.1$, $a_4 = 0.5$, $a_5 = 0.6$, $a_6 = 0.05$, $\alpha_1 = 0.9$, $\alpha_2 = 1.1$ and $K = 1$ and $x_1(0) = 0.3$, $x_2(0) = 1.5$ and $x_3(0) = 0.5$. Note that all densities are exponentially asymptotically stable.

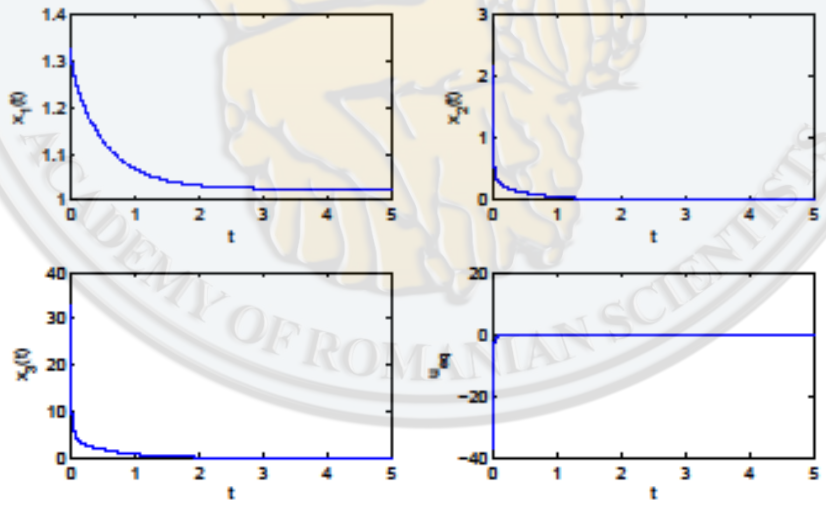

Fig. 4. Trajectories and control function.

In Figure. 5, x_1, x_2 and x_3 the densities of tumor cells, predator hunting cells and resting predator cells respectively and equivalent control u_{eq} in equilibrium point E_2, are

displayed against time for the system parameters and initial densities $a_1 = 3$, $a_2 = 5$, $a_3 = 4$, $a_4 = 3$, $a_5 = 2$, $a_6 = 5, \alpha_1 = 0.9, \alpha_2 = 1.1$ and $K = 0.15$ and $x_1(0) = 0.3$, $x_2(0) = 1.5$ and $x_3(0) = 0.5$. Note that all densities are exponentially asymptotically stable.

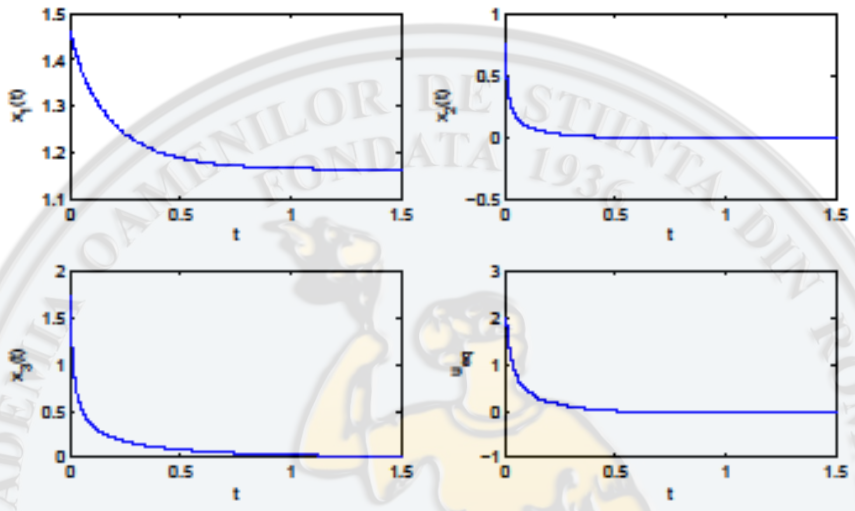

Fig. 5. Trajectories and control function.

6 Conclusion

In this paper the problem of instability of cancer self-remission and tumor system using a sliding mode control approach have been studied. The positive equilibrium points are investigated. The stability and instability of the equilibrium points of this system are studied using the Lyapunov linearization approach. The equivalent control input for asymptotic stability of unstable equilibrium points i.e u_{eq} and sliding surface are derived. Analysis numerical examples for the controlled system were carried out for various parameters values and different initial densities. Matlab has been used for computations in this paper.

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