Minimization of Cancer Cells with ATS Fuzzy Controller: An Application to Androgen Deprivation therapy

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Research Article

Keywords: ATS fuzzy algorithm, super-twisting, LMI algorithm, chaotic behavior, chattering, prostate-specific antigen (PSA)

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Minimization of Cancer Cells with ATS Fuzzy Controller: A Novel Approach to Adaptive Therapy

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Abstract

Androgen deprivation therapy, also known as hormone therapy, is a standard treatment for prostate cancer, but its 5-year survival rate is only 57 percent. Moreover, the prolonged therapy duration results in increased medication toxicity and drug resistance. A solution to this problem is adaptive therapy, which applies chemotherapy or immunotherapy after hormone therapy is withdrawn. In the proposed work, the idea of adaptive therapy is used by applying nonlinear control algorithms to the proposed ADT model and making the drug dosage based on the control laws that result from applying these algorithms. The overall objective is to reduce the cancer cells to zero in a minimum amount of time to reduce prolonged exposure to drugs. For this, a super-twisting sliding mode controller (STSMC) is applied to reduce the number of androgen-independent (AI) and androgen-dependent (AD) cells. Next, an active control algorithm (ATS)-based Takagi-Sugeno fuzzy controller is introduced and compared to the STSMC design. The ATS fuzzy controller has significantly reduced the therapy duration to two months and is also globally asymptotically stable. Using the Linear Matrix Inequality (LMI) algorithm and the YALMIP toolbox, the controller has been built. Theoretical outcomes are validated using MATLAB and Simulink.

Keywords: ATS fuzzy algorithm, super-twisting, LMI algorithm, chaotic behavior, chattering, prostate-specific antigen (PSA).
1 Introduction

Prostate cancer is a widespread disease and one of the major causes of high mortality among men aged 50 and older. In 2022, it is anticipated that more than 0.2 million new instances of prostate cancer will be detected in the country, with around 34,000 deaths. [1]. Around 80 percent of the morbidity is localised, while the remaining 20 percent is caused by advanced prostate cancer. [2]. Currently available PCa treatment options include surgery, radiation, and chemotherapy in addition to androgen deprivation therapy (ADT). Cryotherapy and radiation therapy are primarily used to treat localised cancer, with ADT being the preferred treatment for metastatic and advanced PCas.

This cancer develops within the prostate gland, and androgens play a crucial role in the disease’s evolution [3]. The androgen enters the prostate wall and is transformed to 5\alpha\text{dihydrotestosterone} (DHT), which accelerates cancer cell proliferation. This leads in the secretion of Prostate-specific Antigen (PSA) and, in the presence of cancer cells, a leakage of PSA into the main bloodstream. The PSA level is therefore a biomarker for the detection of prostate cancer. PSA levels determine the presence of prostate cancer in males (PCa). A PSA level below four nanograms per millilitre may be regarded safe, a PSA level between four and ten nanograms per millilitre is questionable, and a PSA level exceeding ten nanograms per millilitre is extremely dangerous [4]. The growth in the number of AI cells above a safe value may result in metastatic prostate cancer with very high PSA values because these cells are unaffected by androgen deprivation [5]. PSA is defined mathematically to be proportional to the sum of both the cells [6][7]. It is either undetectable or zeroes after treatment [8–10]. But in any case, if it rises to even a small value of 0.2 ng/ml, it can cause severe concerns for the patient and doctors. Therefore, PSA levels are a biomarker for detecting PCa [11].

There are numerous ways to suppress androgen production and modulate blood androgen levels, particularly with the use of Androgen receptors (AR). This treatment method of depriving the prostate cells with androgen hormones is named as ADT. Initially, the therapy was employed as Continuous Androgen Suppression (CAS), but it resulted in increased drug toxicity and other side effects due to prolonged exposure to the drugs. Moreover, the cancer cells developed resistance towards this therapy [12][7]. Thus, scientist found an alternative in the form of Intermittent androgen suppression (IAS) therapy. IAS therapy was based on on-off cycle in which the treatment began if the PSA value was above a particular threshold and was drawn once it reaches below the threshold value. This therapy reduced the prolonged exposure to drugs but also became ineffective once the cancer cells developed resistance. Recently, adaptive therapy has been brought into clinical investigations of prostate cancer, resulting in intriguing outcomes and potential. In the adaptive therapy, chemotherapy and immunotherapy can be used as a treatment alternative once the cancer becomes unresponsive to the hormone therapy [13][14].

Nonlinear control research has grown in popularity in recent years. It enables the development of intelligent techniques with inherent intelligence
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and flexibility which are frequently employed in control domain. [15–17]. Table 1 gives a brief review on controllers existing in literature. B.S. Dey et al. developed in 2018 a nonlinear active control approach to eliminate the chaotic behaviour of the cancer model [18][19]. Y. Islam et al. (2020) established 3 distinct leukaemia therapy controllers. They utilised a mathematical model of chemotherapy-treated acute leukaemia. The goals were to reduce the number of cancer cells to zero and the number of healthy cells to a safe level, as well as to build a control law that will limit the drug’s uses to safe levels [20]. In 2010, T.L. Chien employed feedback linearization control for MIMO cancer immunotherapy to reduce cancer burden[21].

In addition to the nonlinear control techniques, artificial intelligence (AI) is

<table>
<thead>
<tr>
<th>Controllers</th>
<th>Merits</th>
<th>Demerits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-linear active control[22][15]</td>
<td>Reduced the chaotic behaviour of cancer cells</td>
<td>Effects of uncertainties and disturbances not considered</td>
</tr>
<tr>
<td>Double-integral SMC[16]</td>
<td>Minimized cancer cells to zero value for leukemic therapy and robust control</td>
<td>No discussion regarding therapy duration</td>
</tr>
<tr>
<td>Higher-order SMC [23][24]</td>
<td>1. Robust control with reduced therapy duration for ADT model of Prostate cancer 2. Relapse avoidance with cancer cell minimization</td>
<td>1. Analysis with different initial conditions is missing 2. No discussion regarding optimal drug delivery and robustness</td>
</tr>
<tr>
<td>Feedback Linearization[17]</td>
<td>Disturbance decoupling and reduction of cancer load</td>
<td>Prolonged therapy duration</td>
</tr>
</tbody>
</table>

also gaining popularity in biomedical research [25–27]. The fuzzy inference system which is an integral part of AI can approximate any given system based on user-defined fuzzy rules [28]. FIS has been used for expert system design in some cases to diagnose cancer stages and schedule treatments accordingly [29–32]. Fuzzy logic has also been used in biomedical fields to estimate the post-treatment survival rates of cancer patients. This research looks at a different aspect of fuzzy systems. The fuzzy rules will aid in the prostate cancer model’s approximation in order to reduce the number of cancer cells to zero. They will also assist with drug dosage scheduling. H. Seker and colleagues developed a fuzzy k-nearest neighbour classifier for breast and prostate cancer surgery and therapy [33]. They proposed that a rule-based model would be more effective in detecting disease.

In this research work, the mathematical model given by G. Tanaka is investigated [34]. His work is extended to introduce the concept of adaptive therapy for prostate cancer treatment. This involves the application of a nonlinear control algorithm to the cancer model and designing the drug dosage based on the control laws obtained using these algorithms. The drug dosage gives an insight
into the chemotherapy treatment. The overall objective is to reduce the cancer cells to zero value in a minimum time to reduce prolonged exposure to drugs. An ATS fuzzy controller is used to achieve the goal. The contributions of the proposed method are:

- The ADT model together with the proposed ATS controller represents the mathematical model for adaptive therapy.
- The duration of treatment has been reduced to two months, which decreases the likelihood of medication toxicity.
- The proposed controller functions well regardless of the initial conditions, and it can achieve its objective even in the presence of parametric variations disturbances thus, making it a robust design.
- The proposed method will help the researchers find the best way to schedule drugs for adaptive therapy, which is a better option when cancer cells stop responding to hormone therapy.

This paper is divided into sections. The section 2 provides a brief description of the prostate cancer mathematical model. Section 3 discusses the controller design methods. 4 depicts the simulation and outcomes obtained with the proposed controllers. Section 6 contains the discussion, and section 5 contains the conclusion.

## 2 Proposed Mathematical model

The mathematical model of G. Tanaka under Androgen-deprivation therapy is investigated and modified to introduce the concept of the adaptive therapy. The state variables $x$, $y$, and $z$ reflect, respectively, the number of AD cells, AI cells, and androgen levels. The original mathematical model, when simulated resulted in unstable dynamics and chaos phenomenon [23]. The control inputs $u_1$, $u_2$ and $u_3$ are added to each state of the ADT model. These inputs represent the drug dosage required for chemotherapy. The ADT model along with the proposed controller will together represent the adaptive therapy model for prostate cancer. The mathematical model for adaptive therapy is given by equation (1). All parameters are dimensionless. Table 1 gives the range of parameter values that will be used for our analysis.

\[
\begin{align*}
\dot{x} &= \left( \alpha_x \left( k_1 + \frac{(1-k_1)z}{z+k_2} \right) \right) - \beta_x \left( k_3 + \frac{(1-k_3)z}{z+k_4} \right) - m_1 \left( 1 - \frac{z}{z_0} \right) x + u_1 \\
\dot{y} &= m_1 \left( 1 - \frac{z}{z_0} \right) x - \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) y + u_2 \\
\dot{z} &= \frac{-z + z_0(1-u)}{\tau} + u_3
\end{align*}
\]  

(1)
Table 2: Comparative analysis using proposed controllers.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Variables</th>
<th>Value/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proliferation rate of AD cells</td>
<td>$\alpha_x$</td>
<td>0.004-0.081[7][35]</td>
</tr>
<tr>
<td>The apoptosis rate of AD cells</td>
<td>$\beta_x$</td>
<td>0.001-0.0525 [33]</td>
</tr>
<tr>
<td>The proliferation rate of AI cells</td>
<td>$\alpha_y$</td>
<td>0.001-0.046 [24][36]</td>
</tr>
<tr>
<td>The apoptosis rate of AI cells</td>
<td>$\beta_y$</td>
<td>0.015-0.00775 [24]</td>
</tr>
<tr>
<td>$\alpha_x k_1$ is the growth rate of AD cells at zero androgen level</td>
<td>$k_1$</td>
<td>0 [35]</td>
</tr>
<tr>
<td>Plausible growth rate curve of AD cells</td>
<td>$k_2$</td>
<td>2</td>
</tr>
<tr>
<td>$\beta_x k_3$ is the death rate of AD cells at $z = 0$</td>
<td>$k_3$</td>
<td>8 [36]</td>
</tr>
<tr>
<td>The slope of the proliferation rate curve of AI cells</td>
<td>$d$</td>
<td>$0 &lt; d &lt; 1$</td>
</tr>
<tr>
<td>Time constant of androgen dynamics</td>
<td>$\tau$</td>
<td>62.5 days</td>
</tr>
<tr>
<td>Normal androgen level</td>
<td>$z_o$</td>
<td>$20 \text{ng/ml}$</td>
</tr>
<tr>
<td>Mutation rate from AD to AI cells at 0</td>
<td>$m_1$</td>
<td>$0.00001 - 0.0001$ [37]</td>
</tr>
</tbody>
</table>

3 Proposed Methodology

This section contains the development of a super-twisting Sliding mode controller and active control based T-S fuzzy algorithms for the prostate cancer model in order to decrease the AI and AD cells that may change into cancer cells.

3.1 Super-twisting SMC

The prostate cancer model may be represented by a generalized equation given by [24]:

$$\dot{\hat{X}} = A(\hat{X}) + B(\hat{X}) u$$  \hspace{1cm} (2)

Choosing a suitable sliding surface as $s = \dot{x}(t)$ with control input $u = B^{-1}(\hat{X}) [u_{st} - A(\hat{X})]$ and $u_{st}$ being the super-twist control input. Here,

$$u_{st} = -q_1 \left[ s \right]^{\frac{1}{2}} + \hat{u}$$  \hspace{1cm} (3)

$$\dot{\hat{u}} = -q_2 \text{sign}(s)$$  \hspace{1cm} (4)

where, $q_1, q_2 \in \mathbb{R}^+$ are positive constants, and the sliding surface is $[s]^{\frac{1}{2}} = |s|^{\frac{1}{2}} \text{sign}(s)$. The matrix $B(\hat{X})$ is invertible and $\hat{B} < p$, for any constant
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$p \in \mathbb{R}^+$. The new control law is $u = B^{-1}\left(\dot{X} - A(\dot{X})\right)\cdot q_2 > p$ is necessary condition for convergence. The Lyapunov function candidate as given in \([38][39]\) ensures the stability of the super-twisting algorithm.

3.2 Active control based Takagi-Sugeno Fuzzy controller

An active algorithm is employed in this part to determine the gain values that will bring the error to zero, and these gain values are then utilised to determine the boundary values for fuzzy modelling. Hence, Active Takagi-Sugeno Controller. Fig 1 represents the Fuzzy Inference System used for modeling the ATS controller.

\[
\begin{align*}
    e_1 &= x - x_r \\
    e_2 &= y - y_r \\
    e_3 &= z - z_r
\end{align*}
\]

Fig. 1: Block diagram of proposed Fuzzy system

3.2.1 The active algorithm

Let us define our desired performances and errors in states. $x_r$ is the desired population of AD cells in a steady state. $y_r$ is the desired population of AI cells in the steady-state. $z_r$ is the desired concentration of androgen hormone in the steady-state. Thus, the error equations are:

$$
\begin{align*}
    e_1 &= x - x_r \\
    e_2 &= y - y_r \\
    e_3 &= z - z_r
\end{align*}
$$

Here, the subscript $r$ stands for reference value of states. The error must converge to zero for the states to converge to their desired values. Considering the time derivatives of error dynamics, we have:
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\begin{align*}
\dot{e}_1 &= \left( \alpha_x \left( k_1 + \left( \frac{1-k_1}{z+k_2} \right) \right) - \beta_x \left( k_3 + \left( \frac{1-k_3}{z+k_4} \right) \right) \right) e_1 \\
&\quad - m_1 \left( 1 - \frac{z}{z_0} \right) e_1 + - m_1 \left( 1 - \frac{z}{z_0} \right) x_d + u_1 - \dot{x}_r \\
&\quad \left( \alpha_x \left( k_1 + \left( \frac{1-k_1}{z+k_2} \right) \right) - \beta_x \left( k_3 + \left( \frac{1-k_3}{z+k_4} \right) \right) \right) x_r
\end{align*}

\begin{align*}
\dot{e}_1 &= m_1 \left( 1 - \frac{z}{z_0} \right) x - \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) e_2 \\
&\quad - \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) y_r + u_2 - \dot{y}_r \\
\dot{e}_3 &= - \frac{(e_3 + z_r)}{\tau} + \frac{z_0 (1-u)}{\tau} - \dot{z}_r + u_3
\end{align*}

The control laws for minimizing the error and to ensure that all the states converge to desired values in minimum time are given by Eq. 9, 10 and 11 respectively.

\begin{align*}
u_1 &= - g_1 \left( \alpha_x \left( k_1 + \left( \frac{1-k_1}{z+k_2} \right) \right) - \beta_x \left( k_3 + \left( \frac{1-k_3}{z+k_4} \right) \right) \right) e_1 \\
&\quad - m_1 \left( 1 - \frac{z}{z_0} \right) e_1 - m_1 \left( 1 - \frac{z}{z_0} \right) x_r + \dot{x}_r \\
&\quad \left( \alpha_x \left( k_1 + \left( \frac{1-k_1}{z+k_2} \right) \right) - \beta_x \left( k_3 + \left( \frac{1-k_3}{z+k_4} \right) \right) \right) x_r \\
u_2 &= - m_1 \left( 1 - \frac{z}{z_0} \right) x + g_2 \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) e_2 \\
&\quad + \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) y_r + \dot{y}_r \\
u_3 &= \frac{(g_3 e_3 + z_r)}{\tau} - \frac{z_0 (1-u)}{\tau} + \dot{z}_r
\end{align*}

Using Eq. 9-11 in Eq. 1, the error equations are modified to:

\begin{align*}
\dot{e}_1 &= \left( \alpha_x \left( k_1 + \left( \frac{1-k_1}{z+k_2} \right) \right) - \beta_x \left( k_3 + \left( \frac{1-k_3}{z+k_4} \right) \right) \right) \left( 1 - g_1 \right) e_1 \\
&\quad - m_1 \left( 1 - \frac{z}{z_0} \right) \left( 1 - g_1 \right) e_1
\end{align*}

\begin{align*}
\dot{e}_2 &= - \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) \left( 1 - g_2 \right) e_2
\end{align*}
\[ \dot{e}_3 = -\frac{(1 - g_3) e_3}{\tau} \] (14)

Here, \( g_1, g_2 \) and \( g_3 \) are the gain values to be decided by the Lyapunov stability. We have the Lyapunov function candidate as:

\[ V = \frac{1}{2} (e_1^T e_1 + e_2^T e_2 + e_3^T e_3) \] (15)

Differentiating Eq. 15 on both sides, we get the derivative of Lyapunov function as:

\[ \dot{V} = e_1 \dot{e}_1 + e_2 \dot{e}_2 + e_3 \dot{e}_3 \]

\[ = \left( \alpha_x \left( k_1 + \frac{(1 - k_1) z}{z + k_2} \right) - \beta_x \left( k_3 + \frac{(1 - k_3) z}{z + k_4} \right) \right) (1 - g_1) e_1^2 \]

\[ - m_1 \left( 1 - \frac{z}{z_0} \right) (1 - g_1) e_1^2 - \left( \alpha_y \left( 1 - \frac{dz}{z_0} \right) - \beta_y \right) (1 - g_2) e_2^2 \]

\[ - \frac{-z + z_0 (1 - u)}{\tau} (1 - g_3) e_3^2 \]

\[ = A (1 - g_1) e_1^2 - B (1 - g_2) e_2^2 - (1 - g_3) e_3^2 \] (16)

Negating both sides of the equation and writing in matrix form:

\[ -\dot{V} = e^T \begin{bmatrix} -(1 - g_1) & 0 & 0 \\ 0 & B (1 - g_2) & 0 \\ 0 & 0 & (1 - g_3) \end{bmatrix} = e^T Q e \] (17)

The matrix \( Q \) must be positive-definite to ensure that \( \dot{V} \) is always negative-definite and so that the selected control technique can achieve asymptotic stability for the system. For \( Q \) to be positive definite, the gain \( g_1, g_2 \) and \( g_3 \) must satisfy the conditions:

\[ -(1 - g_1) > 0; \ (1 - g_2) (1 - g_3) > 0; \ -(1 - g_1) (1 - g_2) (1 - g_3) > 0 \]

Therefore, \( g_1 = 2, g_2 = -1 \) and \( g_3 = -1 \). These values of gain provides the boundary values for T-S fuzzy models.

### 3.2.2 Fuzzy algorithm

Any nonlinear control system can be approximated using the T-S fuzzy model [40]. The \( n^{th} \) rule of the T-S model is given by Eq. 18 [40]:

**Rule n:**

\( z_1 (t) \) is \( M_{n1} \), \( z_2 (t) \) is \( M_{n2} \) and ............. \( z_p (t) \) is \( M_{np} (t) \),
THEN

\[ \dot{x}(t) = A_n x(t) + B_n u(t) \]
\[ y(t) = C_n x(t), \quad \text{for } n = 1, 2, \ldots, r \]  \hspace{1cm} (18)

where \( M_{nj} \) indicates fuzzy set, \( r \) is the total number of rules; \( x(t) \) in \( \mathbb{R}^n \) represents state vector, \( u(t) \) in \( \mathbb{R}^m \) is the input vector, \( y(t) \) in \( \mathbb{R}^q \) is output vector, \( A_i \in \mathbb{R}^{n \times n}, B_i \in \mathbb{R}^{n \times m} \) and \( C_i \in \mathbb{R}^{q \times n} \); \( z_1(t), \ldots, z_p(t) \) are the premise variables that are the function of state variables. Each consequent linear term represented by \( A_n x(t) + B_n u(t) \) are the fuzzy subsystem. The resulting fuzzy systems are:

\[ \dot{x}(t) = \sum_{n=1}^{r} w_n(z(t)) \{ A_n x(t) + B_n u(t) \} \]
\[ y(t) = \sum_{n=1}^{r} h_n(z(t)) C_n x(t) \]  \hspace{1cm} (19)

where,

\[ z(t) = z_1(t), \ldots, z_p(t), \]
\[ w_n(z(t)) = \prod_{j=1}^{p} M_{nj}(z_j(t)), \]
\[ h_n(z(t)) = \frac{w_n(z(t))}{\sum_{n=1}^{r} w_n(z(t))} \]

The term \( M_{nj}(z_j(t)) \) indicates membership function.

Since \( \sum_{n=1}^{r} w_k(z(t)) > 0 \) and \( w_n(z(t)) \geq 0 \) for \( n = 1, 2, \ldots, r \),
we have: \( \sum_{n=1}^{r} h_n(z(t)) = 1 \) and \( h_n(z(t)) \geq 0 \), \( \quad \text{for } n = 1, 2, \ldots, r \). Now, let us define the ATS fuzzy algorithm:
Algorithm 1 Active control based T-S fuzzy algorithm

Require: $e_i$s and $u_i$s corresponding to each state
Lyapunov function $V$

Ensure: $e_i \Rightarrow 0$ $\dot{V} \leq 0$

Obtain: $g_i$s to form the boundary condition for each parameter
Select: Premise variables as input to FIS
Define: Membership function and fuzzy rules
Obtain: Fuzzy systems and LMIs Eqs 26 and 27.
Output: Defuzzification using $h_n(z(t)) = \frac{\sum_{n=1}^{r} w_n(z(t))}{\sum_{n=1}^{r} w_n(z(t))}$

3.2.3 Parallel Distributed Compensation

This method gives a nonlinear fuzzy controller for the corresponding T-S fuzzy model [21]. It requires designing a compensator for each fuzzy rule. The designed PDC controller and the T-S fuzzy model have the same input variables and sets in the IF parts. The $n^{th}$ rule of the PDC is as follows:

**Rule n:**

IF

$z_1(t)$ is $M_{n1}$, $z_2(t)$ is $M_{n2}$ and ................ $z_p(t)$ is $M_{np}(t)$,

THEN

$u(t) = -K_n x(t), \quad n = 1, 2, \ldots, r$ \hspace{1cm} (21)

Therefore, the overall controller is represented by:

$$u(t) = -\frac{\sum_{n=1}^{r} w_n(z(t)) K_n x(t)}{\sum_{n=1}^{r} w_n(z(t))}$$ \hspace{1cm} (22)

Substituting Eq. 22 in Eq. 19, we get the closed-loop system as:

$$\dot{x}(t) = \sum_{n=1}^{r} \sum_{j=1}^{r} h_n(z(t)) h_j(z(t)) \{A_n - B_n K_n\} x(t)$$ \hspace{1cm} (23)

3.2.4 Stability analysis using LMI algorithm

The stability of the T-S fuzzy model is analyzed using the LMI algorithm. The LMI algorithm is given by Theorem 1:
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Theorem 1 The closed-loop fuzzy system given by Eq. 23 is asymptotically stable if there exists a positive definite matrix $P$ such that the following inequalities are satisfied [41]:

$$(A_n - B_n K_n)^T P + P (A_n - B_n K_n) < 0, \text{ for } n = j = 1, 2, \ldots, r$$

and,

$$G_{nj}^T P + P G_{nj} < 0, \text{ for } n < j \leq r \text{ subject to } h_{nj} \neq \emptyset$$

where,

$$G_{nj} = \frac{(A_n - B_n K_j) + (A_j - B_j K_n)}{2}$$

Now, pre-multiplying the Eq. 25 and 24 by $P^{-1}$ and defining $Z = P^{-1}(\text{for } Z > 0)$ and $M_n = K_n Z$ we get:

$$Z A_n^T + A_n Z - M_n^T B_n^T - B_n M_n < 0, \text{ for } n = j = 1, 2, \ldots, r$$

$$Z A_n^T + A_n Z + Z A_j^T + A_j Z - (B_n M_j + B_j M_n) - (M_n^T B_j + M_j^T B_n) < 0, \text{ for } n < j \leq r$$

3.2.5 Fuzzy controller for Prostate cancer model

Considering the Prostate cancer model in Eq. 1 and by assuming $u_1(t), u_2(t)$ and $u_3(t)$ as inputs, we have two nonlinear terms each for state $x$ and $y$ given by $z_1$ and $z_2$:

$$z_1 = \alpha_x \left( \frac{(1 - k_1 z)}{z + k_2} \right) - \beta_x \left( \frac{(1 - k_3 z)}{z + k_4} \right) - m_1 \left( \frac{z}{z_0} \right)$$

$$z_2 = m_1 \left( \frac{z}{z_0} \right) - \alpha_y \left( \frac{dz}{z_0} \right) y$$

The boundary conditions are: $x \in [0, 2]$ $y \in [-1, 1]$ and $z \in [-1, 1]$. The membership functions for $z_1$ and $z_2$ are given by $M_i$s and $N_i$s respectively, where $i = 1, 2$. Each membership function with index 1 represents the minimum value for variable $z_1$ or $z_2$ and each membership function with index 2 represents the maximum value. The resulting fuzzy system using four rules is as follows:

Rule 1:

$$\text{IF } z_1(t) \text{ is } M_1(z_1(t)) \text{ and } z_2(t) \text{ is } N_1(z_2(t)), \text{ THEN } \begin{bmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{bmatrix} = A_1 \begin{bmatrix} x \\ y \\ z \end{bmatrix} + Bu(t)$$

Rule 2:

$$\text{IF } z_1(t) \text{ is } M_1(z_1(t)) \text{ and } z_2(t) \text{ is } N_2(z_2(t)), \text{ THEN } \begin{bmatrix} \dot{x} \\ \dot{y} \\ \dot{z} \end{bmatrix} = A_2 \begin{bmatrix} x \\ y \\ z \end{bmatrix} + Bu(t)$$
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\[
\hat{x}, \hat{y}, \hat{z} = A_2 \begin{bmatrix} x \\ y \\ z \end{bmatrix} + Bu(t) \tag{31}
\]

Rule 3:

\[
\text{IF } z_1(t) \text{ is } M_2(z_1(t) \text{ and } z_2(t) \text{ is } N_1(z_2(t)),} \quad \quad THEN \quad \hat{x}, \hat{y}, \hat{z} = A_3 \begin{bmatrix} x \\ y \\ z \end{bmatrix} + Bu(t) \tag{32}
\]

Rule 4:

\[
\text{IF } z_1(t) \text{ is } M_2(z_1(t) \text{ and } z_2(t) \text{ is } N_2(z_2(t)),} \quad \quad THEN \quad \hat{x}, \hat{y}, \hat{z} = A_4 \begin{bmatrix} x \\ y \\ z \end{bmatrix} + Bu(t) \tag{33}
\]

The values of matrices are:

\[
A_1 = \begin{bmatrix} -0.0938 & 0 & 0 \\ 0.00015 & -0.045 & 0.00071 \\ 0 & 0 & -0.016 \end{bmatrix}; \quad A_2 = \begin{bmatrix} -0.0938 & 0 & 0 \\ 0.00015 & -0.045 & -0.000715 \\ 0 & 0 & -0.016 \end{bmatrix}
\]

\[
A_3 = \begin{bmatrix} -0.2938 & 0 & 0 \\ 0.00015 & -0.045 & 0.00071 \\ 0 & 0 & -0.016 \end{bmatrix}; \quad A_4 = \begin{bmatrix} -0.2938 & 0 & 0 \\ 0.00015 & -0.045 & -0.000715 \\ 0 & 0 & -0.016 \end{bmatrix}
\]

\[
B = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}; \quad M_1 = \frac{(z_1 + 0.01853)}{0.04373}; \quad M_2 = \frac{0.0252 - z_1}{0.04373}
\]

\[
N_1 = \frac{(z_2 + 0.0012125)}{0.00242}; \quad N_2 = \frac{0.0012075 - z_1}{0.00242}
\]

The corresponding four PDC rules are as follows:

Rule 1:

\[
\text{IF } z_1(t) \text{ is } M_1(z_1(t) \text{ and } z_2(t) \text{ is } N_1(z_2(t)),} \quad \quad \text{THEN} \quad u(t) = -K_1 \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix} \tag{34}
\]

Rule 2:

\[
\text{IF } z_1(t) \text{ is } M_1(z_1(t) \text{ and } z_2(t) \text{ is } N_2(z_2(t)),} \quad \quad \text{THEN} \quad u(t) = -K_2 \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix} \tag{35}
\]

Rule 3:

\[
\text{IF } z_1(t) \text{ is } M_2(z_1(t) \text{ and } z_2(t) \text{ is } N_1(z_2(t)),}
\]
THEN \( u(t) = -K_3 \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix} \) \hspace{1cm} \text{(36)}

Rule 4:

\[
IF \ z_1(t) \ is \ M_2(z_1(t)) \ and \ z_2(t) \ is \ N_2(z_2(t)),
THEN \ u(t) = -K_4 \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix}
\] \hspace{1cm} \text{(37)}

Since the fuzzy model of prostate cancer has four rules, the PDC will also have only four rules. So, the resulting PDC fuzzy controller is:

\[
u(t) = -\sum_{k=1}^{4} w_k(z(t)) K_k x(t) \]
\[
= -\sum_{k=1}^{4} h_k(z(t)) K_k x(t)
\] \hspace{1cm} \text{(38)}

Substituting Eq. 38 in Eq. 19, we get the closed-loop system as:

\[
\dot{x}(t) = \sum_{k=1}^{4} h_k(z(t)) \{ A_k - BK_k \} x(t)
\] \hspace{1cm} \text{(39)}

Eq. (39) shows the dynamics of cancer model after application of fuzzy controller. Fig 2 summarizes the steps required for ATS controller design.
Define error equations $e_i$s and corresponding control laws to nullify the error in states

Choose a suitable Lyapunov function candidate $V$ to obtain the gain values

Set the boundary conditions based on $g_i$s value and choose input parameters

Define membership functions and fuzzy rules based on T-S fuzzy algorithm and PDC compensation

Solve LMIs equations using YALMIP toolbox. (4 rules = 10 LMI equations)

Defuzzification

Output

**Fig. 2:** Flowchart for designing ATS fuzzy Controller
4 Simulation Results

This section examines the behaviour of the proposed nonlinear controllers and compares them to one another. The comparison is based on state convergence to their desired values and robustness of the controllers. We have employed scaled versions of the parameters’ values, with a conversion value of ten to the fifth power. All of the parameters have no dimensions (due to the fact that their values are scaled using various conversion factors) \[42\][43]. We have used the clinically relevant initial values and desired values, which are as follows: 
\[x(0) = 0.1, \quad y(0) = 0.1 \quad \text{and} \quad z(0) = 0.1, \quad x_r = 0.05, \quad y_r = 0.005 \quad \text{and} \quad z_r = 8.\]

The unit of time is in days. This paper used YALMIP version R20180612 to solve LMI optimization problems. The semi-definite programming problems are solved using the SDPT3-4.0 solver.

![Fig. 3: The original state trajectory for ADT model. In this case, x stands for the population of AI cells, y indicates the number of AD cells, and z provides the androgen concentration. The states exhibit chaotic behaviour resulting in uncontrolled dynamics](image-url)
Solving the LMI Eq. 26 and 27 using YALMIP toolbox, the matrix $P$ and the feedback gain matrices are as follows:

$$P = \begin{bmatrix} 0.0385 & 0 & 0 \\ 0 & 0.0385 & 0 \\ 0 & 0 & 0.0385 \end{bmatrix}; \quad K_1 = \begin{bmatrix} 0.1919 & 0.0001 & 0 \\ 0.0001 & 0.2407 & 0.0004 \\ 0 & 0.0004 & 0.2697 \end{bmatrix}$$

$$K_2 = \begin{bmatrix} 0.1919 & 0.0001 & 0 \\ 0.0001 & 0.2407 & -0.0004 \\ 0 & -0.0004 & 0.2697 \end{bmatrix}; \quad K_3 = \begin{bmatrix} -0.0081 & 0.0001 & 0 \\ 0.0001 & 0.2407 & 0.0004 \\ 0 & 0.0004 & 0.2697 \end{bmatrix}$$

$$K_4 = \begin{bmatrix} -0.0081 & 0.0001 & 0 \\ 0.0001 & 0.2407 & -0.0004 \\ 0 & -0.0004 & 0.2697 \end{bmatrix}$$

These values of $K_1, K_2, K_3$ and $K_4$ are used to obtain the state trajectories after application of the proposed fuzzy controller.

![3-D phase plot of original cancer model](image)

**Fig. 4:** 3-D phase plot of original cancer model. The phase plot shows the uncontrolled trajectories of the prostate cancer model.
Fig. 5: 3-D phase plot of states after application of active control technique. The plot gives an idea that the nonlinear active control technique successfully eliminated the chaotic behavior of the cancer states.

(a) $M_1$ and $M_2$ vs $z_1$  (b) $N_1$ and $N_2$ vs $z_2$

Fig. 8: The plot of membership function versus the auxiliary variables $z_1$ and $z_2$. 
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Fig. 6: The graph depicts the super-twisting SMC design state variables and control inputs in relation to time. The super-twisting SMC reduced the states to zero, but at the expense of an increase in treatment duration.

Fig. 9: Trajectories after application of T-S fuzzy control technique. The number of cells have been minimized to their zero values.
Fig. 7: Simulation diagram used for T-S fuzzy model. There is one fuzzy operation block, a multiplexer, and four fuzzy subsystems. It consists of four fuzzy operation block with four triangular functions corresponding to each membership function. Each fuzzy subsystems are taking the feedback gain matrices as their inputs.
(a) T-S fuzzy control with chirp signal    (b) T-S fuzzy control with white noise

Fig. 10: The plot after application of some disturbance in the form of chirp signal and white noise. The states converge to their reference values hence proving the robustness of the controlled design.

Table 3: Comparative analysis using proposed controllers.

<table>
<thead>
<tr>
<th>Controller</th>
<th>AD cells $x$</th>
<th>AI cells $y$</th>
<th>androgen level, $z$</th>
<th>time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original model</td>
<td>varying amplitude</td>
<td>$\approx 0$</td>
<td>$\approx 0$</td>
<td></td>
</tr>
<tr>
<td>Super-twist</td>
<td>0.000000056</td>
<td>0.0002039</td>
<td>0.000001</td>
<td>7.5</td>
</tr>
<tr>
<td>T-S fuzzy model</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Fig. 11: The plots showing the convergence of states to their reference values for any initial condition using ATS fuzzy controller. The treatment time for all cases is less than two months.
5 Discussion

We have used the scaled values of parameters [23]. Fig. 3 shows the time response of the original state trajectories of the prostate cancer model. The AD cells exhibit oscillations with more significant deviations. It appears periodic, but after analysing its time response using the 'fft' tool in MATLAB, we found its chaotic behavior. The population of AI cells also oscillates with more minor deviations ($\approx 0$), and the androgen level settles down to zero value. During the treatment period, the androgen concentration reaches its minimum value. Fig. 4 and 5 show the three-dimensional phase plot of the original states and states after applying active control methods. The phase plot of actual state dynamics indicates its oscillatory nature, whereas the active control method’s phase plot seems stable. The gain values obtained using the active control method are used to set the boundary for the T-S fuzzy algorithm. Hence, the proposed method is named “active control-based fuzzy controller.”

Fig. 6 shows the time response of states using the STSMC. All the states exhibit a chattering phenomenon with a smaller amplitude, as given in Table 3. It brings down the number of cells to almost zero. It provides the control law for each state of the STA model, which decides the drug dosage for adaptive therapy.

Fig. 7 shows the simulation diagram of the T-S fuzzy model. It consists of a fuzzy operation block with four triangular functions corresponding to each membership function. In addition, four fuzzy subsystems are taking the feedback gain matrices as their inputs. There are, in total, four fuzzy subsystems corresponding to each fuzzy rule. Fig. 8 shows the triangular membership graph for membership functions $M_i's$ and $N_i's$. The plot of state variables after application of the fuzzy controller is shown in Fig. 9. All the trajectories settle down at zero. The time taken to nullify the AI cells is almost two months. The control law 38 helps decide the required drug dosage for androgen deprivation treatment. The states converge to a zero value for any initial condition. It indicates the global asymptotic stability of the proposed fuzzy controller. Moreover, the proposed controller has minimal effect with respect to the disturbance, such as white noise, and after application of the chirp signal, thus proving its robustness. This is shown in Fig. 10. The initial frequency of the chirp signal is 0.1 Hz. Fig. 11 gives the state trajectories for ATS controller for different initial conditions.

6 Conclusion

The original prostate cancer model has resulted in uncontrolled state trajectories in poor androgen conditions. It led to continuous secretion of PSA protein and increased PSA levels in the prostate gland. The phase plane analysis of the model reflected the unstable behavior of the trajectories. The STSMC controller converged all the states to zero. However, the treatment time was not reduced. Therefore, we went for the active fuzzy controller based on the AI
technique. The proposed T-S fuzzy modeling has converged all the state trajectories to their steady-state values. The domain of stability for the T-S fuzzy model is $x \in [-\infty, \infty]$, $y \in [-\infty, \infty]$, and $z \in [-\infty, \infty]$. The AD and AI cells have been reduced to almost zero values with a therapy duration of only two months. The T-S fuzzy model helps us achieve global asymptotic stability for the model and is therefore, the most suitable choice for achieving the said objective.

There are several other parameters, such as the Gleason score and PSA, which can be considered for mathematical modeling. Our future work will try to implement these parameters to improve the performance of the proposed design further.

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Declarations

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- **Conflict of interest:** None
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- **Authors’ contributions:** Each of the authors has made important contributions during the process of putting together the manuscript.

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