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Observer-based intelligent adaptive iterative time-varying controller for nonlinear of chronic myelogenous leukemia dynamics

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Abstract

An adaptive controller for a time-varying non-linear non-affine system is designed based on the observer for chronic Myelogenous leukaemia (CML) as a blood cancer. Compared to recent research that concentrates on designing controllers for exact models of CML, our approach deals with designing controllers for nonlinear uncertain models in which the function of the system is unknown. This approach deals with the nonlinear observer-based design to reduce both the hardware and sensors for parameter estimation of the diseased. In the proposed method for designing a suitable controller, fuzzy systems are used as a general approximator and also their parameters are calculated in such a way that the stability of the closed-loop system is guaranteed. Compared to the investigated methodologies that concentrate on the designing controller for the known dynamical models, the proposed approach deals with the unknown nonlinear model of Nonlinear of Chronic Myelogenous Leukemia. Furthermore, instead of approximating the unknown function of the disease, this approach concentrates on the approximation of the control input to decrease computational values. This method is a supplementary tool for specialists who study in this field. Furthermore, one of the most important advantages of the proposed method is that the dynamics of systems are uncertain. Simulation results show the effectiveness of the proposed method.

Keywords: Adaptive Controller, Cancer, Chronic Myelogenous Leukemia, Observer, Fuzzy System, Nonlinear Model

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1 Introduction

Cancer is one of the extreme murderers in human life, although medical research has been effective, despite excessive problems, for specific pathologies. Unlimited social energy and financial resources are enthusiastic, with efficacious productivities, to cancer exploration with specific consideration to experimental and theoretic immunology [2].

Chronic myeloid leukaemia (CML), also identified as chronic Myelogenous leukaemia is a kind of cancer that starts in confident blood-forming cells of the bone core and attacks the blood. Consequently, CML results from the wild growing of white blood cells due to the enlarged and unregulated evolution of predominantly myeloid cells in the bone marrow and the gathering of these cells in the blood [3].

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In [6], chronic myeloid leukaemia is blood cancer, and it rises from a stem cell in the first steps of blood cell construction in which the leukemic cells share chromosomal abnormalities. These irregularities don't exist in non-leukemic white blood cells and other cells of the patient in CML. In [3], the reciprocal translocation between one chromosome nine and one chromosome twenty-two causes chromosomes 9 and 22 to be longer and shorter than normal cases, respectively. The PH chromosome which causes a fusion gene shows the production of an irregular tyrosine kinase protein, Bcr-Abl [5], [9]. It is the first successful drug design. Designing classic observers is discussed for the dynamics, of cancer in the presence of external disturbance in [12]. The adaptive output controller design is proposed for cancer dynamics with external disturbances and noise of the output [13].

The first step of this paper is dedicated to describing the dynamics of blood cancer and also the response of the system without any treatment is considered. Afterwards, the neural observer is applied in such a way that the weights of hidden layers and also output layer could be variable, and by using the Back-Propagation algorithm and comparing it with a high-gain observer the effectiveness of this observer is investigated. Finally, through simulation outputs of both observers are compared with the output of the system and these results showed that the performance of neural observers in estimating the dynamics of blood cancer is better than a high-gain observer also this fact can lead to better performance in the treatment of cancer and reducing costs. So far, several mathematical models for modelling the dynamics of blood cancer have been designed and generally, each one comes with its upsides and downsides. All of these models have a complicated non-linear part and the presence of this inherent non-linear part leads to existing difficulty in estimating the state variables of the system. This section followed by introducing these models, which are mentioned in the literature.

Authors in [20] presented a model for treating blood cancer based on Neural-Adaptive control. According to [20] initially, the cells of the body cancel, but as with cancerous cells learning, Neural in [20] by learning Neural-Network and after passing a few days (approximately a week) the behaviour of growth of cells, well can do emergency actions against cancerous cells changes and this process results in destroying cancerous cells. In [19] a model for treating blood cancer is presented based on an optimal control theory.

As mentioned in [19], and using the Hamiltonian method, the optimal dose of the drug is obtained and afterwards numerical methods are applied to two patients' information. finally, the effect of this process on involved cells is investigated and numerical simulations showed that permutation treatment has better performance in a patient with a less destructive form of CML. [15] planned and investigated a dynamical model for CML based on rates of the innocent and effector T cells, and CML cells. The parameter identification as the aim of the proposed methodology plays a critical role in the reduction or authorization of the cancer model. [14] reflected a nonlinear time-delay system to model the dynamics of the interaction between CML, and the anti-leukemia immune comeback. The author developed a theoretical approach to investigate the robustness of the mentioned model in the presence of uncertainties in patient parameters. This approach can aid in developing efficient modelling in cancer treatment. Also, [18] depicted the results of several treatment databases to overcome CML.

The above one is operative handling for CML, and approximately all patients treated with this approach reduced the cancer cells but did not eliminate leukaemia. [21] deals with fuzzy observer-based fractional sliding mode controller for nonlinear dynamics of the cancer disease. The mentioned treatment platforms include strategic behaviour disruptions to stop degenerate leukaemia. These also deliberate the properties of both timing and duration of the treatment interruption based on the sensitivity analysis.

The Authors in [1] derived a new approach to plan a nonlinear model of blood cancer based on multiple observations. The nonlinear dynamical model of CML has been discussed in [22] to imitate post-imatinib behaviour situations. The proposed model is validated for Dasatinib or nilotinib treatment. [7] deals with designing linear controllers for linear models of CML using the Nyquist diagram. Designing a controller based on numerical methods is designated in [17] for the nonlinear model of CML. The main drawbacks of the mentioned references can be listed below:

1- It is assumed the dynamics of the diseases are all known in any references, this is contrary to reality.

2- Any references which concentrate on approximating unknown dynamics, this cause increasing computational values.

In this paper, an adaptive controller based on an observer for time-varying non-affine non-linear systems is presented. Tracking of the reference system, the convergence of tracking error and observer error to zero and robustness against uncertainties are the focal advantages of the proposed method.

The rest of this paper is organized as follows: In section 2, an adaptive controller based on observer for non-canonical non-affine non-linear systems is designed and also necessary mathematical proofs are given in detail. Stability analysis of the proposed method is given in section 3. Simulation results are cited in section 4. Finally, the results of this scheme are summarized in section 5.

2 Notation

The considered items are arranged in the below table 1:

Table 1: Nomenclature

Symbol	Description
N death	Critical number of normal brain cells required
t_D	Tumor doubling time
N_0	Tumor doubling time
T and tt	Time (days) tumor age at presentation
d	Dose
kk2	Proportional coefficient
C_0	Initial number of cancer cells in brain at its presentation
K_c	Rate constant for cancer cell growth
K_n	Rate constant for normal cell damage and deterioration
N(t)	Number of the normal brain cells
C(t)	Number of the brain cancer cells
doseEff	The effect of the dose on normal and cancer cells

3 Adaptive controller based on observer for non-canonical non-affine non-linear systems

In this section, proposed controller and observer for a special class of non-canonical non-linear systems are designed and the necessary mathematical theorem is given in detail. Consider a non-canonical non-linear system as follows:

$$\begin{cases} \dot{x}_l = f_l(X) \quad l = 1, 2, ..., n-1 \\ \dot{x}_n = f_n(X, u, t) + d'(t) \\ \quad y = C^T X \end{cases} \tag{3.1}$$

where X $= \begin{bmatrix} x_1 & ... & x_{n-1} & x_n \end{bmatrix}^T$, u , t and $d'(t)$ are state of the system, input control, time and bounded external disturbance, respectively. One can rewrite equation (3.1) as the following equations:

$$\begin{cases} \dot{X} = A_0 X + \underbrace{(-A_0 X + f(X))}_{f'(X)} + b\left(f_n(X, u, t) + d'(t)\right) \\ y = C^T X \end{cases} \tag{3.2}$$

where$f(X, u, t)$, A_0 and b are given by the following equations. It should be noted that $f'(X)$ is continuous and smooth with respect to X and $f(X, u, t)$ is continuous and smooth according to X, t .

$$\text{A}_0 = \begin{bmatrix} 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 1 \\ 0 & 0 & 0 & \cdots & 0 \end{bmatrix} \in R^{n\times n}, \quad \text{b} = \begin{bmatrix} 0 & ... & 0 & 1 \end{bmatrix}^T \in R^n$$
$$f(X) = \begin{bmatrix} f_1(X) & ... & f_{n-1}(X) & 0 \end{bmatrix}^T, \text{C}^T = \begin{bmatrix} 1 & ... & 0 & 1 \end{bmatrix} \in R^n \tag{3.3}$$

This section will be followed by introducing some assumptions relevant to the system mentioned in equation (3.1) and also reference signal x_m .

Assumption 1: Consider reference signal vector (X_m) which is defined as the following equations:

$$\begin{cases} \dot{X}_m = A_0 X_m + br(t) \\ y_m = C^T X_m \end{cases} \tag{3.4}$$

where A_0 , b and C^T are given in equation (3.3) and furthermore y_m is the output of the reference model mentioned.

Assumption 2: Without loss of generality, it is assumed that the smooth function $f_n(X,u)$ satisfies the following condition:

$$\mathrm{f_u}(X,u,t) \triangleq \frac{\partial \mathrm{f}_n(X,u,t)}{\partial u} \geqslant \mathrm{f_{min}} > 0 \text{ for all } (X,u) \in \mathbb{R}^n \times \mathbb{R} \tag{3.5}$$

where $\mathrm{f_{min}} \in \mathbb{R}$ are constant variables. It is noted that all the design steps in this section could be done for the following inequality:

$$f_u(X,u,t) \leq f_{\min} < 0 \tag{3.6}$$

Consequently, assumption 2 means the sign of the $\mathrm{f_u(X,u,t)}$ is constant throughout the controller design, positive or negative.

Assumption 3: External disturbances mentioned in (3.2) satisfy the following inequality:

$$\|d'(t)\|_\infty \leqslant d_{\max} \tag{3.7}$$

Assumption 4: The system mentioned in (3.2) is controllable and observable. The $\hat{x}(t)$ considers as the estimation of $x(t)$.

$$E = X_m - X, \quad \hat{E} = X_m - \hat{X}, \quad \tilde{E} = E - \hat{E} \tag{3.8}$$

where X_m is the reference signal vector, E is the tracking error vector, $\hat{E}$ is the observer error vector, and $\tilde{E}$ is the observation error vector. Derivative of tracking error in (3.8) results in the following equation:

$$\begin{cases} \dot{E} = \dot{X}_m - \dot{X} = AX_m + br(t) - AX - f'(X) - b\left(f_n(X,u,t) + d'(t)\right) \\ E_y = C^T E \end{cases} \tag{3.9}$$

where E_y is output of the tracking error system. Using the definition of tracking error in (8), the following equation could be defined as:

$$\begin{cases} \dot{E} = A_0 E - f'(X) - b\left(f_n(X,u,t) + d'(t) - r(t)\right) \\ E_y = C^T E \end{cases} \tag{3.10}$$

To design the controller, consider a pseudo input v as follows:

$$v = r(t) + k_c^T \hat{E} + v' \tag{3.11}$$

where $k_c = [\mathrm{k_{c1}, k_{c2}, \ldots, k_{cn}}]^{\mathrm{T}}$ is chosen so that equation $\Upsilon(s) = s^n + \mathrm{k_{cn}} \mathrm{s}^{\mathrm{n}-1} + \ldots + \mathrm{k_{c1}}$ has the roots with negative real parts. By equation (3.11), one can rewrite equation (3.10) as follows:

$$\begin{cases} \dot{\mathrm{E}} = \mathrm{A_0 E} - \mathrm{b} \mathrm{k}_c^{\mathrm{T}} \hat{\mathrm{E}} - f'(X) - \mathrm{b}\{f_n(X,u,t) - v + d'(t) + v'\} \\ \mathrm{E_y} = \mathrm{C^T E} \end{cases} \tag{3.12}$$

Considering the equation (3.11) and the fact that the signal v is not directly dependent on control input$u$, this leads to the following inequality:

$$\frac{\partial (f_n(X,u,t) - v)}{\partial u} = \frac{\partial f_n(X,u,t)}{\partial u} > 0 \tag{3.13}$$

It is obvious that$f_n(X,u,t) - v = 0$ for any control input u. It is considered that an ideal controller $u^*(X,v)$ for $(\mathrm{X,v}) \in {}^{\mathrm{n}} \times$, which must satisfy the following equation:

$$f_n(X,u^*,t) - v = 0. \tag{3.14}$$

Using the mean value theorem, there is a value for $\lambda \in (0,1)$ where$0 < \lambda < 1$ in such defined at a non-linear function $f(X,u,t)$ around u^* could be defined as follows

$$f_n(X,u,t) = f_n(X,u^*,t) + (u - u^*) f_{u_\lambda} = f_n(X,u^*,t) + e_u f_{u_\lambda} \tag{3.15}$$

where $f_{u_\lambda} = \partial f_n(X,u,t)/\partial u|_{u=u_\lambda}$, $u_\lambda = \lambda u + (1-\lambda)u^*$ and $e_u = u - u^*$. The following equation can be obtained by substituting equations (14) and (15) into (12):

$$\begin{cases} \dot{E} = A_0 E - b k_c^T \hat{E} - f'(X) - b\{e_u f_{u_\lambda} + d'(t) + v'\} \\ E_y = C^T E. \end{cases} \tag{3.16}$$

Although the implicit function theorem guarantees that there is an ideal controller$u^*(X,v)$ for equation (3.14), it does not present a method for constructing the structure of the ideal controller.

In the next section, fuzzy systems are used to propose an estimation of $u^*(X,v)$. In the previous section, the existence of control input with the purpose of appropriate performance of the closed-loop system is proven. In this section, a controller and an observer for a non-linear system mentioned in (3.2) are designed. It is recommended that an observer be designed for the dynamics of tracking error instead of the main system. The observer according to equation (3.17) for the system mentioned in (3.16) is proposed, which is as follows:

$$\begin{cases} \dot{\hat{E}} = \underbrace{(A_0 - bk_c^T)}_{A_{oc}} \hat{E} + K_0 C^T \tilde{E} + bk_{no}(\tilde{E},\hat{E}) \left| C^T \tilde{E} \right| \\ \hat{E}_y = C^T \hat{E} \end{cases} \tag{3.17}$$

where K_o, k_{no} are respectively linear gain and non-linear gain of the observer. It is to be noted that K_o is the matrix in such a way that matrix ($\mathrm{A_{oo}}=\mathrm{A_o}-\mathrm{K_0}C^T$) is Hurwitz. Dynamics of observation error are obtained by subtracting equations (3.16) and (3.17) and considering equation (3.8) as follows:

$$\begin{cases} \dot{\tilde{E}} = \underbrace{(\mathrm{A_0}-\mathrm{K_0}C^T)}_{A_{oo}} \tilde{E} - f'(X) - \mathrm{b}\{e_u f_{u_\lambda} + d(t) + v' + k_{no}(\tilde{E},\hat{E}) \left| C^T \tilde{E} \right| \} \\ \tilde{\mathrm{E}}_\mathrm{y} = \mathrm{C^T}\tilde{\mathrm{E}} \end{cases} \tag{3.18}$$

The dynamics of output observation error could be defined as follows:

$$\tilde{\mathrm{E}}_\mathrm{y} = H(s) \left\{ f'(X) + \mathrm{b} \left(e_u f_{u_\lambda} + d(t) + v' + k_{no}(\tilde{E},\hat{E}) \left| C^T \tilde{E} \right| \right) \right\} \tag{3.19}$$

where $H(s)$ is as follows:

$$\mathrm{H(s)} = -\mathrm{C^T} \left(\mathrm{sI} - (\mathrm{A_0}-\mathrm{K_0}C^T) \right)^{-1} \mathrm{B} \tag{3.20}$$

It is noted that $H(s)$ is a stable transformer function and B is the identity matrix. Equation (3.19) can rewrite as follows:

$$\tilde{E}_\mathrm{y} = H(s)L(s) \left\{ f'_f(X) + \mathrm{b} \left(\begin{array}{c} e_u f_{u_{\lambda f}} + d'_f(t) + v'_f \\ + k_{nof}(\tilde{E},\hat{E}) \left| C^T \tilde{E} \right| \end{array} \right) \right\} \tag{3.21}$$

where $v'_f = L(s)^{-1} v'$, $f'_f = L(s)^{-1} f'$, $k_{nof} = L(s)^{-1} k_{no}$ and $d_f(t) = L(s)^{-1} d(t)$. Also $L(s)$ is considered in such a way that $L(s)^{-1}$ would be a stable proper transfer function and also $H(s)L(s)$ would be explicitly positive definite proper transfer function. Moreover, $L(s) = s^m + b_1 s^{m-1} + \cdots + b_m$ is defined for $m = n-1$. The state-space equation of (3.21) is defined as follows:

$$\begin{cases} \dot{\tilde{E}}_s = A_{oo}\tilde{E}_s - B_s f'_f(X) - b_s\{e_u f_{u_{\lambda f}} + d'_f(t) + v'_f + k_{nof}(\tilde{E},\hat{E}) \left| C^T \tilde{E} \right| \} \\ \tilde{E}_y = C_s^T \tilde{E}_s \end{cases} \tag{3.22}$$

where $C_s = [1\ 0...0]^T$ and $b_s = [1\ \ b_1 ...\ \ b_m]^T$. The ideal controller for (3.14) could propose as follows:

$$u^* = f(\Omega). \tag{3.23}$$

The approximation of $f(\Omega)$ using fuzzy systems could be obtained as $f(\Omega) = \theta_1^* w_1(\Omega) + \varepsilon_u$, where θ_1^* and $w_1(\Omega)$ are parameters and basic fuzzy functions and ε_u is the approximation error, which satisfies $|\varepsilon_u| \le \varepsilon_{\max}$ and $\varepsilon_{\max} > 0$. The parameters of θ_1^* using optimization can be attained as follows:

$$\theta_1^* = \arg\min_{\theta_1} \left[\sup \left| \theta_1^T w_1(Z) - f(Z) \right| \right] \tag{3.24}$$

where θ_1 is the estimation of θ_1^* . it is assumed that u is used as the estimation of u^* , which is defined as follows:

$$u = \theta_1^T w_1(zZ) + u_{rob} + \hat{E}^T P_2 \mathrm{K_0} \tag{3.25}$$

where $\theta_1^T w_1(zZ) + \hat{E}^T P_2 \mathrm{K_0}$ is the estimation of the ideal controller and u_{rob} is a part of the controller that is used for compensation of estimation error, uncertainties of system, and external disturbances. In (3.25) u_{rob} is designated as follows:

$$u_{rob} = sign(C_s^T \tilde{E}_s)(u_{com} + \tfrac{u_r}{f_{\min}} + \tfrac{\hat{v}'}{f_{\min}} + \hat{k}_{nof}(\tilde{E},\hat{E}) \left(\left| C_s^T \tilde{E}_s \right| + \left| \hat{E}^T P b \right| \right)) \tag{3.26}$$

where u_{com} is applied to compensate uncertainties and estimation error in the system and u_r is used for decreasing the effects of external disturbances. Moreover, $\hat{v}'$ is the approximation of v' and also $\hat{k}_{nof}$ is the estimation of k_{nof} . It is distinguished that parameters of control input are updated based on adaptive laws as follows:

$$\begin{array}{l} \dot{\theta}_1 = \Gamma_1 C_s^T \tilde{E}_s w_1(Z) \\ \dot{u}_r = \frac{\gamma_{u_r}}{f_{\min}} \left| C_s^T \tilde{E}_s \right| \\ \dot{u}_{com} = \gamma_{u_{com}} \left| C_s^T \tilde{E}_s \right| \dot{\hat{v}}' = \frac{\gamma_{\hat{v}'}}{f_{\min}} \left| C_s^T \tilde{E}_s \right| \\ \dot{\hat{k}}_{no} = \gamma_{ko} \left(\frac{\left| C_s^T \tilde{E}_s \right|^2}{f_{\min}} + \left| C_s^T \tilde{E}_s \right| \left| b^T P_2 \hat{E} \right| \right) \end{array} \tag{3.27}$$

where $\Gamma_1 = \Gamma_1^T > 0, \gamma_{u_r} > 0, \gamma_{u_{com}} > 0, \gamma_{\hat{v}'} > 0, \gamma_{ko} > 0$ are constant parameters. Consider error vector$\tilde{\theta}_1$ which is defined as $\tilde{\theta}_1 = \theta_1 - \theta_1^*$ and by (3.25), tracking error of system mentioned in (3.16) could be rewritten as follows:

$$\begin{cases} \dot{\mathrm{E}} = \mathrm{A_0 E} - \mathrm{b k_c^T} \hat{\mathrm{E}} - f'(X) - \mathrm{b}\{ (\tilde{\theta}_1^T w_1(Z) + u_{rob} + \hat{E}^T P_2 \mathrm{K_0} - \varepsilon_u) f_{u_\lambda} + d'(t) + v' \} \\ \mathrm{E_y} = \mathrm{C^T E} \end{cases} \tag{3.28}$$

Using (3.25), dynamics of observer mentioned in (3.22) could be revised as follows:

$$\begin{cases} \dot{\tilde{E}}_s = A_{oo} \tilde{E}_s - \mathrm{b_s}\{ (\tilde{\theta}_1^T w_1(Z) + u_{rob} + \hat{E}^T P_2 \mathrm{K_0} - \varepsilon_u) f_{u_{\lambda f}} + d_f(t) + {v'}_f + k_{nof}(\tilde{E}, \hat{E}) \left| C^T \tilde{E} \right| \} \\ \tilde{\mathrm{E}}_{\mathrm{y}} = \mathrm{C_s^T} \tilde{E}_s \end{cases} \tag{3.29}$$

It is obvious that (3.17), (3.28), and (3.29) form the dynamics system error and observer error, and to investigate the stability of the closed-loop system. In section 3, the stability of the closed-loop system and also the convergence of the tracking error and observer error to zero is studied in detail.

4 Stability analysis

This section deals with both the boundedness of the closed-loop signals and closed loop stability, using equations (3.17) and (3.29). Consider P_1 and P_2 as positive definite matrix and responses of following equations:

$$\begin{array}{l} A_{oo}^T P_1 + P_1 A_{oo} = -Q_1 \\ A_{oc}^T P_2 + P_2 A_{oc} = -Q_2 \\ b_s^T P_1 = C_s^T \end{array} \tag{4.1}$$

where Q_1 and Q_2 are positive definite matrices. We will mention the results of the previous section in theorem 1, which is mentioned as follows.

Theorem 4.1. Consider the non-linear system mentioned in (3.2), which could satisfy the conditions of assumption (3.1), (3.2), and (3.3). Moreover, using the equation (3.4) and (3.29) as the dynamics of the observation and observer error, by the controller design mentioned in (3.25) and (3.26) and also seeing the laws mentioned in (3.27), it is proved that tracking error and observer error are uniformly ultimately bound and correspondingly all signals in the closed-loop system are limited.

Proof . To prove the stability of the closed-loop system, consider the Lyapunov function as follows:

$$V = \frac{1}{2} \left(\frac{1}{f_{u_{\lambda f}}} \tilde{E}_s^T P_1 \tilde{E}_s + \hat{E}^T P_2 \hat{E} + \tilde{\theta}_1^T \Gamma_1^{-1} \tilde{\theta}_1 + \frac{\tilde{u}_r^2}{\gamma_{u_r}} + \frac{\tilde{u}_{com}^2}{\gamma_{u_{com}}} + \frac{\tilde{k}_{no}^2}{\gamma_{ko}} + \frac{\tilde{v}'^2}{\gamma_{\hat{v}'}} \right) \tag{4.2}$$

where $\tilde{v}' = \hat{v}' - |v'|$, $\tilde{k}_{no} = \hat{k}_{no} - k_{no}$, $\tilde{u}_{com} = u_{com} - \varepsilon_{\max}$, $\tilde{u}_r = u_r - d_{\max}$ and $\tilde{\theta}_1 = \theta_1 - \theta_1^*$. The time derivative of this Lyapunov function is as follows:

$$\begin{array}{l} \dot{V} = \frac{1}{2} \left(\frac{1}{f_{u_{\lambda f}}} \dot{\tilde{E}}_s^T P_1 \tilde{E}_s + \frac{1}{f_{u_{\lambda f}}} \tilde{E}_s^T P_1 \dot{\tilde{E}}_s + \frac{\dot{f}_{u_{\lambda f}}}{f_{u_{\lambda f}}^2} \tilde{E}_s^T P_1 \tilde{E}_s \right) + \tilde{\theta}_1^T \Gamma_1^{-1} \dot{\theta}_1 \\ + \frac{1}{2} \left(\dot{\hat{E}}^T P_2 \hat{E} + \hat{E}^T P_2 \dot{\hat{E}} \right) + \frac{\tilde{u}_r \dot{u}_r}{\gamma_{u_r}} + \frac{\tilde{u}_{com} \dot{u}_{com}}{\gamma_{u_{com}}} + \frac{\tilde{k}_{no} \dot{\hat{k}}_{no}}{\gamma_{ko}} + \frac{\tilde{v}' \dot{\hat{v}}'}{\gamma_{\hat{v}'}} \end{array} \tag{4.3}$$

After some mathematical manipulations and using the equations (3.25), (3.26), and (3.27), the following equation is obtained:

$$\begin{array}{l}\dot{V} \le -\frac{1}{2f_{u_{\lambda f}}}\tilde{E}_s^T Q_1 \tilde{E}_s - \frac{\dot{f}_{u_{\lambda f}}}{2f_{u_{\lambda f}}^2}\tilde{E}_s^T P_1 \tilde{E}_s - \frac{1}{2}\hat{E}^T Q_2 \hat{E} - \underbrace{(u_r - d_{\max})}_{\tilde{u}_r}\frac{\left|C_s^T \tilde{E}_s\right|}{f_{\min}} + \frac{1}{f_{\min}}\left\|f'^T(X)\right\|\left\|B_s^T P_1\right\|\left\|\tilde{E}_s\right\| \\ -\underbrace{(u_{com} - \varepsilon_{\max})}_{\tilde{u}_{com}}\left|C_s^T\tilde{E}_s\right| - \underbrace{(\hat{v}' - |v'_f|)}_{\tilde{v}'}\frac{\left|C_s^T\tilde{E}_s\right|}{f_{\min}} - \tilde{\theta}_1^T w_1(Z) C_s^T \tilde{E}_s - \underbrace{\left(\hat{k}_{nof} - k_{nof}\right)}_{\tilde{k}_{nof}}\left(\left|C_s^T\tilde{E}_s\right|^2 + \left|C_s^T\tilde{E}_s\right|\left|\hat{E}^T Pb\right|\right) \\ +\tilde{\theta}_1^T \Gamma_1^{-1}\dot{\theta}_1 + \frac{\tilde{u}_r \dot{u}_r}{\gamma_{u_r}} + \frac{\tilde{u}_{com}\dot{u}_{com}}{\gamma_{u_{com}}} + \frac{\tilde{k}_{no}\dot{k}_{no}}{\gamma_{ko}} + \frac{\tilde{v}'\dot{v}'}{\gamma_{\hat{v}'}}.\end{array} \tag{4.4}$$

This equation could revise as:

$$\begin{array}{l}\dot{V} \le -\frac{1}{2f_{u_{\lambda f}}}\tilde{E}_s^T Q_1 \tilde{E}_s - \frac{\dot{f}_{u_{\lambda f}}}{2f_{u_{\lambda f}}^2}\tilde{E}_s^T P_1 \tilde{E}_s - \frac{1}{2}\hat{E}^T Q_2 \hat{E} + \frac{1}{f_{\min}}\left\|f'^T(X)\right\|\left\|B_s^T P_1\right\|\left\|\tilde{E}_s\right\| - \tilde{u}_r\left(\frac{\left|C_s^T\tilde{E}_s\right|}{f_{\min}} - \frac{\dot{u}_{com}}{\gamma_{u_{com}}}\right) \\ -\tilde{\theta}_1^T\left(w_1(Z)C_s^T\tilde{E}_s - \Gamma_1^{-1}\dot{\theta}_1\right) - \tilde{v}'\left(\frac{\left|C_s^T\tilde{E}_s\right|}{f_{\min}} - \frac{\dot{v}'}{\gamma_{\hat{v}'}}\right) \\ -\tilde{k}_{nof}\left(\left|C_s^T\tilde{E}_s\right|^2 + \left|C_s^T\tilde{E}_s\right|\left|\hat{E}^T Pb\right| - \frac{\dot{k}_{no}}{\gamma_{ko}}\right) - \tilde{u}_{com}\left(\left|C_s^T\tilde{E}_s\right| - \frac{\dot{u}_r}{\gamma_{u_r}}\right)\end{array} \tag{4.5}$$

Applying the adaptive update laws mentioned in (3.27) to equation (4.5) leads to the following equation:

$$\dot{V} \le -\frac{1}{2f_{u_{\lambda f}}}\tilde{E}_s^T \underbrace{\left(Q_1 + \frac{\dot{f}_u}{f_u}P_1\right)}_{M}\tilde{E}_s - \frac{1}{2}\hat{E}^T Q_2 \hat{E} + \frac{1}{f_{\min}}\left\|f'^T(X)\right\|\left\|B_s^T P_1\right\|\left\|\tilde{E}_s\right\|. \tag{4.6}$$

This equation could reconstruct as follows:

$$\dot{V} \le -\frac{1}{f_{\min}}\left(\lambda_{\min}(M)\left\|\tilde{E}_s\right\| - \left\|f'^T(X)\right\|\left\|B_s^T P_1\right\|\right)\left\|\tilde{E}_s\right\| - \frac{1}{2}\lambda_{\min}(Q_2)\left\|\hat{E}\right\|^2. \tag{4.7}$$

Finally, the above equation is negative out of the compact set $\Omega_{\tilde{e}}$, which is defined as follows:

$$\Omega_{\tilde{e}} = \left\{\tilde{E}_s \,\middle|\, \left\|\tilde{E}_s\right\| \le \frac{\left\|f'^T(X)\right\|\left\|B_s^T P_1\right\|}{\lambda_{\min}(M)}\right\}. \tag{4.8}$$

□

Considering the Lyapunov theorem and the fact that the derivative of a proposed Lyapunov function is negative outside of the compact set $\Omega_{\tilde{e}}$, it is easy to conclude that the observation error and observer error and as a result tracking errors are ultimately bounded outside of this set. Moreover, all the signals involved in the closed-loop system are limited. Choosing appropriate values forQ_1 and K_o leads to guarantee that $\Omega_{\tilde{e}}$ is a small set and the observation error would converge to a small value.

Implementation of the Proposed Controller Algorithm: Initialization: set the parameters based on Tables 1 and 2.

Step 1: the controller parameters are obtained using the update law mentioned in equation (3.27).

Step 2: the robust term is designated as equation (3.26).

Step 3: the control input is derived based on the equation (3.25).

Step 4: the obtained controller mentioned in Step 3 is applied to the system mentioned in equation (5.1).

5 Simulation Results

In this section, the proposed controller and the observer mentioned in the previous section are applied on the cancerous dynamics system [10]:

$$\begin{cases} \dot{N} = -k_n.N.C - N.(1 - DoseEff).(1 - e^{-\alpha.d - \beta.d^2}).kk_2 \\ \dot{C} = k_c.N.C - C.tt.DoseEff(1 - e^{-\alpha.d - \beta.d^2}).kk_2 \\ y = C \end{cases} \tag{5.1}$$

where N is the number of normal cells, C is the number of cancerous cells and other variables are according to nomenclature table. Moreover, the values of this parameter are as follows:

Table 2: Values of parameters of the cancer system [10]

Parameters	Values
C_0	Almost 1E+8
K_n	3.35E-12
K_c	0.0288
α	0.17
doseEff	0.93
β	0.02
Number of dose per day	4
Death time	143th day

Controller and observer mentioned in (3.25) and (3.26) are applied to the system mentioned in (5.1). Six Gaussian membership functions for each input of fuzzy system are used as $\mu_j(\chi) = \exp({(\chi - c)^2}/{2\delta^2})$ with average c and δ variance.

Table 3: Values of parameters of the controller

Parameters	Values
$\theta_1(0), u_r(0), u_{com}(0)$	0
$\hat{k}_{no}(0), \hat{v}'(0)$	0
$f_{\min}$	1
Γ_1	100
$\gamma_{u_{com}}$	90
γ_{u_r}	90
$\gamma_{\hat{v}'_i}$	80
γ_{ko}	100
σ	0.1
ε	0.01

As it is clear from figure 1 if any drug is not injected into the patient, after passing 60 days the patient will be dying. The number of normal cells and cancerous cells after applying the proposed controller are plotted in Figure 2.

As shown in Figure 2, the proposed controller causes 55-day delay in the death of a patient happens and this fact leads to the success of the proposed controller. Altogether, the advantages of the proposed method are as:

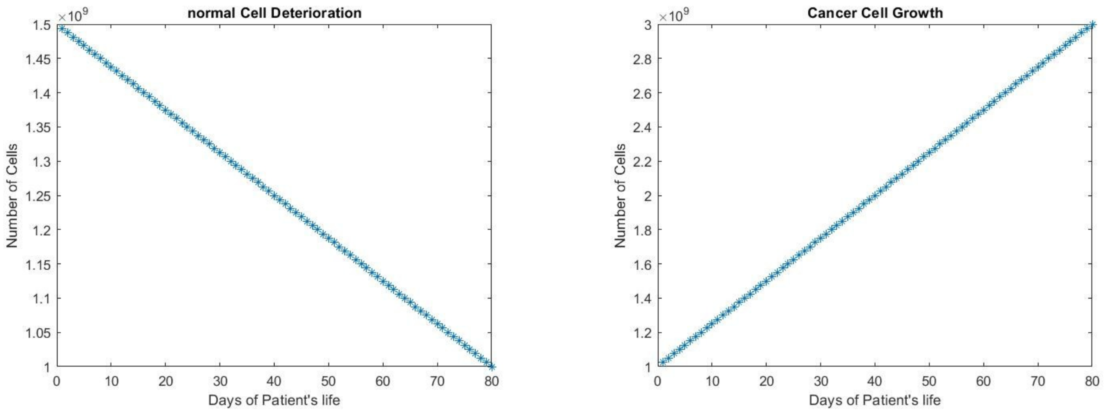
1) Boundedness of all the signals in the closed-loop system,

2) considering the system as a nonlinear non-canonical system,

3) Robustness against uncertainties, approximation error, and external disturbances.

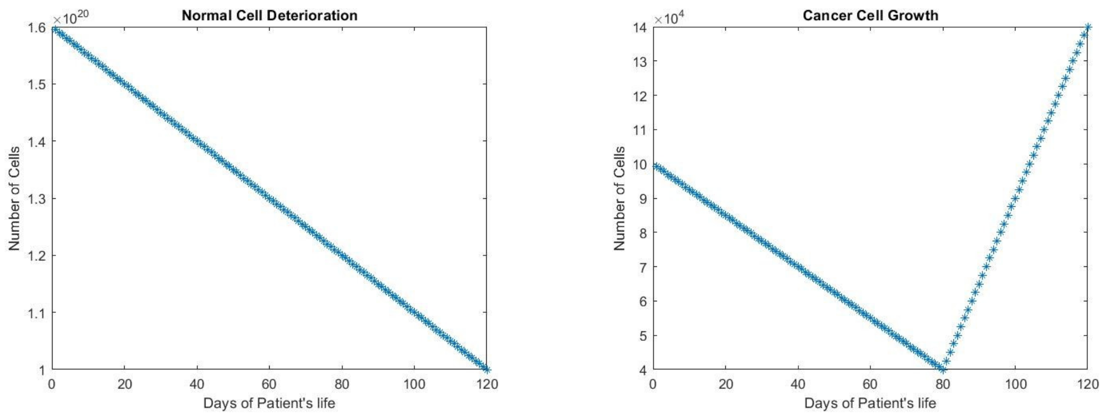
6 Conclusion

In this paper, both the controller and the observer for non-linear non-canonical systems are designated. It is assumed that the systems are time-varying and also the gotten results are applied to a special kind of blood cancer, which is named chronic Myelogenous leukemia (CML) with unknown nonlinear function. The fuzzy systems are developed to approximate the controller input adaptively in the presence of the model uncertainties. Boundedness of tracking and observer error in the closed-loop system, robustness against approximation error, and external disturbances are the focal merits of the proposed scheme. Simulation results also prove the effectiveness of the projected routine. For future research, we concentrate on applying our approach in real case as doctor assistant software.



a b

Figure 1: Normal cells (a) and cancerous cells (b) concerned the model without any drug



a b

Figure 2: The number of normal cells (a) and cancerous cells after applying the proposed controller (b)

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