Discrete-time Neural Observer for HIV infection dynamics

Esteban A. Hernandez-Vargas, Alma Y. Alanis*, Edgar N. Sanchez

***Abstract*— This paper presents a discrete-time neural observer for nonlinear systems, whose mathematical model is assumed to be unknown. The observer is based on a recurrent high order neural network (RHONN), which is trained on-line with an extended Kalman filter (EKF)-based algorithm. The respective stability analysis based on the Lyapunov approach is included. The neural observer is tested by application to an immunological interaction model for HIV. The observer estimates the non-measured number of infected CD4+T cells in the blood torrent, the measured number of non-infected CD4+T cells and the measured concentration of viral load. The observer performance is illustrated via simulations.**

I. Introduction

HIV can lead to acquired immunodeficiency syndrome (AIDS). This syndrome is able to collapse the immune system; for which has currently no known cure. The first reports of homosexual patients suffering from previously rare diseases such as pneumocystis pneumonia and Kaposis sarcoma were published in May 1981 [1]. HIV was defined as the primary cause of the acquired immunodeficiency syndrome [2]. It is estimated that in 2005, 40.3 million people were living with HIV/AIDS, 4.1 million people were infected with the virus, and 3.9 million people died due to progression to AIDS.

HIV is a retrovirus which uses CD4+T cells, fundamental part of the immune system, for replication. After this important discovery, researchers have focused on seeking treatment protocols with the knowledge of the infection cycle. The development of antiretroviral has been one of the most active areas in HIV research.

However, interactions of HIV in the body are very complex, for this reason several researches have been tackled the problem using a mathematical approach [3], [4], [5]. Several models have come to play an important part in HIV infection; some of them are deterministic models based on differential equations [6] while other introduces stochastic models [4]. The main problem to implement control strategies or further information for clinical protocols is that the complete information of the infection dynamic should be known. Due to these facts, state estimation applied to HIV has received special attention by many authors, who have obtained interesting results [7], [8]. These approaches mentioned above require knowing at least partially the model. Neural observers [9], [10], [11], have been provided interesting results without the requirement of the model. Based model and neural observers proposed for HIV [10] have the problem of being in continuous time, which is a drawback for implementation.

This paper presents a discrete-time recurrent high order neural Luenberger-like observer [13]. This observer is based on a RHONN [11], which estimates the state vector of the unknown model dynamics. The learning algorithm for the RHONN is based on an extended Kalman filter (EKF). Moreover, this paper also includes the respective stability analysis, 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 HIV dynamics.

* Corresponding author

E. A. Hernandez-Vargas, Systems Immunology, Helmholtz-Zentrum für Infecktionsforschung, Inhoffenstraße 7, D-38124, Braunschweig, Germany, e-mail: abelardo_81@hotmail.com

A.Y. Alanis, Departamento de Ciencias Computacionales, CUCEI, Universidad de Guadalajara, Av. Revolucion 1500, Col. Olimpica, C.P. 44430, Guadalajara, Jalisco, Mexico

E. N. Sanchez, CINVESTAV, Unidad Guadalajara, Apartado Postal 31-438, Plaza la Luna, Jal. C.P. 45090, e-mail: sanchez@gdl.cinvestav.mx

II. Preliminaries

Through this paper, we use k as the step sampling, $k \in 0 \cup Z^+$, $|\bullet|$ as the absolute value and, $\|\bullet\|$ as the Euclidian norm for vectors and as any adequate norm for matrices. Consider a MIMO nonlinear system

$$x_i(k+1) = F(x(k), u(k)) \tag{1}$$

where $x \in R^n$, $u \in R^m$ and $F \in R^n \times R^m \rightarrow R^n$ is a nonlinear function.

***Definition* 1**. The solution of (1) is semiglobally uniformly ultimately bounded (SGUUB), if for any Ω, a compact subset of R^n and all $x(k) \in \Omega$, there exists an $\varepsilon > 0$ and a number $N(\varepsilon, x(k_0))$ such that $\|x(k)\| < \varepsilon$ for all $k \geq k_0 + N$. In other words, the solution of (1) is said to be SGUUB if, for any a priory given (arbitrarily large) bounded set Ω and any a priory given (arbitrarily small) set Ω_0, which contains (0, 0) as an interior point, there exists an input u, such that every trajectory of the closed loop system starting from Ω enters the set $\Omega_0 = \{x(k) \mid \|x(k)\| < \varepsilon\}$, in a finite time and remains in it thereafter.

III. Discrete-Time Recurrent High Order Neural Network

A discrete-time recurrent high order neural network (RHONN) can be presented as:

$$x_i(k+1) = w_i^T z_i(x(k), u(k)), \; i = 1, \ldots, n \tag{2}$$

where x_i ($i = 1,2,\ldots,n$) is the state of the ith neuron, L_i is the respective number of higher-order connections, n is the state dimension, $\{I_1, I_2, \ldots, I_{Li}\}$ is a collection of non-ordered subsets of $\{1,2,\ldots,n\}$, w_i ($i = 1,2,\ldots,n$) is the respective on-line adapted weight vector, and $z_i(x(k),u(k))$ is given by

$$z_i(x(k),u(k)) = \begin{bmatrix} z_{i_1} \\ z_{i_2} \\ \vdots \\ z_{i_{Li}} \end{bmatrix} = \begin{bmatrix} \Pi_{j\in I_1} y_i^{di_j(1)} \\ \Pi_{j\in I_2} y_i^{di_j(2)} \\ \vdots \\ \Pi_{j\in I_{L_i}} y_i^{di_j(L_i)} \end{bmatrix} \tag{3}$$

$d_{ij}(k)$ being nonnegative integers and y_i is defined as follows:

$$y_i = \begin{bmatrix} y_{i_1} \\ \vdots \\ y_{i_1} \\ y_{i_{n+1}} \\ \vdots \\ y_{i_{n+m}} \end{bmatrix} = \begin{bmatrix} S(x_1) \\ \vdots \\ S(x_n) \\ u_1 \\ \vdots \\ u_m \end{bmatrix} \tag{4}$$

where $u = [u_1,u_2,...,u_m]^T$ is the input vector to the neural network (NN), and $S(\bullet)$ is defined by

$$S(x) = \frac{1}{1+\exp(-\beta x)} + \in \tag{5}$$

We consider now the problem to approximate the nonlinear system (1), by the following discrete-time RHONN series-parallel representation:

$$\chi_i(k+1) = w_i^{*T} z_i(x(k),u(k)) + \in_{z_i},\ i = 1,...,n \tag{6}$$

where χ_i is the ith plant state, ϵ_z is a bounded approximation error, which can be reduced by increasing the number of adjustable weights [10]. Assume that there exists the ideal weight vector w_i^*, such that $\|\epsilon_z\|$ can be minimized on a compact set $\Omega_{Zi} \subset \Re^{L_i}$. In general, it is assumed that this vector exists and is constant but unknown, see [11] for the details. Let us define its estimate as w_i and the estimation error as

$$\hat{w}_i(k) = w_i^* - w_i(k) \tag{7}$$

Theorem 1. The RHONN (2) trained with the EKF algorithm to identify the nonlinear system (1), ensures that the identification error is semiglobally uniformly ultimately bounded (SGUUB); moreover, the RHONN weights remain bounded. For the proof, see [12].

A. The EKF Training algorithm

For KF-based neural network training, the network weights become the states to be estimated. In this case, the error between the neural network output and the measured plant output can be considered as additive white noise. Due to the fact that the neural network mapping is nonlinear, an EKF-type is required [13]. The training goal is to find the optimal weight values which minimize the prediction error [11], [12]. In this work, we use an EKF-based training algorithm described by

$$\begin{aligned} w_i(k+1) &= w_i(k) + \eta_i K_i(k) e_i(k) \\ K_i(k) &= P_i(k) H_i(k) M_i(k) \qquad i = 1,...,n \\ P_i(k+1) &= P_i(k) - K_i(k) H_i^T(k) P_i(k) + Q_i(k) \end{aligned} \tag{8}$$

with

$$\begin{aligned} M_i(k) &= [R_i(k) + H_i^T(k) P_i(k) H_i(k)]^{-1} \\ e_i(k) &= y(k) - \hat{y}(k) \end{aligned} \tag{9}$$

where $e(k) \in \Re^p$ is the observation error. $P_i(k) \in \Re^{L_i \times L_i}$ is the weight estimation error covariance matrix at step k, $w_i \in \Re^{L_i}$ is the weight (state) vector, L_i is the respective number neural network weights, $y \in \Re^p$ is the plant output, $\tilde{y} \in \Re^p$ is the NN output, n is the number of states, $K_i \in \Re^{L_i \times p}$ is the Kalman gain matrix, $Q_i \in \Re^{L_i \times L_i}$ is the NN weight estimation noise covariance matrix and $R_i \in \Re^{p \times p}$ is the error noise covariance. $H_i \in \Re^{L_i \times p}$ is a matrix, in which each entry (H_{ij}) is the derivative of the *i-th* neural output with respect to *ij-th* NN weight, (w_{ij}), given as follows:

$$H_{ij}(k) = \left[\frac{\partial \hat{y}(k)}{\partial w_{ij}(k)} \right]^T \tag{10}$$

where $i=1,\ldots,n$ and $j=1,\ldots,L_i$. Usually P_i and Q_i are initialized as diagonal matrices, with entries $P_i(0)$ and $Q_i(0)$, respectively. It is important to remark that $H_i(k)$, $K_i(k)$ and $P_i(k)$ for the EKF are bounded; for a detailed explanation of this fact see [13]. To obtain H in (10) is not trivial. In this case $\hat{y}(k) = x_i(k)$, so by the chain rule we have

$$\frac{\partial \hat{y}(k)}{\partial w_{ij}(k)} = \frac{\partial \hat{y}(k)}{\partial x_i(k)} \frac{\partial x_i(k)}{\partial w_{ij}(k)} \tag{11}$$

IV. DISCRETE-TIME NEURAL OBSERVER

In this section, we introduce the neural observer proposed in [13]. We consider the state of a discrete-time nonlinear system, which is assumed to be observable, given by

$$\begin{aligned} x(k+1) &= F(x(k),u(k)) + d(k) \\ y(k) &= Cx(k) \end{aligned} \tag{12}$$

where $x \in R^n$ is the state vector of the system, $u \in R^m$ is the input vector, $y(k) \in R^p$ is the output vector, $C \in R^{p \times n}$ is a known output matrix, $d(k) \in R^n$ is a disturbance vector and $F(\bullet)$ is a smooth vector field and $F_i(\bullet)$ its entries; hence (12) can be rewritten as:

$$
\begin{aligned}
x(k+1) &= [x_1(k)...x_i(k)...x_n(k)]^T \\
d(k) &= [d_1(k)...d_i(k)...d_n(k)]^T \\
x_i(k+1) &= F_i(x(k),u(k)) + d_i(k), \quad i = 1,...,n \\
y(k) &= Cx(k)
\end{aligned} \tag{13}
$$

For the system (13), a Luenberger neural observer (RHONO) is proposed with the following structure:

$$
\begin{aligned}
\hat{x}(k) &= [\hat{x}_1(k)...\hat{x}_i(k)...\hat{x}_n(k)]^T \\
\hat{x}_i(k+1) &= w_i^T z_i(\hat{x}(k),u(k)) + g_i e(k) \\
\hat{y}(k) &= C\hat{x}(k), \qquad i = 1,...,n
\end{aligned} \tag{14}
$$

with $L_i \in R^p$, w_i and z_i as in (3). The weight vectors are updated on-line with a decoupled EKF (8)-(9). The output error is defined by

$$
e(k) = y(k) - \hat{y}(k) \tag{15}
$$

and the state estimation error as

$$
\tilde{x}(k) = x(k) - \hat{x}(k) \tag{16}
$$

Hence the dynamic of (16) can be expressed as

$$
\begin{aligned}
\tilde{x}(k+1) &= x_i(k+1) - \hat{x}_i(k+1) \\
&= w_i^{*T} z_i(x(k),u(k)) + \in_{z_i} + d_i(k) \\
&\quad - w_i^T z_i(\hat{x}(k),u(k)) - g_i e(k) \\
&= \tilde{w}_i z_i(\hat{x}(k),u(k)) + \in_{z_i}^{'} \\
&\quad - g_i e(k) + w_i^{*T} z_i(\tilde{x}(k),u(k))
\end{aligned} \tag{17}
$$

where $z_i(x(k),u(k)) = z_i(x(k),u(k)) - z_i(\hat{x}(k),u(k))$ and $\in_{z_i}^{'} = \in_{z_i} + d_i(k)$.

The stability properties of the observer are stated in the following theorem:

Theorem 2*:* For the system (1) the RHONO (2), trained with the EKF-based algorithm, ensures that the estimation error (16) and the output error (15) are semiglobally uniformly ultimately bounded. Moreover, the RHONO weights remain bounded. *For proof see Appendix A.*

Considering (15) and (17)

$$
e(k) = Cx(k) \tag{18}
$$

Then the system (17) can be rewritten as

$$
\begin{aligned}
\tilde{x}(k+1) &= \tilde{w}_i z_i(\hat{x}(k),u(k)) + \in_{z_i}^{'} - g_i C\tilde{x}(k) \\
&\quad + w_i^{*T} z_i(\tilde{x}(k),u(k))
\end{aligned} \tag{19}
$$

On the other hand the dynamics of (8) is

$$
\tilde{w}_i(k+1) = w_i^* - w_i(k+1) = \tilde{w}_i(k) - \eta_i K_i(k) e(k) \tag{20}
$$

V. Observer Design

In order to obtain the dynamics of HIV infection we consider the model proposed by [3], which includes the concentration of infected cells (T^i), non-infected (T) as well as the viral load in the blood torrent (V). The model is presented as follows:

$$
\begin{aligned}
\frac{dT(t)}{dt} &= s(t) - \mu_T T(t) + r\frac{T(t)V(t)}{C+V(t)} - z(t)k_v T(t)V(t) \\
\frac{dT^i(t)}{dt} &= z(t)k_v T(t)V(t) - \mu_T^i T^i(t) - r\frac{T^i(t)V(t)}{C+V(t)} \\
\frac{dV(t)}{dt} &= Nr\frac{T^i(t)V(t)}{C+V(t)} - k_T T(t)V(t) + g_v\frac{V(t)}{b+V(t)} \\
y(t) &= h\left[T(t),T^i(t),V(t)\right]
\end{aligned} \tag{21}
$$

$s(t)$ is the source of new CD4+T cells produced by the Thymus. μ_T is the speed of death toll of the not infected CD4+T cells. μ_T^i is the death rate of infected cells. k_v is the infection rate. k_T is the speed of lymphocytes CD8 eliminating the virus. r is the maximum proliferation of the CD4+T cells population. N is the number of free virus produced by the infected cells. C is the semi-constant of the proliferation process. z is the total daily drug dosage in chemotherapy. b is the half-constant saturation value of an external source of virus. g_v is the level under which other cells (that are not lymphocytes) produce free virus. Parameters values can be found in [3]. The output matrix is given by $h = \begin{bmatrix}1 & 0 & 1\end{bmatrix}^T$.

The neural observer is applied to HIV model (21), whose nonlinear dynamics are considered unknown (black-box). We use a sampling time of 7 hours to estimate the concentration of infected cells with the on-line concentration of viral cells in the blood torrent as well as non-infected measurements. The neural network used for this state estimation is given by

$$
\begin{aligned}
\hat{x}_1(k+1) &= w_{11}S(\hat{x}_3(k)) + w_{12}S(\hat{x}_1(k))S(\hat{x}_3(k))S(u(k)) \\
&\quad + w_{13}S(\hat{x}_1(k))^2 S(\hat{x}_2(k)) + w_{14}S(\hat{x}_1(k))S(\hat{x}_2(k))^2 \\
&\quad + g_1 e(k) \\
\hat{x}_2(k+1) &= w_{21}\hat{x}_3(k)\hat{x}_1(k) + w_{22}S(\hat{x}_3(k))S(u(k))\hat{x}_2(k)\hat{x}_3(k) \\
&\quad + w_{23}\hat{x}_2(k) + g_2 e(k) \\
\hat{x}_3(k+1) &= w_{31}S(\hat{x}_2(k))S(\hat{x}_3(k))S(u(k)) + w_{32}S(\hat{x}_1)S(\hat{x}_3) \\
&\quad + w_{33}S(\hat{x}_1)S(\hat{x}_3)^2 + g_3 e(k)
\end{aligned}
$$

where $\hat{x}_1$, $\hat{x}_2$ and $\hat{x}_3$ are the concentration of non-infected cells, infected cells and the total viral load in the blood torrent, respectively. The input u_1 is the daily drug dosage in chemotherapy. The observer scheme is presented in Fig.1.

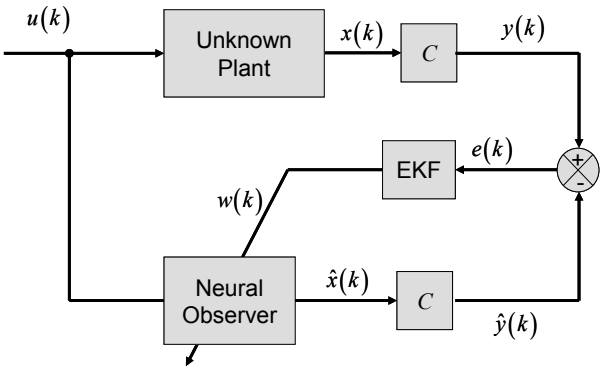


Fig. 1 - Observation Scheme

The training is performed on-line, using a parallel configuration. All the NN states are initialized randomly. The covariance matrices are initialized as diagonal, with nonzero elements as: $P_i(0) = 100000$, $Q_i(0) = 1000$ and $R_i(0) = 1000$, (i=1,2,3), respectively; the Luenberger parameter vector is $g = \begin{bmatrix} 0.2 & 0.01 & 0.0001 \end{bmatrix}^T$.

VI. Simulation Results

The observer simulations are implemented using Matlab/Simulink™. As can be seen in Fig.3, the RHONO exhibits good performance for the three variables. Because the fast convergence to the model it is not easy to observe the estimation transient, therefore we show in Fig.2 the error evolution which confirms the good estimation made by the neural observer. Notice that the estimation for the three states is achieved before the second day, while other works have convergence time around 15 days [9]. Fast-convergence time and discrete-time observers are important in order to realize good medication protocols [3]. For instance, the principal marker for treatment in HIV is the viral load, which provides the insight how the infection is progressing. However, clinicians could use other markers for the scheduling of antiretrovirals. The estimation of other important cells as macrophages [6] should be considered for future directions to the estimation problem in HIV.

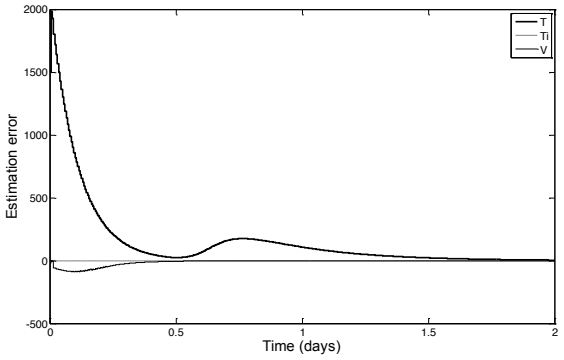
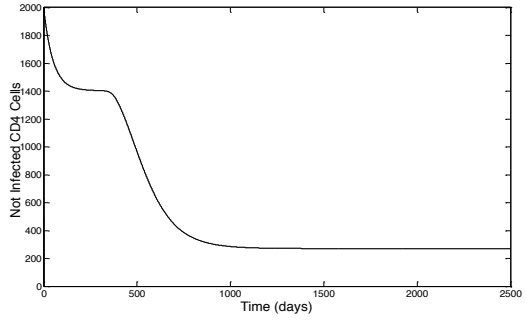
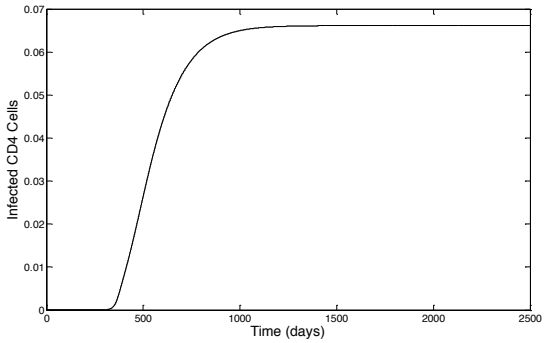


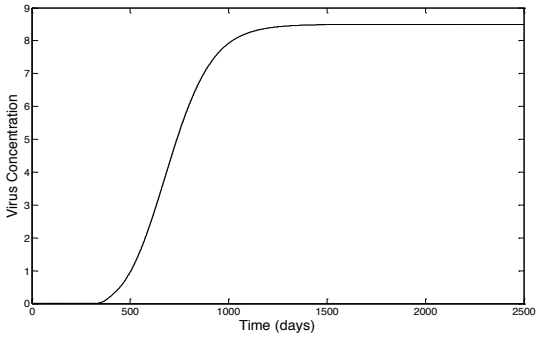
Fig. 2- Estimation errors evolution



(a)



(b)



(c)

Fig. 3- HIV dynamics (model signal in solid line and neural signal in dashed line)

VII. Conclusions

In this paper we showed a discrete-time neural observer trained on-line with the Kalman filter, its respective stability analysis is presented. The estimation of the number of CD4+T cells and viral load in the blood torrent in HIV has been implemented. The RHONO considers on-line measurements of non-infected cells and viral load in blood. Simulations results illustrate the effectiveness of the discrete-time observer and fast-convergence time. This observer scheme provides promising guidelines to design effective medication protocols.

ACKNOWLEDGMENT

The authors thank the support of CONACYT México Project 57801Y.

APPENDIX A

Proof of Theorem 2:

Consider the Lyapunov function candidate

$$\begin{aligned} V_i(k) &= \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) + \tilde{x}_i^T(k) \tilde{x}_i(k) \\ \Delta V_i(k) &= V_i(k+1) - V_i(k) \\ &= \tilde{w}_i^T(k+1) P_i(k+1) \tilde{w}_i(k+1) \\ &\quad + \tilde{x}_i^T(k+1) \tilde{x}_i(k+1) \\ &\quad - \tilde{w}_i^T(k) P_i(k) \tilde{w}_i(k) - \tilde{x}_i^T(k) \tilde{x}_i(k) \end{aligned} \tag{22}$$

Using (18), (19) and (22) we obtain the following expression:

$$\begin{aligned} V_i(k) &= \left[\tilde{w}_i(k) - \eta_i K_i(k) C\tilde{x}(k)\right]^T \left[P(k) - A(k)\right] \\ &\times \left[\tilde{w}_i(k) - \eta_i K_i(k) C\tilde{x}(k)\right] \\ &+ \left[\tilde{w}_i z_i(\hat{x}(k), u(k)) + w_i^{*T} z_i(\tilde{x}(k), u(k)) - g_i C\tilde{x}(k) + \epsilon_{z_i}^{'}\right]^T \\ &\times \left[\tilde{w}_i z_i(\hat{x}(k), u(k)) + w_i^{*T} z_i(\tilde{x}(k), u(k)) - g_i C\tilde{x}(k) + \epsilon_{z_i}^{'}\right] \\ &- \tilde{w}_i^T(k) P(k) \tilde{w}_i(k) - \tilde{x}_i^T(k) \tilde{x}_i(k) \end{aligned}$$

with $A(k) = K_i(k) H_i^T(k) P_i(k) + Q_i(k)$, then (22) can be written as

$$\begin{aligned} \Delta V_i(k) \le & -\|\tilde{w}_i(k)\|^2 \|A_i(k)\| - \|\tilde{x}(k)\| \|\eta_i P_i(k) K_i(k) C\| \|\tilde{w}_i(k)\| \\ & + \|\tilde{x}(k)\| \|\eta_i A_i(k) K_i(k) C\| \|\tilde{w}_i(k)\| - \|\tilde{w}_i(k)\| \|\eta_i P_i(k) K_i(k) C\| \|\tilde{x}(k)\| \\ & + \|\tilde{w}_i(k)\| \|\eta_i A_i(k) K_i(k) C\| \|\tilde{x}(k)\| + \|\tilde{x}(k)\|^2 \|\eta_i K_i(k) C\|^2 \|A_i(k)\| \\ & + \|\tilde{x}(k)\|^2 \|\eta_i K_i(k) C\|^2 \|P_i(k)\| + \|\tilde{w}_i(k)\|^2 \|z_i(\hat{x}(k), u(k))\|^2 \\ & + \|\tilde{w}_i(k)\|^2 \|z_i(\hat{x}(k), u(k))\| \|z_i(\tilde{x}(k), u(k))\| - \|g_i\| \|z_i(\hat{x}(k), u(k))\| \|C\| \|\tilde{w}_i(k)\| \|\tilde{x}(k)\| \\ & + \|\tilde{w}_i(k)\| \|z_i(\tilde{x}(k), u(k))\| \|\epsilon_{z_i}^{'}\| + \|\tilde{w}_i(k)\| \|z_i(\tilde{x}(k), u(k))\| \|w_i^*\| \|z_i(\hat{x}(k), u(k))\| \\ & + \|z_i(\tilde{x}(k), u(k))\|^2 \|w_i^*\|^2 - \|\tilde{x}(k)\| \|z_i(\tilde{x}(k), u(k))\| \|g_i w_i^*\| + \|z_i(\tilde{x}(k), u(k))\| \|\epsilon_{z_i}^{'} w_i^*\| \\ & + \|\tilde{x}(k)\| \|g_i C\| \|z_i(\hat{x}(k), u(k))\| \|\tilde{w}_i(k)\| - \|\tilde{x}(k)\| \|z_i(\tilde{x}(k), u(k))\| \|g_i C\| \|w_i^*\| \\ & + \|\tilde{x}(k)\|^2 \|g_i C\|^2 - \|\tilde{x}(k)\| \|g_i C \epsilon_{z_i}^{'}\| + \|\tilde{w}_i(k)\| \|z_i(\hat{x}(k), u(k))\| \|\epsilon_{z_i}^{'}\| \\ & + \|z_i(\tilde{x}(k), u(k))\| \|\epsilon_{z_i}^{'} w_i^*\| - \|\tilde{x}(k)\| \|g_i C \epsilon_{z_i}^{'}\| + \|\epsilon_{z_i}^{'}\|^2 - \|\tilde{x}(k)\|^2 \end{aligned} \tag{23}$$

finally (23), can be expressed as

$$\begin{aligned} \Delta V_i(k) \le & -\|\tilde{x}(k)\| F_i(k) - \|\tilde{w}_i(k)\|^2 \|A_i(k)\| + \|\tilde{w}_i(k)\|^2 \|z_i(\hat{x}(k), u(k))\|^2 \\ & + 2\|\tilde{w}_i(k)\| \|z_i(\hat{x}(k), u(k))\| \|\epsilon_{z_i}^{'}\| + \|\epsilon_{z_i}^{'}\|^2 \end{aligned}$$

with

$$\begin{aligned} F_i(k) &= \|\eta_i P_i(k) K_i(k) C\| \|w_i^* - w_{iM}(k)\| \\ &- 2\|\eta_i A_i(k) K_i(k) C\| \|w_i^* - w_{iM}(k)\| \\ &+ \|w_i^* - w_{iM}(k)\| \|\eta_i P_i(k) K_i(k) C\| - \|\tilde{x}(k)\| \|\eta_i K_i(k) C\|^2 \|A_i(k)\| \\ &- \|\tilde{x}(k)\| \|\eta_i K_i(k) C\|^2 \|P_i(k)\| \\ &- \|w_i^* - w_{iM}(k)\|^2 \|z_i(\hat{x}(k), u(k))\| L_{z_i} \\ &+ |g_i| \|z_i(\hat{x}(k), u(k))\| \|C\| \|w_i^* - w_{iM}(k)\| \\ &- \|w_i^* - w_{iM}(k)\| L_{z_i} \|w_i^*\| \|z_i(\hat{x}(k), u(k))\| - L_{z_i}^2 \|\tilde{x}(k)\| \|w_i^*\|^2 \\ &+ L_{z_i} \|\tilde{x}(k)\| \|g_i w_i^*\| - L_{z_i} \|\epsilon_{z_i}^{'} w_i^*\| - \|g_i C\| \|z_i(\hat{x}(k), u(k))\| \|w_i^* - w_{iM}(k)\| \\ &+ L_{z_i} \|\tilde{x}(k)\| \|g_i C\| \|w_i^*\| - \|\tilde{x}(k)\| \|g_i C\|^2 + 2\|g_i C \epsilon_{z_i}^{'}\| - L_{z_i} \|\epsilon_{z_i}^{'} w_i^*\| + \|\tilde{x}(k)\| \end{aligned}$$

where w_{iM} is the upper bound of w_i and L_{z_i} is the Lipchitz constant of $z_i(x(k), u(k))$, as defined in (3). Then, there is η_i and g_i such that $\Delta V_i(k) < 0$, when the following two conditions are hold

$$\Delta \|\tilde{w}_i(k)\| > \frac{\|\tilde{w}_i(k)\| \|z_i(\hat{x}(k), u(k))\| + \epsilon_{z_i}^{'}}{\sqrt{\|A_i(k)\|}}$$

and

$$\|x(k)\| > \frac{I_i(k)}{G_i(k)}$$

with

$$\begin{aligned} G_i(k) &= -\|\eta_i K_i(k) C\|^2 \left[\|A_i(k)\| + \|P_i(k)\|\right] + L_{z_i} \|g_i w_i^*\| - L_{z_i}^2 \|w_i^*\|^2 \\ &+ L_{z_i} \|g_i C\| \|w_i^*\| - \|g_i C\|^2 + 1 \end{aligned}$$

$$\begin{aligned} I_i(k) &= -\|\eta_i P_i(k) K_i(k) C\| \|w_i^* + w_{iM}(k)\| \\ &+ 2\|\eta_i A_i(k) K_i(k) C\| \|w_i^* - w_{iM}(k)\| \\ &- \|w_i^* - w_{iM}(k)\| \|\eta_i P_i(k) K_i(k) C\| \\ &+ \|w_i^* - w_{iM}(k)\|^2 \|z_i(\hat{x}(k), u(k))\| L_{z_i} \\ &- |g_i| \|z_i(\hat{x}(k), u(k))\| \|C\| \|w_i^* - w_{iM}(k)\| \\ &+ \|w_i^* - w_{iM}(k)\| L_{z_i} \|w_i^*\| \|z_i(\hat{x}(k), u(k))\| \\ &+ L_{z_i} \|\epsilon_{z_i}^{'} w_i^*\| + \|g_i C\| \|z_i(\hat{x}(k), u(k))\| \|w_i^* - w_{iM}(k)\| \\ &+ L_{z_i} \|\epsilon_{z_i}^{'} w_i^*\| - 2\|g_i C \epsilon_{z_i}^{'}\| \end{aligned}$$

Therefore the solution of (2) and (20) is stable. Moreover the estimation error and the RHONO weights are SGUUB [11]. Considering (15) 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.

$$\begin{aligned} e(k) &= Cx(k) \\ \|e(k)\| &\le \|C\| \|x(k)\| \end{aligned}$$

■

REFERENCES

[1] Centers for Disease Control (1981a). Pneumocystis pneumonia-Los Angeles. MMWR Morb Mortal Wkly Rep 1981, Vol. 30: 250-2. http://hiv.net/link.php?id=144

[2] L. Montagnier, J.C. Chermann, F. Barre-Sinoussi, D. Klatzmann, S. Wain-Hobson, M. Alizon, F. Clavel, F. Brun-Vezinet, E. Vilmer, and C. Rouzioux, Lymphadenopathy associated virus and its etiological role in AIDS. Princess Takamatsu Symp, Vol. 15, (1984), 319.

[3] D. Kirschner, Using mathematics to understand HIV immune dynamics, Notices American Mathematics, Vol.43, (1996), 51-60.

[4] N. Dalal and D. Greenhalgh, A stochastic model for interval HIV dynamics, Journal of Mathematical Analysis and Applications, (2007), 1084-1101.

[5] L. Dan and M. Wanbiao, Asymptotic properties of HIV-1 infection model with time delay, Journal of Mathematical Analysis and Applications, (2006), 683-691.

[6] E.A. Hernandez-Vargas and R.H. Middleton, Modeling the three stages in HIV infection, Journal of Theoretical Biology, (2011) under revision.

[7] D. Campos-Delgado and E. Palacios, Non-linear observer for the estimation of CD8 count under HIV-1 infection**,** American Control Conference, (2007), 4101-4105

[8] X. Xiaohua, Estimation of HIV/AIDS parameters, Automatica, Vol.39, (2003), 1983-1984.

[9] I. Chairez, A. Cabrera, A. Pozniak and T. Pozniak, A continuous time neuro-observer for human immunodeficiency virus (HIV) dynamics, Proceedings of the 15th IFAC World Congress, Vol. 15, (2002)

[10] G.A. Rovithakis and M.A., Chistodoulou, Adaptive Control with Recurrent High-Order Neural Network, (Springer-Verlag, New York, USA, 2000).

[11] J. Sarangapani, Neural Network Control of Nonlinear Discrete-Time Systems, (Taylor and Francis Grouo, New York, USA, 2006).

[12] A.Y. Alanis, E.N. Sanchez and G. Loukianov, Discrete-Time Recurrent High Order Neural Observer for Induction Motors, Vol. 4529, (Springer-Verlag, Berlin Heidelberg, Germany, 2007), 1611-3349

[13] Y. Song, The extended Kalman filter as local asymptotic observer for discrete-time nonlinear systems, Journal of Mathematical Systems, Estimation and Control, Vol.5, (1995), 59-78.