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Observers for biological systems

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Abstract

Cell counts and viral load serve as major clinical indicators to provide treatment in the course of a viral infection. Monitoring these markers in patients can be expensive and some of them are not feasible to realize. An alternative solution to this problem is the observer based estimation. Several observer schemes require the previous knowledge of the model and parameters, such condition is not achievable for some applications. A linear output assumption is required in the majority of the current works. Nevertheless, the output of the system can be a nonlinear combination of the state variables. This paper presents a discrete-time neural observer for non-linear systems with a non-linear output; the mathematical model is assumed to be unknown. The observer is trained on-line with the extended Kalman filter (EKF)-based algorithm and the respective stability analysis based on the Lyapunov approach is addressed. We applied different observers to the estimation problem in HIV infection; that is state estimation of the viral load, and the number of infected and non-infected CD4+ T cells. Simulation results suggest a good performance of the proposed neural observer and the applicability to biological systems.

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1. Introduction

For different engineering applications it is required to estimate quantities due to the lack of a complete access to the system states. Therefore, during the past four decades, state estimation of dynamical systems has been an active topic of research in different areas such as: fault detection, monitoring, process control and biomedical systems among others [1].

Automatic control techniques usually assume complete accessibility for the system state, which is not always possible (cost, technological constraints, etc.) [2, 3, 4]. Several observers consider a nonlinear transformation [5] or a linearization technique [6, 7]. In real applications, there are external disturbances and parameter uncertainties, nevertheless several approaches do not consider them [8, 9, 10]. Robust observers have shown good performance even in the presence of uncertainties, however their design can be complex [1, 11, 12, 13].

Nowadays, intelligent methods (fuzzy systems, neural networks and genetic algorithms, etc.) have shown to play an important role in the development of state observers. On one hand genetics algorithms (GAs) have been used to find the optimal parameters for the observer design [14, 15, 16]. On the other hand Takagi Sugeno (TS) fuzzy models have been shown to be an efficient approach to deal with analysis in the design of model based observers [17, 18, 19, 20, 21]. However, TS approach can be impractical for common forms in biological systems, for instance $\dot{x} = x(t)u(t)$, where $x(t)$ is a state variable and $u(t)$ is a scalar control [19].

Using the well-known approximation capabilities of neural networks, neural observers have emerged [4, 22, 23, 24, 25, 26]; one of the main advantages of this kind of observers is its robustness to uncertainties, external disturbances, among others. In [27, 28, 29, 30, 31, 32], neural observers are designed to estimate the state for continuous-time nonlinear systems. Although discrete-time observers are preferred for real time applications, the discrete-time case has not been exploited as the continuous one. In [26, 33] neural observers are proposed to estimate the state for discrete-time nonlinear systems. However, several approaches

mentioned above need the previous knowledge of the plant model at least partially [28, 29, 30, 31, 32, 33]. The problem of unknown model dynamics are considered in [26, 27, 34, 35, 36], these only consider the presence of external disturbances. The main disadvantage of these schemes is that only can work for systems with linear output. There are several real life applications where the output is a non-linear combination of the state variables [37], [38]. These works tackle the estimation problem for systems with non-linear output. Nevertheless, the previous knowledge of the model and parameters is also required.

Measurements in biomedical systems have demonstrated to be expensive, difficult and sometimes not possible to achieve. State estimation by neural observer may play an important role to provide clinicians a better understanding of the immune markers in patients with viral infection diseases. Among the different classes of infection diseases during last 30 years, HIV has been extensively studied, that is because HIV can lead to acquired immunodeficiency syndrome (AIDS). According to statistics in the global summary of the AIDS epidemic from the World Health Organization (WHO) [39], by the end of 2007 an estimation of 33 million people were living with HIV worldwide. That same year, approximately 2 million died of AIDS. Nonetheless, there is currently no known cure to tackle the infection. Clinicians need more information of the infection in patients, therefore the necessity of novel tools to provide immune function markers in patients with HIV infection [40].

Observers in HIV infection have been a growing area [36, 40, 41, 42, 43, 44, 45, 46]. The majority of these works have considered continuous time measurements, nevertheless measurements are performed a few times per year. Moreover, the requirement of the model for the observer design is a drawback in these approaches.

In this paper we propose a discrete-time recurrent high order neural Luenberger-like observer for non-linear systems with a non-linear output. This observer is based on a RHONN (recurrent high-order neural networks), which estimates the state vector of the unknown model dynamics. The learning algorithm for the

RHONN is based on an extended Kalman filter (EKF). The respective stability analysis is included on the basis of the Lyapunov approach, for the neural observer trained with the EKF. Applicability of the scheme is illustrated via simulations to the state estimation problem in HIV infection.

2. Mathematical Preliminaries

Throughout this paper, \Re denotes the field of real number, \Re^n stands for the vector space of all n -tuples of real numbers, $\Re^{n \times n}$ is the space of $n \times n$ matrices with real entries, and \mathbb{Z}^+ denotes the set of natural numbers. We use k as the sampling step, $k \in 0 \cup \mathbb{Z}^+$, $|\bullet|$ as the absolute value and $\|\bullet\|$ as the Euclidean norm for vectors and as any adequate norm for matrices. To follow a discrete-time approach, we consider a nonlinear model, see Figure 1, in the following form:

$$\begin{aligned} x(k+1) &= F(x(k), u(k)) + d(k) \\ y(k) &= h(x(k)) \end{aligned} \tag{1}$$

where $x \in \Re^n$ is the state vector of the system, $u(k) \in \Re^m$ is the input vector, $y(k) \in \Re^p$ is the output vector, $h(\bullet)$ is a known output function which is Lipschitz in $x(k)$, $d(k) \in \Re^n$ is a disturbance vector and $F(\bullet)$ is a smooth vector field and $F_i(\bullet)$ its entries; hence (1) can be rewritten as:

$$\begin{aligned} x(k) &= \begin{bmatrix} x_1(k) & \dots & x_i(k) & \dots & x_n(k) \end{bmatrix}^\top \\ d(k) &= \begin{bmatrix} d_1(k) & \dots & d_i(k) & \dots & d_n(k) \end{bmatrix}^\top \\ x_i(k+1) &= F_i(x(k), u(k)) + d_i(k) \quad , \quad i = 1, \dots, n \\ y(k) &= h(x(k)) \end{aligned} \tag{2}$$

The system (1) is said to be forced or have inputs. In contrast the system described without explicit presence of an input u is said to be unforced. For the design of the observer, the next stability definitions are introduced:

Definition 1 A subset $S \in \mathfrak{R}^n$ is bounded if there exists $r > 0$ such that $|x| \leq r$ for all $x \in S$.

Definition 2 The solution of the system (1) is said to be semiglobally uniformly ultimately bounded (SGUUB), if for any Ω a compact subset of \mathfrak{R}^n and all $x(k_0) \in \Omega$, there exists an $\varepsilon > 0$ and a number $N(\varepsilon, x(k_0))$ such that $|x(k)| < \varepsilon$ for all $k \geq k_0 + N$.

3. Discrete Time Neural Observer

In this section, we estimate the state of a discrete-time nonlinear system (1), which is assumed to be observable. Using (2), we propose a recurrent neural Luenberger observer (RHONO) with the following structure:

$$\begin{aligned}\hat{x}(k) &= \begin{bmatrix} \hat{x}_1(k) & \dots & \hat{x}_i(k) & \dots & \hat{x}_n(k) \end{bmatrix}^\top \\ \hat{x}_i(k+1) &= w_i^\top z_i(\hat{x}(k), u(k)) + g_i e(k) \\ \hat{y}(k) &= h(\hat{x}(k)), \quad i = 1, \dots, n\end{aligned}\tag{3}$$

with $g_i \in \mathfrak{R}^p$, $z_i(x(k), u(k))$ defined as

$$z_i(x(k), u(k)) = \begin{bmatrix} z_{i1} \\ z_{i2} \\ \vdots \\ z_{iL_i} \end{bmatrix} = \begin{bmatrix} \prod_{j \in I_1} \xi_{ij}^{di_j(1)} \\ \prod_{j \in I_2} \xi_{ij}^{di_j(2)} \\ \vdots \\ \prod_{j \in I_{L_i}} \xi_{ij}^{di_j(L_i)} \end{bmatrix}\tag{4}$$

with $d_{j_i}(k)$ being non-negative integers, and ξ_i defined as follows:

$$\xi_i = \begin{bmatrix} \xi_{i_1} \\ \vdots \\ \xi_{i_n} \\ \xi_{i_{n+1}} \\ \vdots \\ \xi_{i_{n+m}} \end{bmatrix} = \begin{bmatrix} S(x_1) \\ \vdots \\ S(x_n) \\ u_1 \\ \vdots \\ u_m \end{bmatrix} \quad (5)$$

In (5), $u = [u_1, u_2, \dots, u_m]^\top$ is the input vector to the neural network, and $S(\bullet)$ is defined by

$$S(\varsigma) = \frac{1}{1 + \exp(-\beta \varsigma)}, \quad \beta > 0 \quad (6)$$

where ς is any real value variable.

As discussed in [47], the general discrete-time nonlinear system (1) which is assumed to be observable, can be approximated by the following discrete-time RHONN representation:

$$x(k+1) = w^{*\top} z(x(k), u(k)) + \varepsilon_z \quad (7)$$

where each state component x_i has the following form:

$$x_i(k+1) = w_i^{*\top} z_i(x(k), u(k)) + \varepsilon_{z_i}, \quad i = 1, \dots, n \quad (8)$$

where x_i is the i -th plant state, ε_{z_i} is a bounded approximation error, which can be reduced by increasing the number of the adjustable weights [47]. Let assume that there exists the optimal weights vector $w_i^* \in \mathcal{R}^{L_i}$ such that $\|\varepsilon_{z_i}\|$ is minimized on a compact set $\Omega_{z_i} \subset \mathcal{R}^{L_i}$; which is an artificial quantity required only for analytical purpose [47]. In general it is assumed that this vector exists and it is constant but unknown. To the best of our knowledge, a principal disadvantage of this kind of NN is that does not exist an established methodology to determine its detailed

structured.

Let us define the w_i^* estimate as w_i ; then, the weights estimation $\tilde{w}_i(k)$ and state observer $\tilde{x}_i(k)$ errors are defined respectively as:

$$\tilde{w}_i(k) = w_i^* - w_i(k) \quad (9)$$

and

$$\tilde{x}_i(k) = x_i(k) - \hat{x}_i(k) \quad (10)$$

Since w_i^* is constant, then

$$\tilde{w}_i(k+1) - \tilde{w}_i(k) = w_i(k+1) - w_i(k), \quad \forall k \in 0 \cup \mathbb{Z}^+$$

The weight vectors are updated on-line with a decoupled EKF, described by

$$\begin{aligned} w_i(k+1) &= w_i(k) + \eta_i K_i(k) e(k) \\ K_i(k) &= P_i(k) H_i(k) M_i(k), \quad i = 1, \dots, n \\ P_i(k+1) &= P_i(k) - K_i(k) H_i^\top(k) P_i(k) + Q_i(k) \end{aligned} \quad (11)$$

with

$$M_i(k) = \left[R_i(k) + H_i^\top(k) P_i(k) H_i(k) \right]^{-1} \quad (12)$$

and the output error

$$e(k) = y(k) - \hat{y}(k) \quad (13)$$

Thus the dynamics of $x_i(k+1)$ can be expressed as

$$\tilde{x}_i(k+1) = x_i(k+1) - \hat{x}_i(k+1)$$

Therefore

$$\tilde{x}_i(k+1) = w_i^{*\top} z_i(x(k), u(k)) + \varepsilon_{z_i} - w_i^\top(k) z_i(\hat{x}(k), u(k)) - g_i e(k)$$

Adding and subtracting $w_i^{*\top} z_i(\hat{x}(k), u(k))$, it can be written as

$$\tilde{x}_i(k+1) = \tilde{w}_i(k) z_i(\tilde{x}(k), u(k)) + \varepsilon'_{z_i} - g_i e(k) \quad (14)$$

with

$$\begin{aligned} \varepsilon'_{z_i} &= w_i^{*\top} z_i(\tilde{x}(k), u(k)) + \varepsilon_{z_i} \\ z_i(\tilde{x}(k), u(k)) &= z_i(x(k), u(k)) - z_i(\hat{x}(k), u(k)) \end{aligned}$$

Moreover, the dynamics of (9) can be expressed as follows:

$$\tilde{w}_i(k+1) = \tilde{w}_i(k) - \eta_i K_i(k) e(k) \quad (15)$$

The proposed neural observer scheme is portrayed in Figure 2. Thus, considering (2)-(11) it is possible to establish the following result for an unknown non-linear system with a non-linear output as follows:

Theorem 1. *For system (2), the RHONO (3), trained with the EKF-based algorithm (11), ensures that the i -th ($i = 1, 2, \dots, n$) estimation error (10) and the output error (13) are semiglobally uniformly ultimately bounded (SGUUB); moreover the RHONO weights remain bounded.*

Proof:

If $h(\bullet)$ is a known output function which is Lipschitz in $x(k)$, then

$$\|h(x(k)) - h(\hat{x}(k))\| \leq L \|x(k) - \hat{x}(k)\| \quad (16)$$

with L the Lipschitz constant [48].

First, let us consider the following candidate Lyapunov function

$$V_i(k) = \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) + \tilde{x}_i^T(k) P_i(k) \tilde{x}_i(k) \quad (17)$$

whose first increment is defined as

$$\begin{aligned} \Delta V_i(k) &= V(k+1) - V(k) \\ &= \tilde{w}_i^T(k+1) P_i(k+1) \tilde{w}_i(k+1) \\ &\quad + \tilde{x}_i^T(k+1) P_i(k+1) \tilde{x}_i(k+1) \\ &\quad - \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) \\ &\quad - \tilde{x}_i^T(k) P_i(k) \tilde{x}_i(k) \end{aligned} \quad (18)$$

Using (11) and (9) in (18), then

$$\begin{aligned} \Delta V_i(k) &= [\tilde{w}_i(k) - \eta_i K_i(k) e(k)]^T [A_i(k)] \\ &\quad \times [\tilde{w}_i(k) - \eta_i K_i(k) e(k)] \\ &\quad + [f(k) - g_i e(k)]^T [A_i(k)] \\ &\quad \times [f(k) - g_i e(k)] - \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) \\ &\quad - \tilde{x}_i^T(k) P_i(k) \tilde{x}_i(k) \end{aligned} \quad (19)$$

with

$$\begin{aligned} A_i(k) &= P_i(k) - D_i(k) + Q_i \\ D_i(k) &= K_i(k) H_i^T(k) P_i(k) \\ f(k) &= \tilde{w}_i^T(k) z_i(x(k), u(k)) + \varepsilon'_{z_i} \end{aligned}$$

Hence, (19) can be expressed as

$$\begin{aligned}
\Delta V_i(k) = & 2\tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) - 2\tilde{w}_i^T(k) [B_i(k)] \tilde{w}_i(k) \\
& + 2\eta_i^2 e^T(k) K^T [A_i(k)] K_i(k) e(k) \\
& + 2f^T(k) A_i(k) f(k) \\
& + 2e^T(k) g_i^T [A_i(k)] g_i e(k) \\
& - \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) - \tilde{x}_i^T(k) P_i(k) \tilde{x}_i(k)
\end{aligned} \tag{20}$$

with $B_i(k) = D_i(k) - Q_i$. Now, using the following inequalities

$$\begin{aligned}
X^T X + Y^T Y & \geq 2X^T Y \\
X^T X + Y^T Y & \geq -2X^T Y \\
-\lambda_{\min}(P) X^2 & \geq -X^T P X \geq -\lambda_{\max}(P) X^2
\end{aligned} \tag{21}$$

which are valid $\forall X, Y \in \Re^n$, $\forall P \in \Re^{n \times n}$, $P = P^T > 0$, and using (16), then (20), can be rewritten as

$$\begin{aligned}
\Delta V_i(k) \leq & \|\tilde{w}_i(k)\|^2 \lambda_{\max}(P_i(k)) \\
& - \|\tilde{w}_i(k)\|^2 \lambda_{\min}(B_i(k)) \\
& + 2\|\tilde{x}(k)\|^2 \|\eta_i K_i L\|^2 \lambda_{\max}(A_i(k)) \\
& + 2\|f(k)\|^2 \lambda_{\max}(A_i(k)) \\
& + 2\|\tilde{x}(k)\|^2 \|g_i L\|^2 \lambda_{\max}(A_i(k)) \\
& - \|\tilde{x}(k)\|^2 \lambda_{\min}(P_i(k))
\end{aligned} \tag{22}$$

Substituting $f(k) = \tilde{w}_i^T(k) z_i(x(k), u(k)) + \varepsilon'_{z_i}$, in (22), then

$$\begin{aligned}
\Delta V_i(k) \leq & \|\tilde{w}_i(k)\|^2 \lambda_{\max}(P_i(k)) \\
& - \|\tilde{w}_i(k)\|^2 \lambda_{\min}(P_i(k)) \\
& + 2 \|\tilde{x}(k)\|^2 \|\eta_i K_i L\|^2 \lambda_{\max}(A_i(k)) \\
& + 4 |\varepsilon'_{z_i}|^2 \lambda_{\max}(A_i(k)) \\
& + 4 \|\tilde{w}_i(k)\|^2 \|z_i(x(k), u(k))\|^2 \lambda_{\max}(A_i(k)) \\
& + 2 \|\tilde{x}(k)\|^2 \|g_i L\|^2 \lambda_{\max}(A_i(k)) \\
& - \|\tilde{x}(k)\|^2 \lambda_{\min}(P_i(k))
\end{aligned} \tag{23}$$

Defining

$$\begin{aligned}
E_i(k) &= 2 \|\eta_i K_i L\|^2 \lambda_{\max}(A_i(k)) \\
&\quad + 2 \|g_i L\|^2 \lambda_{\max}(A_i(k)) - \lambda_{\min}(P_i(k)) \\
F_i(k) &= \lambda_{\max}(P_i(k)) - \lambda_{\min}(P_i(k)) \\
&\quad + 4 \|z_i(x(k), u(k))\|^2 \lambda_{\max}(A_i(k))
\end{aligned}$$

then (23) can be rewritten as

$$\begin{aligned}
\Delta V_i(k) \leq & -\|\tilde{x}(k)\|^2 E_i(k) - \|\tilde{w}_i(k)\|^2 F_i(k) \\
& + 4 |\varepsilon'_{z_i}|^2 \lambda_{\max}(A_i(k))
\end{aligned}$$

Hence, $\Delta V_i(k) < 0$ when

$$\|\tilde{x}(k)\| > \sqrt{\frac{4 |\varepsilon'_{z_i}|^2 \lambda_{\max}(A_i(k))}{E_i(k)}} \equiv \kappa_1(k) \tag{24}$$

or

$$\|\tilde{w}_i(k)\| > \sqrt{\frac{4 |\varepsilon'_{z_i}|^2 \lambda_{\max}(A_i(k))}{F_i(k)}} \equiv \kappa_2(k) \tag{25}$$

Therefore the solution of (14) and (15) is SGUUB; hence, the estimation error and the RHONO weights are SGUUB [22]. Now following with the proof, let us consider the Lyapunov function candidate:

$$V_i(k) = \sum_{i=1}^n \left(\tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) + \tilde{x}_i^T(k) P_i(k) \tilde{x}_i(k) \right) \quad (26)$$

$$\begin{aligned} \Delta V_i(k) &= \sum_{i=1}^n \left(\tilde{w}_i^T(k+1) P_i(k+1) \tilde{w}_i(k+1) \right. \\ &\quad \left. + \tilde{x}_i^T(k+1) P_i(k+1) \tilde{x}_i(k+1) \right. \\ &\quad \left. - \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) \right. \\ &\quad \left. - \tilde{x}_i^T(k) P_i(k) \tilde{x}_i(k) \right) \end{aligned} \quad (27)$$

Therefore, as above, (26) can be expressed as:

$$\begin{aligned} \Delta V_i(k) &\leq \sum_{i=1}^n \left(-\|\tilde{x}(k)\|^2 E_i(k) - \|\tilde{w}_i(k)\|^2 F_i(k) \right. \\ &\quad \left. + 4 \left| \varepsilon'_{z_i} \right|^2 \lambda_{\max}(A_i(k)) \right) \end{aligned}$$

with

$$\begin{aligned} E_i(k) &= 2 \|\eta_i K_i L\|^2 \lambda_{\max}(A_i(k)) \\ &\quad + 2 \|g_i L\|^2 \lambda_{\max}(A_i(k)) - \lambda_{\min}(P_i(k)) \\ F_i(k) &= \lambda_{\max}(P_i(k)) - \lambda_{\min}(P_i(k)) \\ &\quad + 4 \|z_i(x(k), u(k))\|^2 \lambda_{\max}(A_i(k)) \end{aligned}$$

As a result $\Delta V_i(k) < 0$ when

$$\|\tilde{x}(k)\| > \kappa_1(k)$$

or

$$\|\tilde{w}_i(k)\| > \kappa_2(k)$$

and if $\|\tilde{x}(k)\| > \kappa_1(k)$ and $\|\tilde{w}_i(k)\| > \kappa_2(k)$, $\forall i = 1, \dots, n$ holds, then $\Delta V_i(k) < 0$.

Finally, considering (3) and (13), it is easy to see that the output error has an algebraic relation with $\tilde{x}(k)$; for that reason if $\tilde{x}(k)$ is bounded $e(k)$ is bounded as well.

$$\begin{aligned} e(k) &= h(\tilde{x}(k)) \\ \|e(k)\| &= \|h\| \|\tilde{x}(k)\| \end{aligned}$$

■

Remark 1. *Due to the results presented in Theorem 1, the boundedness of the state estimation error, the output error and the weights estimation error are established on the basis of the Lyapunov methodology without the need of persistent excitation condition. The proposed learning algorithm (11) is performed on-line. Therefore neural weights are updated at each sampling for all $k \in 0 \cup \mathbb{Z}^+$ and there is no stopping criteria for the learning algorithm. The training development is ensured by results presented in Theorem 1. This theorem establishes the accuracy and sensitivity of the state estimation according to bounds (24) and (25).*

The main advantage of the proposed RHONO consists on the state estimation of discrete-time unknown nonlinear systems even though the measurement of the output system is a nonlinear combination of the states. However, the main drawback of this scheme is that does not exist an established methodology to determine its detailed structured.

4. Estimation problem in HIV infection

HIV is a retrovirus which kidnaps CD4+ T cells for replication, a fundamental part of the immune system. After this discovery, researchers have focused on seeking drug treatments to inhibit HIV infection cycle [55]. The development of antiretroviral treatments has been one of the most active areas in HIV research. The main problem to implement clinical protocols is the lack of complete information of the infection. Laboratory tests are important for evaluating HIV infected patients upon entry into care, they provide virologic and immunologic efficacy of antiretroviral therapy [55].

Two surrogate markers are used routinely: CD4+ T-cell counts and plasma HIV RNA levels (viral load). On one hand plasma HIV RNA levels should be measured in all patients on a regular basis thereafter, that is because viral load is the most important indicator of response to antiretroviral therapy. On the other hand CD4+ T cell counts serve as the major clinical indicator of immune function in patients with HIV infection, which is one of the key factors in deciding whether to initiate or change antiretroviral therapy [55]. The number of infected cells is an unknown parameter in clinical practice, practitioners could consider this marker for further decisions to schedule treatments [40].

State estimation in HIV infection has received special attention [41, 42, 43, 44, 45, 46]. These approaches mentioned above require knowing at least partially the model. Authors in [42] proposed a neural observer with application to HIV infection. However, this scheme is in continuous time (a drawback for implementation).

In order to obtain the dynamics of HIV infection, we assume the model proposed by [49] as a black box, which includes the concentration of infected cells (T^*), non-infected (T) as well as the viral load in the blood torrent (V). The schematic representation is presented in Figure 3 and the model is presented as follows:

$$\begin{aligned}
\dot{T}(t) &= s_T - k_T T(t)V(t) - \delta_T T(t) \\
\dot{T}^*(t) &= k_T T(t)V(t) - \delta_{T^*} T^*(t) \\
\dot{V}(t) &= \rho T^*(t) - k_d T(t)V(t) - \delta_V V(t)
\end{aligned} \tag{28}$$

s_T is the source term and represents the generation rate of new CD4+ T cells. The infection of CD4+ T cells is represented by the term $k_T T(t)V(t)$. The amount of virus produced from infected CD4+ T cells is given by ρT^* , where ρ is the rate of production per unit time in CD4+ T cells. The death rate of CD4+ T cells in humans is not well characterized, this parameter has been chosen in a number of works as $\delta_T = 0.01 \text{ day}^{-1}$ [49].

The immune system response is not included explicitly in the model, but this response is generally considered in the death rate of infected cells; which is a mixture of natural death and immune system action, in specific the CTL cell response. Therefore δ_{T^*} is larger than uninfected CD4+ T cells, values (from 0.26 to 0.68 day^{-1}) were taken from [49]. Clearance of free virions is the most rapid process, occurring on a time scale of hours. The values of δ_V range from 2.06 to 3.81 day^{-1} [49]. There is a loss of virus due to infection, this is represented by the term $k_d T(t)V(t)$. For more details of the model and parameter values, the interested reader is referred to research monographs such as [49, 52].

Remark 2. *Note that several mathematical models have been proposed to represent HIV dynamics [49, 50, 51, 52, 53, 54]. However, (28) is a simple model that has been accepted to model different viral infections: HIV, influenza and hepatitis [49].*

Previous works [36, 41, 42, 43, 44, 45, 46] take into consideration the measurement of CD4+ T cells only as the uninfected population, but in practice this measurement is a mixed of uninfected and infected number of CD4+ T cells, see

Figure 4. Therefore, based on the model (28) the output of the system can be written as follows:

$$y(k) = \begin{bmatrix} y_1(k) \\ y_2(k) \end{bmatrix} = \begin{bmatrix} T(k) + T^*(k) \\ V(k) \end{bmatrix} \quad (29)$$

Remark 3. *Fast viral dynamics*

Analysing parameter values at the system proposed in [49]; [54] remarked the possibility to approximate the differential equation for the viral load as an algebraic equation if the viral clearance is larger than one day ($\delta_V \gg 1$).

$$V(t) = \frac{\rho_T}{k_d T(t) + \delta_V} T^*(t) \quad (30)$$

4.1. Neural observer

The neural observer RHONO proposed in (3) is applied to the HIV model (28), whose nonlinear dynamics are considered unknown (black-box). We estimate the concentration of infected cells with the on-line viral load in the blood torrent as well as the total CD4+ T cell concentration. Therefore the only input to our RHONN is (29) and $V(t)$ as presented in (30). The following RHONN for infected cells is considered:

$$\hat{T}^*(k+1) = w_{11}S(\hat{T}^*(k))S(\hat{V}(k)) + w_{12}S(\hat{T}^*(k)) \quad (31)$$

Note that we only need to estimate the infected number of CD4+ T cells, then the non-infected cell population can be computed from the measurement of total cells, that is $\hat{T}(t) = y(t) - \hat{T}^*(t)$.

The training is performed on-line using a parallel configuration, see Figure 2, that means we update the observer only when the output measurements are sampled. All the NN states and weights are initialized randomly. The covariance matrices are initialized as diagonal, with non-zero elements as follows: $P(0) = 1 \times$

10^5 , $Q(0) = 1 \times 10^4$ and $R(0) = 1 \times 10^3$ respectively. The Luenberger parameter is $g = 0.01$ and $\eta = 1.3$.

It is important to remark that for simulations presented in this section the RHONO is training on-line; this means that neural weights are updated at each sampling for all $k \in 0 \cup \mathbb{Z}^+$.

4.2. Takagi-Sugeno observer

The discrete-time Takagi-Sugeno (TS) fuzzy observer is obtained by using local linearisation in several representative points which may or may not be equilibria [56, 57] given the output measurements (29). The following TS model is presented:

$$\begin{aligned} x(k+1) &= \sum_{i=1}^m w_i(z)(A_i x(k)) + B_i u(k) \\ y(k) &= \sum_{i=1}^m w_i(z) C_i x(k) \end{aligned} \quad (32)$$

where A_i , B_i , C_i are the matrices of the local linear model, z is the scheduling vector that determines which of the rules are active, and w_i , $i = 1, 2, \dots, m$ are normalised membership functions. The consequent matrices are:

$$A_i = \left. \frac{\partial f}{\partial x} \right|_{z_{0,i},0}, \quad B_i = \left. \frac{\partial f}{\partial u} \right|_{z_{0,i},0}, \quad C_i = \left. \frac{\partial h}{\partial x} \right|_{z_{0,i},0}.$$

The TS observer has the following form:

$$\begin{aligned} \hat{x}(k+1) &= \sum_{i=1}^m w_i(z)(A_i \hat{x}(k)) + B_i u(k) + L_i(y(k) - \hat{y}(k)) \\ \hat{y}(k) &= \sum_{i=1}^m w_i(z) C_i \hat{x}(k) \end{aligned} \quad (33)$$

where $\hat{x}(k)$ is the state estimate of $x(k)$, the matrices L_i , $i = 1, 2, \dots, m$ are the observer gains, and z is a scheduling vector depending on the output measurements. For the HIV estimation problem, the following linearisation points are considered:

$T \in \{250, 400, 500\}$, $V \in \{2, 3.5, 18\}$, and the TS fuzzy model having 9 rules i is given as follows:

If $y_1(k)$ is Z_1^i and $y_2(k)$ is Z_2^j then the model rule is:

$$\begin{aligned} x(k+1) &= A_f x(k) \\ y(k) &= Cx(k) \end{aligned} \quad (34)$$

where Z_i^j are fuzzy sets, $i = 1, 2, 3$ and $j = 1, 2, 3$. The TS observer takes the next form:

$$\begin{aligned} \hat{x}(k+1) &= \sum_{i=1}^9 w_i(z) (A_i \hat{x}(k)) + L_i (y(k) - \hat{y}(k)) \\ \hat{y}(k) &= \sum_{i=1}^9 w_i(z) C \hat{x}(k) \end{aligned} \quad (35)$$

4.3. High-Gain Observers

The high-gain observer can be performed as simple as the linear case if the nonlinear function g_h depends only on the output $y(t)$ and the control input $u(t)$ [48]. The observer is as follows:

$$\dot{\hat{x}} = A\hat{x}(t) + g_h(y(t), u(t)) + H(y(t) - h\hat{x}(t)) \quad (36)$$

where H are the observer gains. If $A - Hh$ is Hurwitz then (36) converges asymptotically.

5. Observer Results

For comparison purposes, we compute the the root mean square (RMS) value between the estimated values of the observer X_i and the data given by the model \bar{X}_i from (28) in the following form:

$$RMS = \sqrt{\sum_{i=1}^n (\log X_i - \log \bar{X}_i)^2} \quad (37)$$

Figure 5 reveals the performance of the previous observer strategies under different sampling times (k). We can note that the proposed neural observer provides the best estimations for sampling times less than 24 hours, the high-gain observer also gives good estimations. Results suggest that the fuzzy observer gives bad performance for small sampling times compared with the other two strategies. This could be attributed to the gains for the fuzzy observer that introduce noise in the estimations. Furthermore, we note that the three observer schemes provide similar estimations for large sampling times, that is more than 80 hours. However, the estimation errors are very large for any prediction.

The sampling time is a parameter that should be selected on the trade-off between good state estimations, sampling costs and frequent patient visits to the hospital. Of course the shorter sampling time, the better estimation is obtained. Nevertheless, HIV tests are bothersome to the patient and expensive to health services (approximately \$250 for a single test). Figure 5 suggests we could consider a sampling time of 12 hours to provide good estimations.

Results presented in Figure 6(a) reveal that the three schemes provide good estimations for the healthy CD4+ T cells at the end of the first month. However, for the estimation of infected cells in Figure 6(b) we note there are differences between the observer schemes. The high-gain and fuzzy observers present longer transients than the neural observer. After the second month, a constant estimation error is remained for the fuzzy scheme. The viral load estimations in Figure 6(c) are similar in the three schemes, however the high-gain observer gives a high peak at month 1.

The error dynamics of the neural observer are bounded as is shown in Figure 7, showing that we can achieve a reasonable good estimation (error less than 20%) for infected cells after the first month. Clinicians could consider the number of infected CD4+ T cells as an additional marker for the scheduling of antiretroviral therapy. Because measurements can not be performed during small time intervals, discrete-time observer schemes are important in order to obtain good estimations. It is important to note that both observers used for comparison purposes (high-gain

observer and fuzzy one) require the previous knowledge of the model.

6. Conclusions

In this paper, we showed a discrete-time neural observer trained with the Kalman filter, its respective stability analysis is also presented. The estimation of CD4+ T cells and viral load in the blood torrent in HIV has been implemented. The RHONO considers measurements of total CD4+ T cells and viral load in blood. Simulations results and comparisons with other schemes illustrate the effectiveness of the neural observer. This observer scheme provides promising guidelines to help in the design of effective medication protocols. Simulation results suggest that good estimations can be achieved only after the primary stage of the infection (first months after infection).

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8. References

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Figures

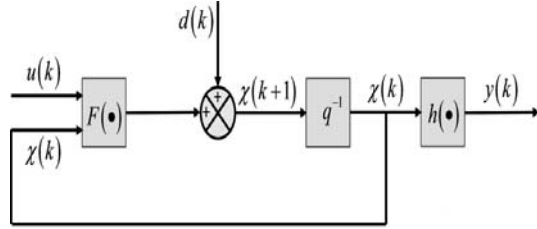


Figure 1: Schematic representation for a unknown discrete-time nonlinear system with nonlinear output

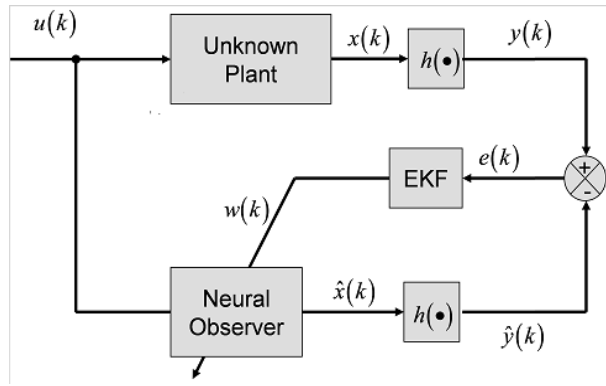


Figure 2: Neural observer scheme

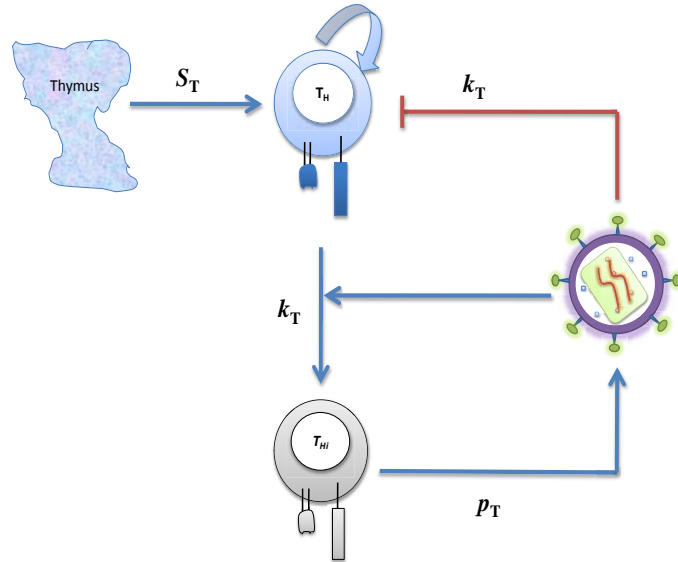


Figure 3: HIV infection scheme

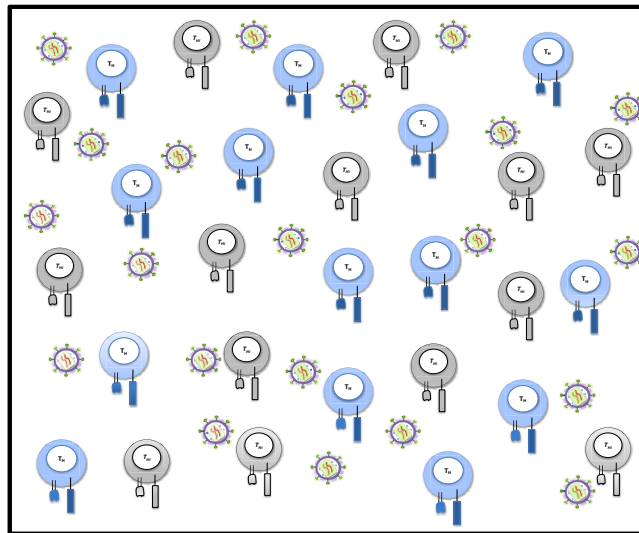


Figure 4: CD4+ T cells and viral load in blood sample

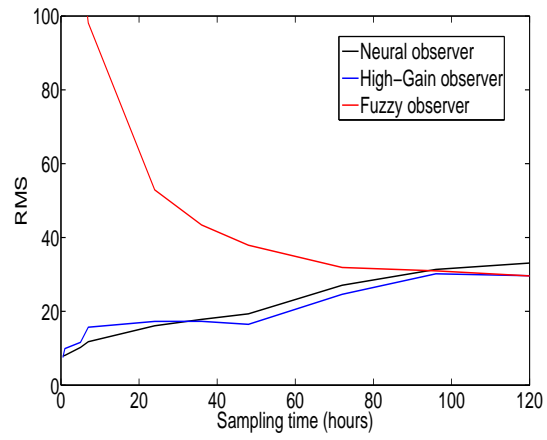


Figure 5: Observer performances for different sample times

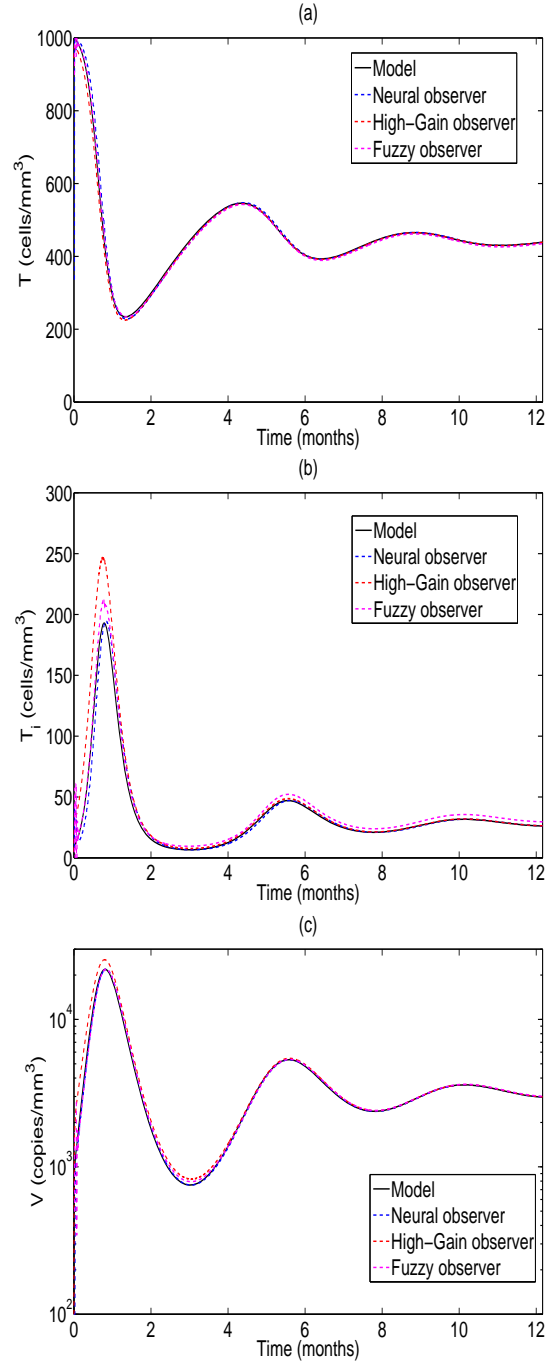


Figure 6: Estimation results for different observer schemes: Panel (a) shows healthy CD4+ T cell estimations, panel (b) shows infected CD4+ T cell estimations and panel (c) shows virus estimations

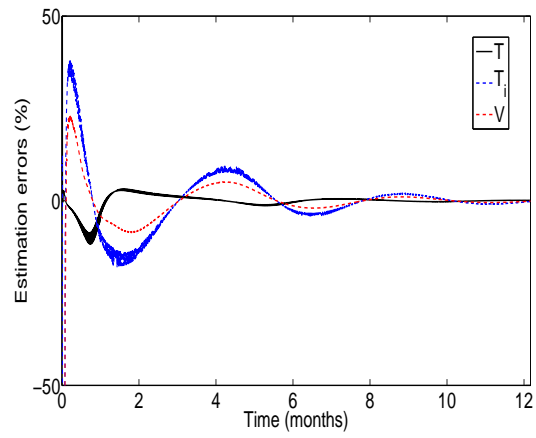


Figure 7: Neural observer estimation error