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A CONTINUOUS TIME NEURO-OBSERVER FOR HUMAN IMMUNODEFICIENCY VIRUS (HIV) DYNAMICS

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Abstract: The continuous time observer design based on differential neural networks (DNN) is presented. It is tested by the application to an immunological interaction model for HIV. To give the corresponding data interpretation and to justify the observability property the Kirschner's model is used. The suggested observer estimates the model's variables behavior providing the evolution of the number of infected and not infected lymphocyte T-CD4 cells during 10 days approximately starting from the treatment using Zidovuina (AZT). This approach does not require any model of this process to be in use. The obtained results are shown to allow the programming a high-quality medication protocol for zero-positive patients or AIDS patients.
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Keywords: Differential Neural Networks, Neuro-observer, Observability, HIV, AIDS.

1. INTRODUCTION

The implementation of Artificial Neural Networks (ANN) was shown to provide a successful modelling and control of processes with a high degree of uncertainties in different fields of the science. The ANN have been used to realize some identification and control processes (Narendra and Parthasarathy, 1990) such as chemical reactions and water's treatment (Hunt et. al., 1992), fermentation process (Gauthier *et. al*., 1992), etc. This paper is intended to test a neuro-observer's application for the design of some continuous time "virtual" sensors providing the "non-direct" state estimation which do not admit direct measurements. In this case we study the epidemic model (Kirshner, 1996) of the human immunodeficiency virus (HIV), causing the Syndrome of the Acquired Immunodeficiency (AIDS).

The syndrome of acquired immunodeficiency (AIDS) is the most mortal epidemic in XX century that is only comparable to the black death in XIV century. The HIV causes the illness development affecting mainly to the human immunology system. When the antibodies of the HIV are detected, the patients are considered infected and they are called *zero-positive* or having a contract with AIDS (according to the affection level on the T-CD4 cells). In the developed countries, the presence of the virus and their propagation was associated with the homosexual community, but a few years later it was demonstrated that the illness' permanency and its range of action reaches involved pregnant women, heterosexual, homosexual and recently born children (Blower *et al*., 1991).

When a strange substance is introduced in the body, the human being immune system chooses an appropriate reaction with the purpose of eliminating this strange agent (virus) quickest possible way. This reaction can be only of two types: cellular or hormonal. The first action against the virus is exercised by the macrophage-cells that examine and absorb the strange particles. These cells incorporate the phagocyte substance in their membrane activating another cells (T-CD4), providing by this a biochemical reactions cascade which become a messenger in the production and activation the CD8 cells. The last ones eliminate definitively the phatogen entity located inside of the body (Jerne, 1973; Marchuck, 1993).

When this virus enters in an organism, its cell targets are the CD4 cells playing an important role in the immune respond. The protein GP120 acting on the virus surface has a great likeness for the protein CD4 located on the surface of the lymphocyte T cells. By this way, the virus can enter into the cells. The HIV is a particular type of well-known virus called

retrovirus whose characteristics involve a load of ribonucleic acid (RNA), introduced in the cell's nucleus, and from there, it is able to produce an auto-transcription. This process generates a chain of deoxyribonucleic acid (DNA), which is added then to genetic code of the same lymphocytes. With the chain of DNA, implanted in the human chromosomes, the virus starts a replication of protein and lipids, when, which combining, they generate a new virus, and so on. Since this process is continuous and fast, new copies of the virus are liberated quickly to the blood torrent where they can infect new cells. The virus spreading along through all the organs provides an organism's immunodeficiency that leaves the organism to be exposed to the attack of any bacteria or another virus. This causes an illness because the opposition of the corporal system defense can not be received. This process can provoke a great deterioration in the patient's health, and in serious cases, until its decease (Chavez, 1989; Hahn, 1986).

2. STUDY MOTIVATION

Any treatment against of an illness is based on the administration of a certain pharmaceutical drugs. Among those, the most important ones are the Zidovuina (AZT), the DDC, DDI and D4T. All of these drugs are inhibitors of the inverse *transcriptase* representing the protein in charge of carrying out the conversion of RNA in DNA when a cell is infected. Unfortunately, these substances are not cures, but they are able to make more slow the immunodeficiency effect. They also reduce the risk levels of sexual transmission as gestation. A lot of controversy exists among the doctors about "how, when and how much?" that is, which quantity and strategy of the treatment should be applied to a patient (if the protocol for an efficient doesn't exist) in the zeal to limit the dissemination of the virus through the blood torrent. These questions are shown to be studied by means of digital simulation with the application of the mathematical immunology interaction designed for the VIH model (Anderson and May 1989; Kirshner 1996). To realize this study, researchers should be provided a complete information on the process behaviour that demands an on-line estimation of all model variables. Some of them are practically unmeasured on-line because of a high cost of such testing or the physical properties of these compounds excluding such current measurements. That's why, the design of "virtual" sensors providing the on-line state estimation seems to be very important for the practical needs.

3. MODEL DESCRIPTION

The modelling of the interaction between the immune system and the HIV begins in the statistics of the cells CD4. This model (Kirschner, 1996) includes the concentration of infected cells (T^i) as well as non-infected (T) together with the number of viral cells in the blood torrent (V):

$$\begin{aligned}
\frac{dT(t)}{dt} &= s(t) - \mu_T T(t) + r\frac{T(t)V(t)}{C+V(t)} - z(t)k_v T(t)V(t) \\
\frac{dT^i(t)}{dt} &= z(t)k_v T(t)V(t) - \mu_T{}^i T^i(t) - r\frac{T^i(t)V(t)}{C+V(t)} \\
\frac{dV(t)}{dt} &= Nr\frac{T^i(t)V(t)}{C+V(t)} - k_T T(t)V(t) + g_v\frac{V(t)}{C+V(t)} \\
y(t) &= H(T(t), T^i(t), V(t))^T
\end{aligned} \tag{1}$$

Here

- $s(t)$ is the source of new cells CD4 produced by the Timo;
- μ_t is the speed of death toll of the not infected CD4 cells;
- $\mu_t{}'$ is the speed of the infected cells died;
- k_v is the speed of the not infected cells become cells with the virus;
- k_t it is the speed of the lymphocytes CD8 eliminating the virus;
- r is the maximum proliferation of the CD4 cells population;
- N is the number of free virus produced by the infected cells;
- C is the semi-constant of the proliferation process;
- 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) add free virus to the blood.,
- H =(1;1;0) is the given output matrix, reflecting the fact of two first components on-line measurement availability.

Using this model, one can observe the possible dynamic evolution both of the infected cells, and of those that they are not. The use of this model has allowed to the clinical HIV experts to establish the procedures and dosages to the patients as well as to limit the virus growth population. Nevertheless, the procedure effectiveness turns out to be very low because of continuous and constant blood extractions in the patients for the cells sampling and the dose regulation. Besides, last the medications cost (mainly Azidovuina) are very high. So, to give the corresponding data interpretation and to justify the observability property the Kirschner's model is used below. But to apply the approach suggested here

any model is not required for the state estimation of the VIH process.

4. METHODOLOGY

In the case of high uncertainty related to the absence of *a priory* information a model structure of the considered process or when some variables can not be measured directly, the *Neural Networks* (NN) approach seems to be an effective tool to solve the corresponding identification and control problems (Haykin, 1994). The *NN* can be classified as *Static* and *Dynamic*. The last ones have some advantages with respect to the first, since they incorporate the feedback within their structure (Poznyak *et al*, 2001). Here we willl follow this DNN-approach. The dynamic (differential) neuro-observer for the HIV-treatment model is proposed to estimate the evolution of the model's variables describing the interaction between the immune system and the HIV, that is, the special "virtual" sensor is proposed to obtain the current estimates of the unmeasurable variables.

4.1 Observability Analysis

First, before the designing of any state observer, it seems to be natural (and, may be, necessary) to consider the problem of observability of the given system. If it turns out that the system is not observable, then it makes no sense to design any observer. So, below we will show which states of HIV immunology interaction model should be measured on-line to provide the observability property for the corresponding model, that is, to guarantee a qualitative estimation of the rest of variables. To do this, we will apply the approach given in (Gauthier and Bornard, 1981). So, for the non-lineal model (1), it is said to be observable within the interval time $[t_0, t_1], t_1 > t_0$ when the output data $y(t)$ determine the initial state $x(t_0)$ completely. This definition implies that the system states are observable, if the observability matrix defined by

$$Q_t = \frac{d\Theta_t}{dx_t} \qquad (2)$$

is not singular for any $x_t \in \Re^n$, i. e., $\det Q_t \neq 0$. The variable Θ_t represents the new variables vector defined as

$$\Theta(t) = \begin{bmatrix} Hx_t \\ L_f Hx_t \\ L_{f^2} Hx_t \\ L_{f^3} Hx_t \\ \vdots \end{bmatrix} \qquad (3)$$

where

- $f(x_t, t)$ represents the non lineal system's vectorial fields (the right-hand side of (1));
- $L_{f^n} Hx_t$ is the n-th Lie's derivative.

For the system (1), the considered output is the single dimensional and the considered model turns out to be measurable. So, it makes sense to design the DNN-observer to estimate the variable *V(T)* using the output data presenting the summation of two first model variables.

4.2 Differential Neural Network (DNN)

The differential neural network (DNN) structure is proposed as in (Poznyak *et. al*. 2001) to develop the state estimate (*V(t)*) of the HIV model given by (1). The structure of this DNN is presented in (Fig. 1) and corresponds to a multilayer ANN of Hopfield's (Catfollis, 1994). The DNN-observer dynamics is continuous in time is given by

$$\frac{d}{dt}\hat{x}_t = A\hat{x}_t + W_{1,t}\sigma(V_{1,t}\hat{x}_t) + W_{2,t}\phi(V_{2,t}\hat{x}_t)\gamma(u_t) + K\left[y - H\hat{x}_t\right] \qquad (4)$$

where:

- $\hat{x}_t \in \Re^n$ is the neural network vector of states,
- $u_t \in \Re^m$ is the input,
- the matrix $A \in \Re^{n*n}$ is a feedback stable matrix , and should be selected a priori,
- the matrices $W_{1,t} \in \Re^{n*m}$, $V_{1,t} \in \Re^{m*n}$, $W_{2,t} \in \Re^{n*k}$ and $V_{2,t} \in \Re^{k*n}$ are the weights matrices describing the connection among the hidden layers and output layer,
- , $\gamma(u_t) \in \Re^k$ is the control vector field, $\sigma(\cdot) \in \Re^m$ they are functions of the sigmoidal type and are diagonal:

$$\sigma(\cdot) = diag\left[\sigma_1\left(V_{2,t}\hat{x}_t\right)_1, \ldots, \sigma_k\left(V_{2,t}\hat{x}_t\right)_{min\{p,m\}}\right] \qquad (5)$$
$$\phi(\cdot) = diag\left[\phi_1\left(V_{2,t}\hat{x}_t\right)_1, \ldots, \phi_k\left(V_{2,t}\hat{x}_t\right)_{min\{r,k\}}\right]$$

with the elements as the sigmoidal functions

$$\sigma_i(x)=\frac{a_i}{1+e^{-b_i^T x}}-c_i;\ \phi_i(x)=\frac{\tilde{a}_i}{1+e^{-\tilde{b}_i^T x}}-\tilde{c}_i \qquad (6)$$

The structure of the net is shown in the fig. 1.

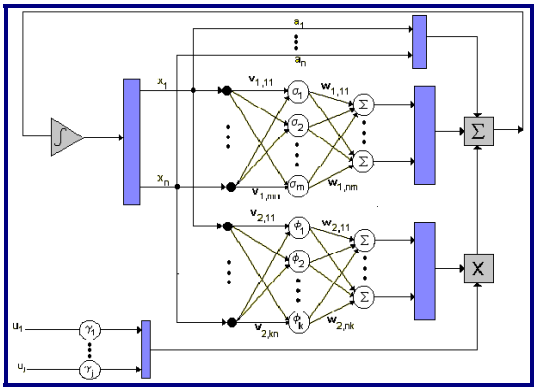

Fig. 1. The Differential Neural Network structure.

The learning laws for the weights of the DNN are given by a system of differential equations defining the matrix evolutions for $W_{1,t}\in\Re^{n*m}$, $V_{1,t}\in\Re^{m*n}$, $W_{2,t}\in\Re^{n*k}$ and $V_{2,t}\in\Re^{k*n}$:

$$\begin{cases}\dot{W}_1=-k_1PN_\delta^{-1}\left[\frac{1}{2}\left(H^T\Lambda_\xi^{-1}H+\delta\Lambda_{W1}\right)^T N_\delta^{-1}\right.\\ \left.P\left(W_{1,t}-W_1^*\right)\sigma\left(V_{1,t}\hat{x}_t\right)-H^T\left(y_t-H\hat{x}_t\right)\right]\sigma\left(V_{1,t}\hat{x}_t\right)^T\\ \dot{W}_2=-k_2PN_\delta^{-1}\left[\frac{1}{2}\left(H^T\Lambda_\xi^{-1}H+\delta\Lambda_{W2}\right)^T N_\delta^{-1}\right.\\ \left.P\left(W_{2,t}-W_2^*\right)\phi_t\left(V_{2,t}\hat{x}_t\right)\gamma(u_t)-H^T\left(y_t-H\hat{x}_t\right)\right]\\ \cdot\gamma(u_t)\phi_t^T\left(V_{2,t}\hat{x}_t\right)\\ \dot{V}_1=-k_3L_\sigma^2\left(V_{1,t}-V_1^*\right)\hat{x}_t\overline{W}_1\hat{x}_t^T\\ \dot{V}_2=-k_4\|\gamma(u_t)\|L_\phi^2\overline{W}_2\left(V_{2,t}-V_2^*\right)\hat{x}_t\hat{x}_t^T\\ W_{1,0}=W_1^*,W_{2,0}=W_2^*,V_{1,0}=V_1^*,V_{2,0}=V_2^*\end{cases} \qquad (7)$$

where $k_i\ (i=\overline{1,4})$ are positive constants, and P is the positive solution of the following Riccati equation given by

$$\begin{aligned}&A^TP+PA+PRP+Q=0\\ &Q=\delta\left(\Lambda_{W1}^{-1}+\Lambda_{W2}^{-1}\right)+2\bar{\gamma}^2L_\phi^2V_2^{*T}\overline{W}_2V_2^*+\\ &2L_\sigma^2\,tr\{\overline{W}_1\}V_1^{*T}V_1^*+Q_0-H\Lambda_\xi H^T\\ &R=\Lambda_{W1}^{-1}+\Lambda_{W2}^{-1},\overline{W}_i:=W_i^{*T}\Lambda_{Wi}W_i^*\ (i=1,2)\end{aligned} \qquad (8)$$

Here A is a Hurwitz (stable) matrix providing the existence of a positive solution for (8) and

$$N_\delta:=\left[H^TH+\delta I\right],\ \delta\rangle 0 \qquad (9)$$

The function $\gamma(\cdot):\Re^s\to\Re^k$ is assumed to be bounded within a working zone, that is, $\|\gamma(u)\|\le\bar{u}$. Below we select $\gamma(u)=u$. The gain-matrix is $K=P^{-1}H\Lambda_\xi\in\Re^{m\times n}$. The constant matrices Λ_{W1}^{-1}, Λ_{W2}^{-1}, Λ_ξ^{-1}, Λ_{Wi} are the procedure parameters that should be selected by the "*try-to-test method*".

The main purpose this neuro-observer is to determine the plant observed state *V(t)*. In our case it is the number of viral cells in the blood.

5. RESULTS

5.1 Observability analysis

To test the non-singularity property of $\Theta(t)$, its determinant calculation was done for different possible system outputs. But only the output composed by the first and second states (the cells infected CD4 and those not infected) have the determinant evolution different to zero (Fig. 2). In view of this analysis, the variable $V(t)$ has been selected to be estimated by the proposed DNN.

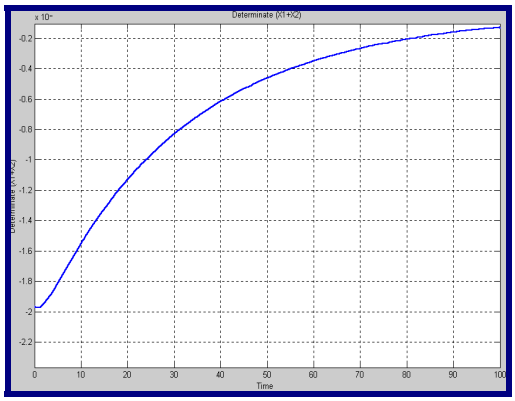

Fig. 2. Determinant evolution from the observability analysis.

5.2 The DNN Parameters

DNN was implemented with the following parameters, the matrices sizes are $n=d=k=3$, $r=p=3$, the matrix A in (4) has been selected as *A=diag [-4, -5, -3]* and

$$R=\begin{bmatrix}5 & 1 & 1\\ 1 & 1 & 0\\ 1 & 0 & 3\end{bmatrix},\ Q=\begin{bmatrix}2 & 2 & 1\\ 2 & 3 & 2\\ 1 & 2 & 4\end{bmatrix} \tag{10}$$

that leads to the P solution of (4) equal to

$$P=\begin{bmatrix}0.0648 & 0.0937 & 0.0468\\ 0.0937 & 0.2868 & 0.1926\\ 0.0468 & 0.1926 & 0.5150\end{bmatrix} \tag{11}$$

The sigmoid functions and the initial conditions to the dynamic neural network have been designed as follows:

$$\sigma(x)=diag\begin{bmatrix}\dfrac{2}{-0.5+2e^{-25x_1}}-5.2\\ \dfrac{2}{-0.5+2e^{-25x_2}}-0.25\\ \dfrac{2}{-0.5+2e^{-0.1x_3}}-0.25\end{bmatrix} \tag{14}$$

$$\phi(x)=diag\begin{bmatrix}\dfrac{0.2}{-0.05+0.2e^{-25x_1}}-0.25\\ \dfrac{0.2}{-0.05+0.2e^{-25x_2}}-0.25\\ \dfrac{0.2}{-0.05+2e^{-1x_3}}-0.25\end{bmatrix} \tag{15}$$

and the gain parameters were $k_4=0.005$. Finally, the initial weights were

$$W_{1,0}=\begin{bmatrix}0.1 & 0.1 & 0.2\\ 0.1 & 0.2 & 0.1\\ 0.1 & 0.1 & 0.2\end{bmatrix};W_{1,0}=W_{2,0}=V_{1,0} \tag{16}$$

$$V_{2,0}=\begin{bmatrix}1 & 1 & 2\\ 1 & 2 & 1\\ 1 & 1 & 2\end{bmatrix}$$

As for the not infected CD4 cells state estimates, it is shown that the behavior of the DNN-observer is closed to model state trajectories started during seven days after the treatment with AZT (Fig. 3); the error evolution confirms the good estimation made by the DNN-observer. (Fig. 7). As for the infected cell case, the estimate state is achieved at one time of five days, improving the acting of the net for the not infected CD4 lymphocyte concentration (Fig. 4). Physiologically, this has repercussions in the medication protocol and their efficiency in the long-term treatment, according to the studies made by Kishner. (Kirshner, 1996).

The estimates of the free virus concentration in blood were obtained at fifteen days (see Fig. 5).

The adjustment of the DNN-observer through the weights components evolution of the layers of the DNN-observer has a bounded behavior (Fig. 6).

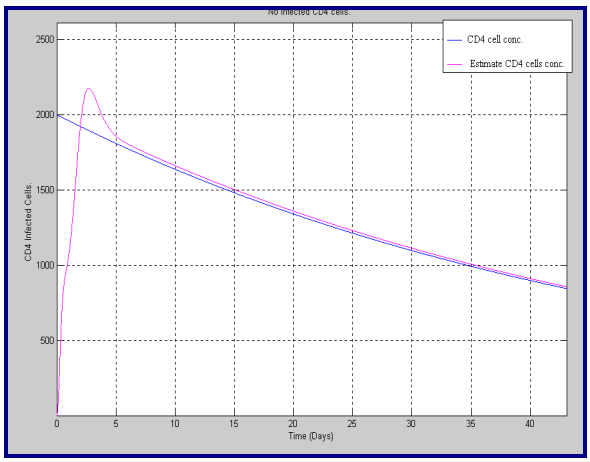

Fig. 3. Not infected CD4 cells evolution and its state estimate for 50 days of treatment.

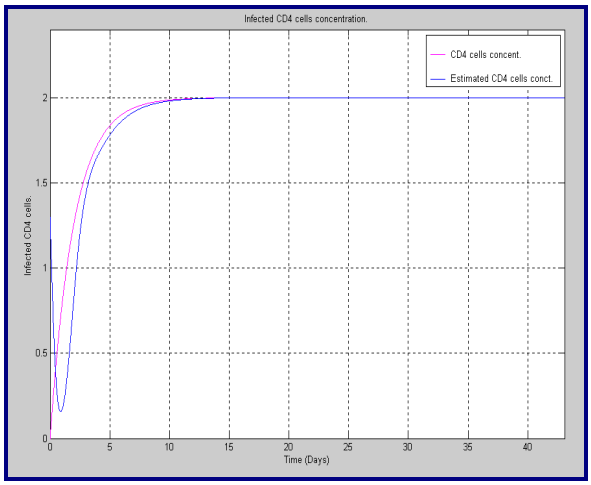

Fig. 4. Infected CD4 cells evolution and its state estimate for 50 days of treatment.

6. CONCLUSIONS

According to the suggested approach, the state estimation of the HIV immunology process has been realized using the DNN-observer providing the exact trajectory information for the infected cells, the healthy cells and the free virus into the blood torrent, when the patient presented AIDS.

The neural network application to a complex HIV immunology system demonstrates a great efficiency in the state estimation process. In view of this

possibility, the development of a DNN-observer based controller seems to be an attractive approach for the design of an automatic system for pharmacological (AZT) treatment.

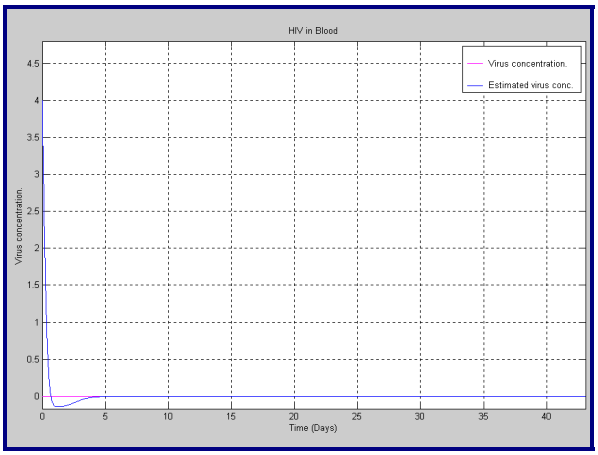

Fig. 5. The concentration of free HIV in blood for 50 days of treatment.

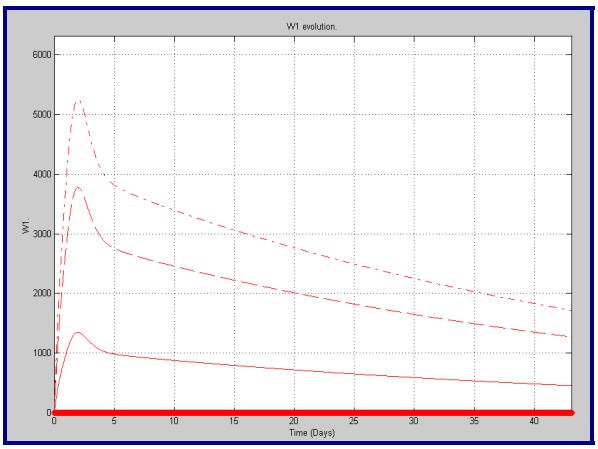

Fig. 6. Weights Wi components evolution.

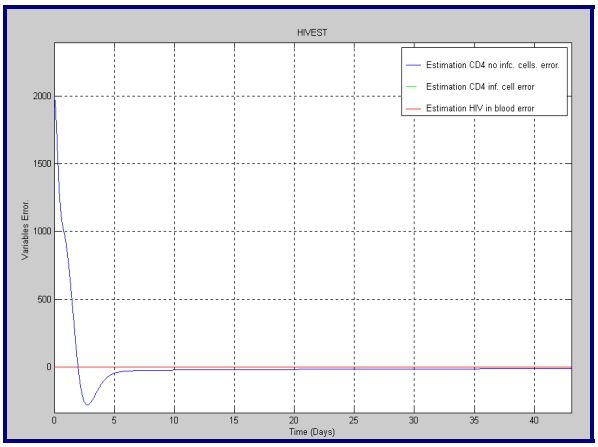

Fig 7. Estimation errors evolution.

REFERENCES

Anderson, R.M. and May. R. M. (1989). *Complex dynamical behavior interaction between HIV an the immune system. In cell to cell signaling* (Goldbeter, A. Ed). Academic Press, New York, pp. 335-349.

Blower, S. M., Hartel, D., Dowlabata, H. and Anderson, R. M. (1991). Drugs, sex, and HIV (a mathematical model) for New York City. Phil Trans. Roy. Soc.London Serv., *Biol. Sci.* **331**,1260, pp. 171-187.

Catfollis T. (1994). Generating Adaptive models of dynamic systems with recurrent neural networks, *Conference on Neural Networks and IEEE World Congress on Computational Intelligence,* pp. 3238-3243.

Chavez, C. (1989) On the role of on incubation periods in the dynamics of acquired immunodeficiency syndrome. *Lecture notes in biomathematics* **81**, Springer New York.

Gauthier J. P.; Bornard G. (1981). Observability for any u(t) of a class of Nonlinear Systems*, IEEE Trans. And Aut. Cont.*, **AC-26**.

Gauthier J. P.; H. Hammori and S. Othman (1992). A simple observer for nonlinear systems: applications to bioreactors, *IEEE Trans. On Aut. Cont, **37**,* pp. 875-880.

Hahn, B.H., and Shaw M. (1986). Genetic variation in HTLV-3/LAV over time in patients with AIDS or at risks of AIDS. *Science* **232**, pp. 1548-1563.

Haykin S. (1994). *Neural Networks: A Comprehensive Foundation*, IEEE Press, NY.

Hunt K. J., Sbarbarbaro D., Zbinkowski R. and Gawthrop P. J. (1992), Neural networks for control systems-A survey, *Automatica* **38**, pp. 1083-1112.

Kirschner D. (1996). Using mathematics to understand HIV immune dynamics. *Notices American Mathematics Society* **43**, pp. 191-202.

Jerne, N. (1973). Immune system. *Scientific American* **229**, pp. 51-60.

Marchuck, G.I., (1993). Mathematical modeling in immunology. *Optimization software*. Inc. New York.

Narendra K. S.; Parthasarathy K. (1990). Identification and Control of Dynamical Systems Using Neural Networks, *IEEE Transactions on neural networks*, **1**, pp. 4-27.

Poznyak A. S.; Sanchez E. N. and Wen Yu (2001). *Differential Neural Networks Nonlinear for Robust Non linear Control (Identification, State Estimation and Trajectory Tracking),* World Scientific Publishing, ISBN 981-02-4624-2.