NARMA-L2-based Antiviral Therapy for Infected CD4+ T Cells in a Nonlinear Model for HIV Dynamics: Protease Inhibitors-based Approach

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Abstract: The present paper uses the learning ability of neural networks (NN) to design a nonlinear model and a nonlinear controller that reduces the number of infected/uninfected CD4+ T cells into the HIV dynamic when an antiviral therapy based on protease inhibitors is applied. The dynamic of the closed-loop system based on such therapy is analyzed to understand the stability of infected/uninfected CD4+ T cells according to a global feedback law that regards un-modeled dynamic terms. To this end, a robust control scheme based on NARMA-L2 approach and a modified version of an already existing dynamic backpropagation algorithm is used to improve the antiviral therapy performance (strongly related to the tracking error). The robustness of the proposed model shows that antiviral therapy performance guarantees less infected CD4+ T cells.

1 INTRODUCTION

The study on the behavior of sensitive and resistant cells infected by AIDS, a communicable disease caused by the human immunodeficiency virus (HIV), by using retroviral drugs and the study of responses of these cells to certain treatments have been a highlight in last years (Althaus and Boer, 2011; Hattaf et al., 2009; Luo et al., 2012; Magnus and Regoes, 2011; Roy and Wodarz, 2012; Wang et al., 2014; Wilson, 2012; Wodarz and Hamer, 2007; Wodarz and Hamer, 2007). The treatment for HIV/AIDS relies on anti-retroviral drugs that suppress HIV viral load below the limit of detection. Some drug classes are reverse transcriptase inhibitors (RTI) and protease inhibitors (PIs). HIV is a deadly disease in a lack of treatment. Time since the initial infection till death in an untreated patient is 9-10 years. HIV infection dilapidates the patients' health since it attacks three extremely important cell populations, the CD4+ T cells, macrophages, and dendritic cells. In recent works, the main goal has been to understand the behavior of an infected CD4+ T cells population or the rate of infected CD4+ T cells when therapy is applied (Pinto and Carvalho, 2015b; Pinto and Carvalho, 2015a; Gumel et al., 2001; Karrakchou et al., 2006; Min et al., 2008; Allali et al., 2018; Loudon and Pankavich, 2016; Korpusik, 2017; Wang et al., 2019). However, the correctness of any HIV model depends on suitable approaches whereas by using suitable parameters for deterministic models or by finding a suitable performance for learning algorithms in computational methods (Wang et al., 2019). Nevertheless, the adjusting process of the parameters and the performance of the computational model yields a big complexity on the better way to find the optimal solution in nonlinear programming problems. Such complexity can be defined in terms of the constraints for stochastic models as well as choosing the right particles to model (Liu et al., 2019; Pandit and Boer, 2019; Cheng et al., 2019; Shi and Dong, 2019). Artificial intelligence (AI) techniques have been used extensively in numerous approaches to model HIV around several CD4+ T cells (Xiang et al., 2019; Zhang et al., 2019; Wang et al., 2019; Gupta et al., 2019). Amongst AI numerous techniques, the Artificial Neural Networks (ANN) has dominated in its capability and applicability in different fields (Cybenko, 1989). In the work reported here, it will be presented an approach to model the behavior of uninfected/infected CD4+ T cells based on NARMA approach, which will be implemented with neural networks and known as NARMA-L2. In this approach, the performance

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of the dynamic model is mainly composed by using an improved learning rule in neural networks based on sigmoid-functions, as activation function, and the dynamic backpropagation of the training error. The controller developed on this approach uses the inverse model principle to synthesize an antiviral therapy based on PI whose adjusting method updates the value of weights of the neurons that model the HIV dynamics. Next, it is hoped that a good adjusting of those values implies a better efficiency of antiviral therapy according to the response of resistant CD4+ T cells.

This paper presents the proposal as follows: in Section 2 will be reviewed the stochastic model based on the approach in (Wang et al., 2014). It will be assumed that all antiviral therapy based on PI can be decomposed in decoupled inputs such that the infected/uninfected CD4+ T cells have independent responses. In order to impose a performance on the antiviral therapy and the decreasing/increasing of infected/uninfected CD4+ T cells, an optimal control law based on the NARMA-L2 approach will be proposed. To this end, in Section 3 will be synthesized a control scheme with the aid of NNs and suitable learning algorithms. In Section 4 are shown different parametric structures for the NARMA-L2 model by means different learning rules in order to adjust the synaptic weights of NNs into NARMA-L2 scheme as well as the performance of the antiviral therapy represented by the controller. Finally, closing remarks are made in Section 5.

2 THEORETICAL BACKGROUND ON HIV

As well known, a deterministic model can be based on a system of ordinary differential equations that represent the dynamic of uninfected CD4+ T cells, drug-sensitive infectious virus, drug-resistant infectious virus, drug-sensitive infected CD4+ T cells, and drug-resistant infected CD4+ T cells. In (Wang et al., 2014) such dynamics is defined by ODE system (1a)-(1e), where T, V_s, V_r, T_s and T_r represent uninfected CD4+ T cells, drug-sensitive infectious virus, drug-resistant infectious virus, drug-sensitive infected CD4+ T cells, and drug-resistant infected CD4+ T cells, respectively. According to the epidemiology of the disease, the uninfected CD4+ T cells (T) are produced at a rate of λ and die at a rate of d. These cells, when in contact with HIV, are infected at a rate k_s, by drug-sensitive viruses and move τ time units later, to the T_s class. Furthermore, T cells may be infected at a rate of k_r by drug-resistant viruses and move to the T_r class after τ time units later. The term $e^{-m\tau}$ is the probability of T_s and T_r cells surviving in the interval τ, where $\frac{1}{m}$ represents the average life of infected CD4+ T cells before they become actively productive. The terms $1-n_{rt}^s$ and $1-n_{rt}^r$ represent the proportion of T_s and T_r cells eliminated by reverse transcriptase inhibitors (RTIs). The infected CD4+ T cells and the virus particles die at rates δ and c, respectively. The V_s and V_r particles are produced by the infected CD4+ T cell populations with bursting sizes of drug-sensitive strain (N_s) and of drug-resistant strain (N_r). Throughout the infection, a proportion s ($0<s<1$) of T_s cells can become T_r cells. The proportion of virus particles that are not eliminated by PIs is represented by $1-n_p^s$ and $1-n_p^r$, where n_p^s is the efficacy of PIs for wild type strain and n_p^r is the efficacy of PIs for mutants.

According to (Pinto and Carvalho, 2015b), on stochastic approach for model (1a)-(1e), it is believed that the death rates d, δ and c can be substituted by random parameters, more specifically, $d+\sigma_1\dot{B}_1$, $\delta+\sigma_1\dot{B}_1$ and $c+\sigma_2\dot{B}_2$, respectively, where $B_1(t)$ and $B_2(t)$ are independent standard wiener processes. In the next sections, such wiener processes will be used as exogenous variables into the learning algorithms.

2.1 HIV Model by Including PI

By assuming that the constant recruitment number of new uninfected cells T and that the rate of infection of CD4+ T cells k_s by a free virus has been saturated probably because of overcrowding of free virus the model (1a)-(1e) can be rewritten as

$$\dot{h} = G(h) \tag{2}$$

where $h = [T\ T_s\ V_s\ T_r\ V_r]^T \in \mathbb{R}^5$ is the state vector and $G(h) = [G_1(h)\ G_2(h)\ G_3(h)\ G_4(h)\ G_5(h)]^T \in \mathbb{R}^5$ is assumed continuously differentiable on the parameters $(T, T_s, V_s, T_r, V_r, t) \in D_T \times D_{T_s} \times D_{V_s} \times D_{T_r} \times D_{V_r} \times [0,t]$, being $D_T, D_{T_s}, D_{V_s}, D_{T_r}, D_{V_r} \subset \mathbb{R}_+$ open and convex sets, and each $G_i(h)$, for $i = 1,\ldots,5$, represents the right-hand side of (1a)-(1e), respectively.

Now, let $p = (p_1, p_2, p_3, p_4, p_5)$ be an equilibrium point of the nonlinear system (1a)-(1e) and suppose that the functions G_i, for $i = 1,\ldots,5$, are continuously differentiable. Expanding the right-hand side of (2) into its Taylor series on the point p yields

$$\dot{h} = M(p)h + \Delta(p)u + N(p) \tag{3}$$

where $M(p)$ is the Jacobian matrix at equilibrium point p, defined by $M(p) = [\partial G(h)/\partial h_i]$ (for $i = 1,\ldots,5$), $u \in \mathbb{R}^2$ is the antiviral therapy defined by $u = [n_p^s \quad n_p^r]^T$, $\Delta(p)$ is the input matrix with full rank, defined by $\Delta(p) = [\partial G(h)/\partial u_i]$ (for $i = 1,2$) and $N(p) = N(h)|_{h=p} \in \mathbb{R}^5$ represents the higher-order terms of expansion. In the antiviral therapy,

$$\frac{dT}{dt} = \lambda - dT(t) - K_s(1-n_{rt}^s)V_s(t)T(t) - k_r(1-n_{rt}^r)V_r(t)T(t) \tag{1a}$$
$$\frac{dT_s}{dt} = (1-s)k_s e^{-m\tau}(1-n_{rt}^s)V_s(t-\tau)T(t-\tau) - \delta T_s(t) \tag{1b}$$
$$\frac{dV_s}{dt} = N_s\delta(1-n_p^s)T_s(t) - cV_s(t) \tag{1c}$$
$$\frac{dT_r}{dt} = sk_s e^{-m\tau}(1-n_{rt}^s)V_s(t-\tau)T(t-\tau) + k_r e^{-m\tau}(1-n_{rt}^r)V_r(t-\tau)T(t-\tau) - \delta T_r(t) \tag{1d}$$
$$\frac{dV_r}{dt} = N_r\delta(1-n_p^r)T_r(t) - cV_r(t) \tag{1e}$$

Figure 1.

the efficacy of PI, n_p^s and n_p^r, are considered bounded Lebesgue integrable functions, i.e.,

$$\sum_{j=1}^{\infty}\int n_{p,j}^s < \infty \quad \text{and} \quad \sum_{j=1}^{\infty}\int n_{p,j}^r < \infty.$$

If, for instance, $n_p^s = 1$, the blockage is 100% effective. On the other hand, if $n_p^s = 0$, there is no blockage.

The term $N(h)|_{h=p}$ is associated with an unmodeled dynamic and it has an important role to measure the performance of the alternative model based on neural networks, which will be shown in the next sections.

2.2 Analysis on Inner Close-loop

In the work reported here, it will be assumed that there exists an initial quantity of uninfected CD4+ T cells, $T^* > 0$, such that the antiviral therapy guarantees a number of uninfected CD4+ T cells close to T^*. From (3), if $T^* > \delta_v(t) > 0$, being $\delta_v(t)$ a known 1-diffeomorphism, and h is assumed to be the control input of the inner close-loop system associated to (3) then the error converges exponentially to small ball in $\mathcal{W}$ containing the origin whose radius will be adjusted by any known constant. The following lemma explains this idea:

Lemma 1. *Let e be the error associated with inner close-loop system defined by $e = \Pi_1(h)$, where $\Pi_1(h) \in \mathbb{R}^5$ is a known matrix. If $T^* > \delta_v(t) > 0$ and $h = \rho$, then e converges exponentially to a small ball containing the origin whose radius can be adjusted by a k-th known constant $M_k^* < 0$, for $k = 1,\ldots,5$, $\forall t \geq 0$, being $\rho = [T^* \cdots]^T = \Pi_2(e) \in \mathbb{R}^5$ such that $\dot{\Pi}_2(e) < M$ and*

$$M = [M_1^*, M_2^*, \ldots, M_5^*]^T$$

being $M_k^* < 0$ a known constant.

Proof: Let the Lyapunov function

$$V = \frac{1}{2}\left(\sum_{i=2}^{5} e_i^2\right) = \frac{1}{2}\left(\sum_{i=2}^{5}\left[\Pi_1^i(h)\right]^2\right),$$

differentiating it along the close-loop defined by $e = \Pi_1(h)$, $h = \rho$ and $\rho = \Pi_2(e)$ one obtains

$$\begin{aligned}
\dot{V} &= \sum_{i=2}^{5}\left(\sum_{k=1}^{5}\frac{\partial\Pi_1^i}{\partial h_k}\dot{h}_k\right)\Pi_1^i(h) \\
&= \sum_{i=2}^{5}\left(\sum_{k=1}^{5}\frac{\partial\Pi_1^i}{\partial h_k}\dot{\Pi}_2^k(e)\right)\Pi_1^i(h) \\
&= \sum_{i=2}^{5}\left(\sum_{k=2}^{5}\frac{\partial\Pi_1^i}{\partial h_k}\dot{\Pi}_2^k(e)\Pi_1^i(h) + \frac{\partial\Pi_1^i}{\partial h_k}\dot{\delta}_v\Pi_1^i(h)\right) \\
&< \sum_{i=2}^{5}\left(\sum_{k=2}^{5}\frac{\partial\Pi_1^i}{\partial h_k}\dot{\Pi}_2^k(e)\Pi_1^i(h)\right) \\
&= -\sum_{i=2}^{5}\left(\sum_{k=2}^{5}\frac{\partial\Pi_1^i}{\partial h_k}M_k^*\Pi_1^i(h)\right) < 0.
\end{aligned}$$

where M_k^* is the k-th element of M, $\Pi_1^i(h)$ and $\Pi_2^k(e)$ are the i-th and k-th elements of $\Pi_1(h)$ and $\Pi_2(e)$, respectively.

Noting $T^* \geq \delta_v(t) > 0$ (i.e., $\dot{\delta}_v(t) < 0$) it can be seen that V exponentially converges to a small ball containing the origin. The convergence rate is at least defined by $\Pi_1(h)$. The radius of the ball can be adjusted by a constant M_k^*, for $k = 1,\ldots,5$. Therefore, e converges exponentially to the small ball containing the origin, and the radius of the ball can also be adjusted by any constant M_k^*. This ends the proof □.

So, the control problem considered in this paper is to find an improved version of a global feedback controller that represents the antiviral therapy such that the inner close-loop of system (3) guarantees that the number of uninfected CD4+ T cells remains close to T^*. To this end, in the next sections, it will be used neural networks (NNs) to adjust this optimal global feedback law.

3 NARMA-L2-BASED THERAPY

The optimal control problem will an objective functional, a set of state variables h and a set of control variables u in time t, $0 \leq t \leq t_f$ such that there is a generic global feedback control $u = \lambda_1(h, h_r)$ where h_r is the target response, $\lambda_1 : \mathbb{R}^5 \times \mathbb{R}^5 \rightarrow \mathbb{R}^2$ is a known nonlinear function such that there is an optimal control law $u \triangleq \lambda_1^*$ that satisfies $J(\lambda^*(h, h_r)) = \max_{\lambda_1^*(h,h_r)\in\mathbb{U}} J(u)$ being $\mathbb{U} \subseteq \mathbb{R}^2$ and

$$J(u) = \int_0^{t_f} \left\{ T(t) - u^T R u \right\} dt$$

for $t_f > 0$ and any symmetric definite positive matrix R. Our goal is to seek to maximize the objective functional $J(u)$ by increasing the population of the uninfected CD4+ T cells, reducing viral load, and minimizing the cost treatment. To this end, the nonlinear model (1a)-(1e) will be designed by using a robust adaptive neural network (NN) with the aid of NARMA-L2 approach and its learning ability. In this way, the maximization problem will be associated with the nonlinear programming problem restricted to the learning rule of NNs.

Let $\tilde{h} = h - \rho$ be the error between the state vector h and the state vector defined by Lemma 1 on the close-loop system. Thus, for $\tilde{h}$ one obtains

$$\dot{\tilde{h}} + M(p)\tilde{h} = \Delta(p)u - \Gamma(p, \rho) \tag{4}$$

where

$$\Gamma(p, \rho) \triangleq \dot{\rho} + M(p)\rho + N(p).$$

Noting the learning ability of NN, the term $\Gamma(p, h)$ can be approximated on-line by using NNs whose activation function is a sigmoid. Let $\sigma(p, h) \in \mathbb{R}^{m^*}$ be a vector of continuous sigmoid functions, according to the approximation property of neural networks in (Cybenko, 1989), if $\Gamma(p, \rho)$ is a continuous function of p and ρ then

$$\Gamma(p, \rho) = \psi^T \sigma(p, \rho) + \varepsilon_n(p, \rho), \tag{5}$$

where $\psi \triangleq \{\psi_{ij}\} \in \mathbb{R}^{m^* \times 3}$ is an unknown optimal constant weight vector, previously calculated, and defined by

$$\psi = \arg \min_{\varsigma \in \mathbb{R}^{m^* \times 3}} \left\{ \max_{(p,\rho)\in\Omega} \| \Gamma(p, \rho) - \varsigma^T \sigma(p, \rho) \| \right\}$$

where Ω is a compact set and ε_n is the error associated with reconstruction of the optimal weight vector. The approximations results for NN indicate that if m^* is sufficiently large then the reconstruction error can be arbitrarily small on Ω. In this way, it will assumed that $\|\varepsilon_n(p, \rho)\| \leq \varphi^*$, for $\forall (p, \rho) \in \Omega$, where φ^* is an unknown constant.

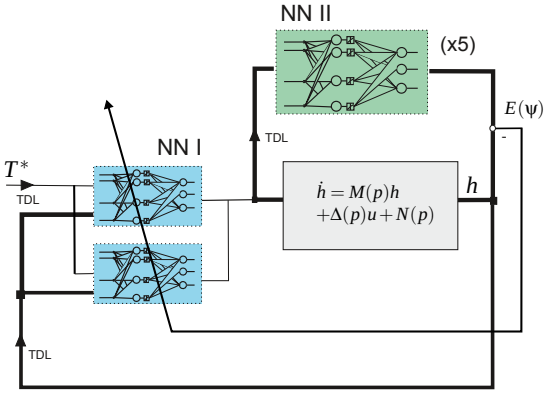

Figure 2: Closed-loop system by using NARMA-L2 approach in antiviral therapy.

Without loss of generality, by using (5), the equation (4) can be rewritten as

$$\dot{\tilde{h}} + M(p)\tilde{h} = \Delta(p)u - \psi^T \sigma(p, \rho) - \varepsilon_n(p, \rho) \quad \text{s.t. } \|\varepsilon_n(p, \rho)\| \leq \varphi^*, \tag{6}$$

where ψ and φ^* must be estimated in order to guarantee the robustness of the model (4). Thus, let $\hat{\psi}$ and $\hat{\varphi}^*$ be the estimates of ψ and φ^*, respectively. With aid of Lemma 1 the following theorem is obtained:

Theorem 1. *Assuming $T^* > \delta_v(t) > 0$, the global feedback law*

$$u = \Delta^{-1}(p) \left[-K_p \tilde{h} + \hat{\psi}^T \sigma - \hat{\varphi}^* T(\tilde{h}) \right], \tag{7}$$

guarantee that e, $\tilde{h}$, $(\hat{\psi} - \psi)$ and $(\hat{\varphi}^* - \varphi^*)$ converge to a ball containing the origin whose radius can be made as small as possible by selecting a suitable value for γ_1, γ_2, δ_1, δ_2, ψ_0, and φ_0, where

$$\dot{\hat{\psi}} = -\gamma_1 \sigma \tilde{h}^T - \delta_1(\hat{\psi} - \psi_0) \tag{8}$$

$$\dot{\hat{\varphi}}^* = \gamma_2 \tilde{h}^T T(\tilde{h}) - \delta_2(\hat{\varphi}^* - \varphi_0) \tag{9}$$

are update laws, K_p is a positive definite constant matrix, $T(\tilde{h})$ is a known sigmoid function and γ_i, δ_i (for $i = 1, 2$) are positive constants.

Proof: Let the Lyapunov function

$$V = \frac{1}{2}\left(\sum_{i=2}^{5} e_i^2 \right) + \frac{1}{2}\tilde{h}^T \tilde{h} + \frac{\gamma_1^{-1}}{2}(\hat{\psi} - \psi)^T (\hat{\psi} - \psi) + \frac{\gamma_2^{-1}}{2}(\hat{\varphi}^* - \varphi^*)^2,$$

and differentiating it along of the closed-loop represented by Lemma 1 and (7), one obtains

$$\dot{V} = \sum_{i=2}^{5} \sum_{k=1}^{5} \frac{\partial \Pi_1^i}{\partial h_k} \dot{h}_k + \tilde{h}\dot{\tilde{h}} + \gamma_1^{-1}(\hat{\psi} - \psi)^T \dot{\hat{\psi}} + \gamma_2^{-1}(\hat{\varphi}^* - \varphi^*)^T \dot{\hat{\varphi}}^*$$

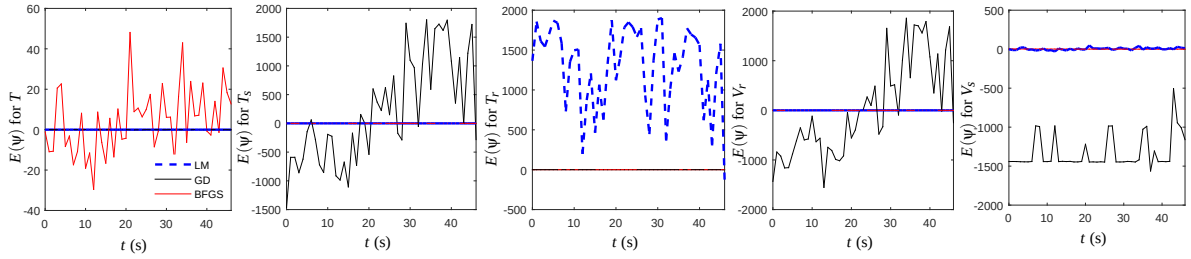

Figure 3: Training error for $B_1(t)$, $E(\psi)$, of NN II by using three algorithms: Levenberg-Marquardt (LM), gradient descent (GD), Broyden-Fletcher-Goldfarb-Shanno (BFGS).

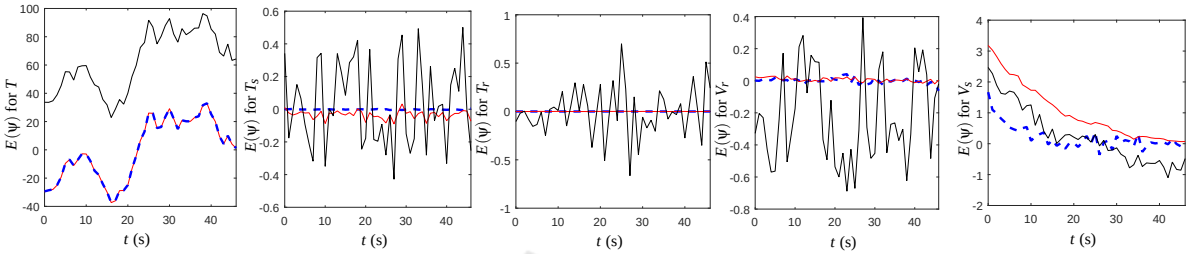

Figure 4: Training error for $B_2(t)$, $E(\psi)$, of NN II by using three algorithms: Levenberg-Marquardt (LM), gradient descent (GD), Broyden-Fletcher-Goldfarb-Shanno (BFGS).

or, by using (7) into (4),

$$\dot{V} = \sum_{i=2}^{5}\sum_{k=1}^{5}\frac{\partial \Pi_1^i}{\partial h_k}\dot{h}_k + \tilde{h}\left(-K_p\tilde{h} + \hat{\psi}^T\sigma - \hat{\varphi}^* T(\tilde{h}) - \Gamma(p,\rho) + M(p)\tilde{h}\right) + \gamma_1^{-1}(\hat{\psi}-\psi)^T\dot{\hat{\psi}} + \gamma_2^{-1}(\hat{\varphi}^*-\varphi^*)^T\dot{\hat{\varphi}}^* < -c_1 V + c_2,$$

where c_1 is a positive constant which depends on K_p, γ_1, γ_2, δ_1, δ_2, and

$$c_2 = \frac{\gamma_1^{-1}\delta_1}{2}(\hat{\psi}-\psi_0)^T(\hat{\psi}-\psi_0) + \frac{\gamma_2^{-1}\delta_2}{2}(\hat{\varphi}^*-\varphi_0)^2 + 2b^*,$$

being b^* a constant which satisfies $b^* = e^{-(b^*+1)}$ [i.e., $b^* = 0.2785$]. Without loss of generality, it can be noted that V converges exponentially to a small ball containing the origin and the radius of the ball depends on γ_1, γ_2, r, δ_1, δ_2, ψ_0 and φ_0. Therefore, e, $\tilde{h}$, $(\hat{\psi}-\psi)$ and $(\hat{\varphi}^*-\varphi^*)$ will converge exponentially to the small ball of the origin. This ends the proof □.

The NN-based controller (7) uses the update laws (8)-(9) to approximate un-modeled dynamics. In this way, the laws (8)-(9) represent the learning ability of the NN responsible to optimize the synaptic weights ($\hat{\psi}^T\sigma$) that indirectly will ensure that the reconstruction and tracking errors converge toward a small ball containing the origin in the sets Ω and $\mathcal{W}$. Therefore, in the work reported here, the global feedback law in

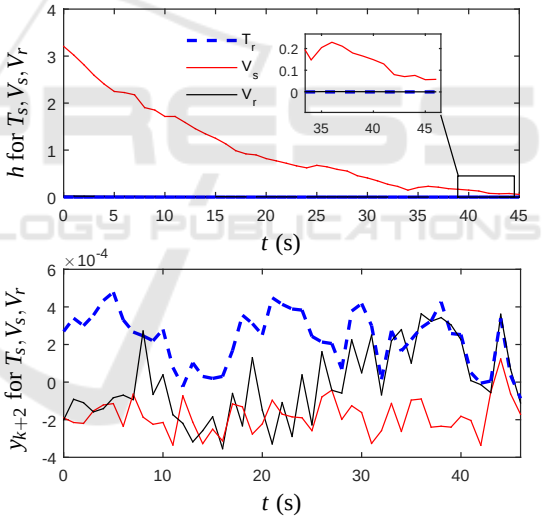

Figure 5: Validation of NARMA-L2 model by comparing (y) of NN II with output (h) of model defined by (3), with exogenous brownian noise $B_1(t)$.

Theorem 1 will be based on an alternative learning rule that combines the laws (8)-(9) with an already existing algorithm for dynamic backpropagation.

3.1 NARMA-L2 Training Algorithm

The NARMA-L2 scheme to design the antiviral therapy u is based on two NNs, the NN II is composed of five NNs and it will be used to model the system (3). The NN I will be used as antiviral therapy by

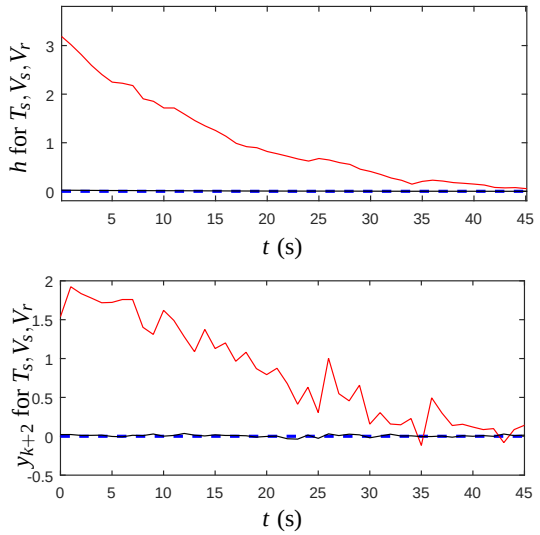

Figure 6: Validation of NARMA-L2 model by comparing (y) of NN II with output (h) of model defined by (3), with exogenous brownian noise $B_2(t)$.

means of the global feedback law in Theorem 1 (see Fig. 2). The input T^* represents a reference for $T(t)$, and with this last one the main objective of the proposal reported here is to find an antiviral therapy that guarantees a better decreasing of drug-sensitive infectious virus V_s, drug-resistant infectious virus V_r and drug-resistant infected CD4+ T cells T_r.

In order to verify the effectiveness of the NARMA-L2, the NN II is trained by using three algorithms: Levenberg-Marquardt, Gradient Descent, and BFGS[1]. All these, based on the error backpropagation principle for off-line mode. It will be chosen the algorithm more suitable to model each state variable of the h vector in order to guarantee a better performance between the system and the controller represented by NN I. On the other hand, the NN I is trained by using only dynamic backpropagation and to this end, the BFGS approach is modified according to feedback law in Theorem 1.

Since the inputs associated with PIs were assumed to be mutually decoupled, the NARMA-L2 model was designed individually for each state variable. A standard NARMA-L2 model can be defined by

$$y_{k+2} = \bar{f}_0\,[\mathrm{TDL}(y_k,n), \mathrm{TDL}(u_k,n)] + \bar{g}_0[\mathrm{TDL}(y_k,n), \mathrm{TDL}(u_k,n)]u_k,$$

where $\mathrm{TDL}(p_k,n) \triangleq p_k,\ldots,p_{k-n+1}$ represents a tapped delay line with n regressors (see TDL blocks in Fig. 2); $\bar{f}_0 \triangleq \bar{F}$ and $\bar{g}_0 \triangleq \partial\bar{F}/\partial u_k$ are evaluated around $\mathrm{TDL}(y_k,n)$, $\mathrm{TDL}(u_k,n)$ (with $u_k = 0$) for any nonlinear function $\bar{F}(\cdot)$ (Narendra and Parthasarathy, 1990).

[1]Broyden-Fletcher-Goldfarb-Shanno.

To guarantee the laws $\hat{\psi}$ and $\hat{\varphi}^*$, a segmented training based on BFGS algorithm will be used to compute the synaptic weights of NN I from a modeling error between the system (3) and NN II. Now, the learning rule proposed here can be described by using $\|\varepsilon_n(p,\rho)\| \triangleq \|\varepsilon_n(\psi)\|$ as goal function according to next steps:

s 1. Init $B_0 = I$, $\|\varepsilon_n(\psi_0)\| = n_e$ and $\hat{\varphi}^* = n_v$,

where B_0 is the initial condition for a Hessian matrix of $\varepsilon_n(\psi)$, $n_e \geq 100$ and $n_v < 0.001$. From (9), if $\hat{\varphi}^* = n_v$ then

$$\hat{\varphi}^* = \frac{\gamma_2}{\delta_2}\tilde{h}_k^T T(\tilde{h}) + \frac{\varphi_0}{\delta_2},$$

thus the BFGS algorithm becomes as

s 2. While $\|\varepsilon_n(\psi_k)\| > \frac{\gamma_2}{\delta_2}\tilde{h}_k^T T(\tilde{h}) + \frac{\varphi_0}{\delta_2}$ do

s 3. $\Delta\psi_k = -\alpha_k B_k^{-1}\nabla\varepsilon_n(\psi_k)$;

s 4. Compute $\nabla\varepsilon_n(\psi_{k+1})$;

where $\nabla\varepsilon_n(\psi_k)$ represents the gradient descent as first-order iterative optimization tool. So,

s 5. $E_k(\psi) = \nabla\varepsilon_n(\psi_{k+1}) - \nabla\varepsilon_n(\psi_k)$;

s 6. $\beta_k = I - E_k\Delta\psi_k^T/E_k^T\Delta\psi_k$;

Next, from step (s3.) and (8), by using the pseudoinverse of $\sigma(p,h)$, $\sigma^+(p,h)$ yields

s 7. $\tilde{h}_k^T = -\frac{\sigma^+}{\gamma_1}\left[\delta_1(\psi_k - \psi_0) - \alpha_k B_k^{-1}\nabla\varepsilon_n(\psi_k)\right]$;

s 8. $B_{k+1}^{-1} = \beta_k B_k^{-1}\beta_k + \Delta\psi_k^T\Delta\psi_k/E_k^T\Delta\psi_k$;

s 9. $\psi_{k+1} = \psi_k + \Delta\psi_k$;

s 10. Compute $\|\varepsilon_n(\psi_k)\|$ and go to step (s2.);

It can be seen that the term $-K_p\tilde{h}$ is used to make h converge to ρ while the term $-\hat{\varphi}^* T(\tilde{h})$ is used to compensate the reconstruction error $\|\varepsilon_n(\psi_k)\|$ of NN I. The term $\hat{\psi}^T\sigma$ in (7) uses a dynamic learning rule based on laws (8)-(9) and BFGS algorithm to adjust the synaptic weights of NN I and to enhance the robustness of the un-modeled dynamics $N(p)$.

4 SIMULATION

The simulation tests were done by using the nonlinear NARMA-L2-based controller with a two-layer NN in order to implement (7) (in Theorem 1). All this, when the antiviral therapy is applied with initial uninfected CD4+ T cells.

The NARMA-L2 model was set with $n = 3$ regressors (in TDL blocks), 20 iterations at BFGS algorithm and 30 hidden neurons at the middle layer of NNI. In previous simulation tests, it was noted that when the number of hidden neurons is less than

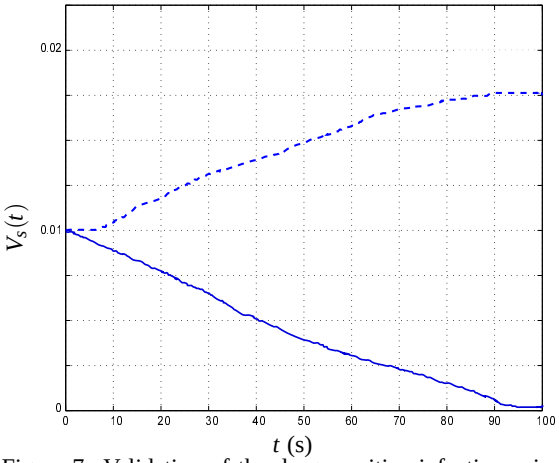

Figure 7: Validation of the drug-sensitive infectious virus V_s based on the global feedback law (7), in Theorem 1, by comparing the behavior of each variable with control u (solid line) and without control u (dash line).

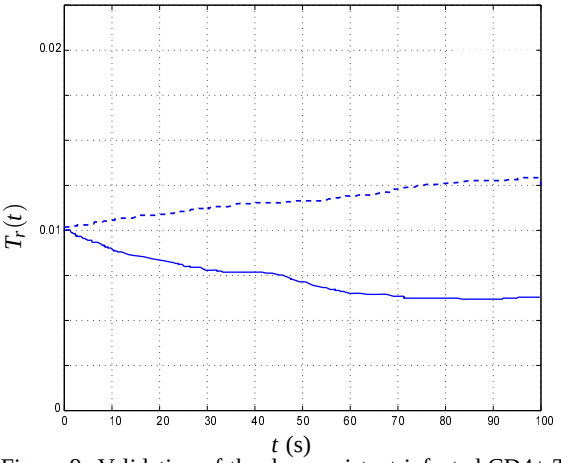

Figure 9: Validation of the drug-resistant infected CD4+ T cells T_r based on the global feedback law (7), in Theorem 1, by comparing the behavior of each variable with control u (solid line) and without control u (dash line).

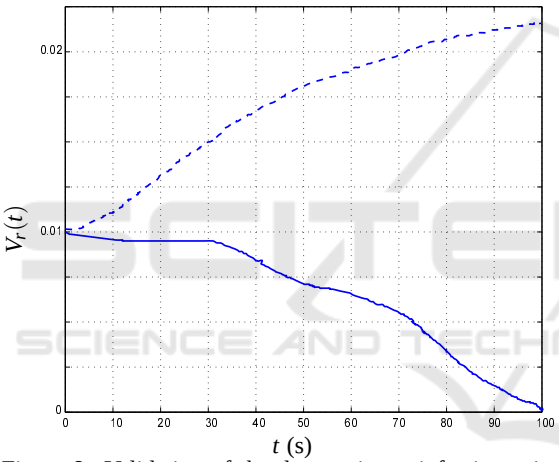

Figure 8: Validation of the drug-resistant infectious virus V_r based on the global feedback law (7), in Theorem 1, by comparing the behavior of each variable with control u (solid line) and without control u (dash line).

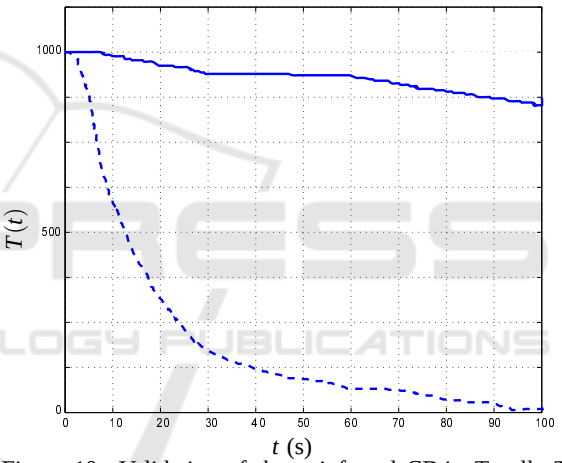

Figure 10: Validation of the uninfected CD4+ T cells T based on the global feedback law (7), in Theorem 1, by comparing the behavior of each variable with control u (solid line) and without control u (dash line).

30 the weights were adjusted to values that were not enough robust. In order to train the NNI, it was considered that the antiviral therapy u represents 10% at PIs efficacy, i.e., $n_p^s = 0.1$ and $n_p^r = 0.1$ for $\forall\, t > 0$. Complementary, since the signals $B_i(t)$, for $i = 1,2$, have independent increments for $\forall t > 0$, the future increments of the death rates are independent of the past values. So, such signals were set as pseudo-random binary signals (PRBS) with maxim amplitude 1 and samples between 10 and 100 ms. The parameters of model (1a)-(1e) were set as in (Wang et al., 2014; Pinto and Carvalho, 2015b): $\lambda = 100$; $d = 0.1$; $m = 0.01$; $k_s = 2.4 \times 10^{-6}$; $k_r = 2 \times 10^{-6}$; $s = 3 \times 10^{-5}$; $\delta = 1$; $N_s = 4800$; $N_r = 4000$; $c = 23$; $\tau = 1$; $n_{rt}^s = 0.4$; $n_{rt}^r = 0.2$; $\sigma_1 = \sigma_2 = 0.1$; with initial conditions $T(0) = T^* = 1000$, $T_s(0) = 1$ and $T_r(0) = V_s(0) = V_r(0) = 0.01$. In order to set the controller, the parameters of nonlinear law (7) were set as $K_p = \gamma_1 = \gamma_2 = k_2 = k_3 = 1$, $\delta_1 = \delta_2 = 0.01$ and $T(\tilde{h}) = \tanh(\tilde{h})$.

In Fig. 5 and Fig. 6 can be seen the behavior of variables V_s, V_r and T_r modeled by NN II on NARMA-L2 approach by considering $B_i(t)$, for $i = 1,2$, as Brownian signals. Complementarily, in Fig. 3 and Fig. 4 can be seen the adjustment error of five signals associated with the NN II. For each NN was used three algorithms based on the error backpropagation principle. It can be noted that the BFGS algorithm has a better approximation than Levenberg-Marquardt (LM) and Gradient Descent (GD) approaches, except for the behavior of T. For this reason, it will be used the BFGS approach to model the responses of

the variables T_s, T_r, V_r and V_s, while the Levenberg-Marquardt algorithm will be used to model the response of T.

4.1 Validation of the Antiviral Therapy

Since the main objective is to reduce drug-resistant infected CD4+ T cells in order to guarantee T close to T^*, then the global feedback law (7) will use the ability of NNs to approximate nonlinear and un-modeled behaviors (i.e., $N(p)$) in order to improve the performance of the antiviral therapy. To this end, the signals B_i, for $i = 1,2$, will be set as exogenous inputs to the closed-loop of (2) and the input u will be represented by the outputs of the NARMA-L2-based controller.

By comparing the Fig. 7 and Fig. 8 can be seen that the drug-sensitive infectious virus (V_s) decreases faster than the drug-resistant infectious virus (V_r) when the antiviral therapy u is applied during 100 days. It can be noted that the antiviral therapy guarantees a decreasing of the contagion effect of the HIV, see that T_r decreases significantly on time domain instead of the case when the antiviral therapy is not used (see dash lines in Fig. 8).

Although the behavior of T was model by using the LM approach in NN II, Fig. 10 shows that the control law (7) guarantees that the concentration of uninfected CD4+T cells decreasing close to a neighborhood of T^* ($= T(0) = 1000$). Without treatments (without control u), the number of uninfected cells decreases drastically.

5 FINAL REMARKS

The controller in Theorem 1 differs from other contributions mainly because the optimization approach used to maximize any objective functional $J(u)$ is based on a nonlinear programming rule. Nevertheless, here was chosen the use of NARMA-L2 approach together with nonlinear programming for training NN because it improves the performance of the model and the controller used as antiviral therapy, both reducing viral load, and minimizing the cost treatment. Here, it was assumed that un-modeled information could be related to the learning ability of the NNs as well as it was proposed an alternative learning technique based on the dynamic of the back-propagation approach. In this way, the robustness of the NN-based controller (7) was improved by including the nonlinear term $-\hat{\varphi}^* T(\tilde{h})$ into the nonlinear control law (see (7) in Theorem 1 and step (s2.)) such that the convergence radius of the tracking error can be regulated by known parameters. It is hoped that in future works the NN-based controller can be designed by using three or more layers to improve the performance of the term $\hat{\psi}^T \sigma(q^*, h)$ and the compensation of the un-modeled dynamics $N(p)$.

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