Hepatitis C Viral Load Control Applying Hamilton Jacobi And Sliding Mode Techniques

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Abstract. Hepatitis C is one of the illness which has affected a great deal of people all over the world, it is suffered approximately by the world population's three percent and it has become an important social problem that has shown to be in continuous growing. For that strong reason it is presented a control description based on Hamilton-Jacobi Technique (HJT) and Sliding Mode Approach (SMA) working jointly with a nonlinear observer (NO), carried out with Differential Neural Networks (DNN) and Sliding Mode Approach, the one which has proven to be useful in real medical procedures to expense of the mathematical model that describes the Hepatitis C Virus (HCV) dynamics is similar to the real Interferon Alpha 2b (IFN $\alpha - 2b$) patients response. This Hamilton Jacobi and Sliding Mode Control (HJSMC) gives us the exact dosage that ought to be given to a patient with the purpose of maintaining controlled, in very low levels, the viral load.

1. Introduction

Mathematics, control techniques and computational intelligence have been used in the study of a great deal of process showing to be quite fruitful when having good results, specially in biological sciences because computational and mathematical models are helping biological scientist to know many aspects of the complex realm of living matter [2], [3]. In particular cases, these mathematical principles have been used to understand the life cycle of chronic viral infections development [4], [5] and the behavior under several treatments of Hepatitis C infection [2], [6]. The simulation results demonstrate how the present techniques are allowed to create software to solve emerging problems of therapy optimization, however, many of these models do not consider all possible systems variations and they strongly depend on the input function. Hepatitis C Virus (HCV) has infected about 170 million of people around the world [7], and this sickness could provoke serious injuries in hepatic tissue like cirrhosis, which has a slow and progressive development and the ways of contracting this illness are: sharing intravenous devices, sexual contact, using the parenteral pathway, etc. [8]. Despite the important scientific and technological advances in medicine, there in no cure or vaccine the one that control the virus or keep it contained until now. The main method proven until now uses some pharmacological products as Lamivudine, Adefovir, Ribavirine and the Interferon alpha presented as Interferon alpha - 2a and Interferon alpha 2b (IFN $\alpha - 2b$) whose many studies has demonstrated that is the best option to treat Hepatitis C [9]. There are some processes that have gain scientific groups' attention like chemical and biological ones (i.e. hepatitis C virus dynamics) because exists several nonlinearities in they structure and almost always they are

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difficult to model since the resulting models are often heavily dependent on the number of states and the parameter set. in addition to that they are very expensive in computational time. Nonlinear black box models may overcome this problem because this method does not use the internal process of the model; they just need the input-output data pair. Artificial Neural Networks (ANN) are computational tools that have obtained considerable attention in biological studies as good as academic research or industrial applications. Their universal approximation abilities and the access to a wide range of software tools qualify the ANN for the building of nonlinear dynamics black-box models which can be applied as prediction models or state estimator devices. Two types of ANN are known: static, they are those that use the so-called back-propagation technique (for example) [10], [11] and dynamic neural networks [12], [13]. The second approach, exploiting the feedback properties of the applied DNN, allows avoiding many problems related to global extremum search converting the updating (training) process to an appropriate feedback design. As it has already been seen in [14] to carry out a control with DNN trajectory tracking, it is necessary to identify the estimated states by a DNN identifier to guarantee the convergence of the error, what implies extra computational spending. With Hamilton Jacobi's Algorithm for trajectory tracking it is possible to simplify this spending since this control algorithm uses the estimated states of a DNN. The system's behavior of prospective control is to displace the states such that it is possible to make a track of a sign generated by some reference model. The Sliding Mode Approach (SMA) allows powerful advantages than other identification and control techniques like good transient behavior, global exponential stability with small estimate error, capability to reject no modeled disturbances, insensitivity to plant nonlinearity or parameter variations and remarkable stability and performance robustness [15], [16]. Such in [17] the SMA approach is used to obtain the algebraic (non differential) weight-learning procedure for on-line identification of a nonlinear plant with completely available states. DNN observers containing sign-term are also considered in [17] but in that approach, the weight adjustment is governed by a "standard" Ordinary Differential Equation (ODE) with time varying parameters. No relay terms are used within the learning procedure.

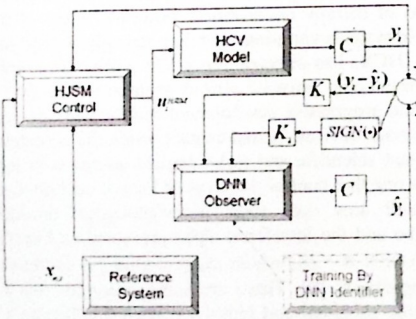

Fig. 1. Block diagram of the complex process.

2. Methodology

The corresponding methodology was carried out in three procedures (figure 1): the first one is the training process with a DNN identifier, then the estimate procedure using a DNN observer and finally the proper control via Hamilton Jacobi and SMA.

2.1 Mathematical Model of the Hepatitis C Viral Load Dynamics

The mathematical model that describes the dynamics of the HCV and their changes when IFN $\alpha - 2b$ is applied into patient is:

$$\dot{T}_t = s - dT_t - (1-\eta)\beta V_t T_t; \quad \dot{I}_t = (1-\eta)\beta V_t T_t - \delta I_t; \quad \dot{V}_t = (1-u_t\varepsilon)pI_t - cV_t \tag{1}$$

where $\dot{T}_t$ [mIU / mL] describes changes in the number of target cells $\dot{I}_t$ [mIU / mL] represents variations in the number of productively infected cells and $\dot{V}_t$ [mIU / mL] shows how viral load changes in time when IFN $\alpha - 2b$ is applied as an input function u_t. The target cell's production is given by the constant rate s $(1000[mL\,dia]^{-1})$ and these cells die with a constant rate d $(0.014[mL\,dia]^{-1})$, η (0.001) is the possible effect of the IFN $\alpha - 2b$ and the immunological system to contain the *novo* infection given by β $(3\times10^{-7}[mL\,dia]^{-1})$ which is the constant rate associated with novo infection entrance, once the target cells become productively infected cells, they die by the constant rate δ $(0.14[mL\,dia]^{-1})$, ε (0.8) is the possible effect of the IFN to break viral production, p $(100[mL\,dia]^{-1})$ is the constant rate of new virus reproduction and c $(6.2[mL\,dia]^{-1})$ is the viral clearances constant rate. This analysis searches the major initial effect of IFN $\alpha - 2b$ is to break viral production. This mathematical model plays an important roll since the whole work carried out in this paper supposes that the model resembles each other to the patients' real response and this can be used for the corresponding computer simulations.

HCV model (1) could be generalized, in a mathematical sense, as (2).

$$\dot{x}_t = f(x_t, u_t, t) + \xi_{1,t}; \qquad y_t = Cx_t + \xi_{2,t} \tag{2}$$

where $x_t \in \Re^n$ is the state vector, $y_t \in \Re^p$ is a linear combination of the state elements that it is commonly assumed as the output system, $u_t \in \Re^m$ is the external supply of IFN $\alpha - 2b$, $C \in \Re^{p\times n}$ selected as $C = [0 \;\; 0 \;\; 1]$ since the viral load is the only measurable variable using clinical tests like PCR probe [5]. The vectors $\xi_{1,t}$ and $\xi_{2,t}$ represent the state and output bounded (immeasurable) disturbances, i.e., $\|\xi_{j,t}\|^2_{\Lambda_{\xi_j}} \le \Upsilon_j$, $\Lambda_{\xi_j} > 0$, $j = 1, 2$ that could be associated with the different medical responses of each patient and the experimental errors in the PCR probe [18]. Hereinafter it is supposed that the class of nonlinear functions in (2) satisfies all the restrictions associated with the existence of the differential equation solution. Notice

that the nonlinear system (2) could always be described as: $\dot{x}_t = f_0(x_t, u_t, t\,|\Theta) + \tilde{f}_t$ and $\tilde{f}_t := f(x_t, u_t, t) - f_0(x_t, u_t, t\,|\Theta) + \xi_1$, where $f_0(x_t, u_t, t\,|\Theta)$ is is known as *"nominal dynamics"* which can be selected according to the DNN theoretical results [17] and $\tilde{f}_t$ is a vector called *"no modelled dynamics"* that should be minimized during the common training process. According to DNN approach, the nominal dynamics are assumed as:

$$f_0(x_t, u_t, t \mid \Theta) = A^{(0)}x + W_1^{(0)}\sigma(x) + W_2^{(0)}\varphi(x)u$$

$$\Theta := A^{(0)}, W_1^{(0)}, W_2^{(0)} \in \Re^{n\times n}$$

$$W_1^{(0)} \in \Re^{n\times l}, \sigma(\cdot) \in \Re^{l\times 1}, \quad W_2^{(0)} \in \Re^{n\times l}, \varphi(\cdot) \in \Re^{l\times m}$$

The activation functions $\sigma(\cdot) := [\sigma_i(\cdot)]_{l\times 1}$ and $\varphi(\cdot) := [\varphi_{ij}(\cdot)]_{l\times m}$ are chosen sigmoidal functions i.e. $\sigma_i^{-1}(x) := a_{\sigma i}^{-1}\left(1 + b_{\sigma i}\exp\left(-\sum_{j=1}^{n} c_{\sigma_{ij}} x_j\right)\right)$ and $\varphi_{ij}^{-1}(x) := a_{\varphi ij}^{-1}\left(1 + b_{\varphi ij}\exp\left(-\sum_{j=1}^{n} c_{\varphi_{ij}} x_j\right)\right)$. The admissible control set for u_t is supposed to be described as a state estimate feedback $U^{adm} := \left\{u = u(\hat{x}) : \|u\|_{\Lambda_u}^2 \le v_0 + v_1\|\hat{x}\|_{\Lambda_x}^2\right\}$ where $\hat{x}$ is a estimated state and the matrix $\Lambda_u > 0$.

2.2. Procedure 1. Training Process

Let's consider the dynamics of a patient infected with HCV without previous treatment described by (2) where the entire state vector is known by any clinical method. So, a DNN will be applied to derive the best possible approximation to this nonlinear model just by using the input-output data pair. The mathematical description of this kind of DNN is:

$$\dot{\hat{x}}_t = A\hat{x}_t + W_{1,t}\sigma(\hat{x}) + W_{2,t}\varphi(\hat{x})u_t \tag{3}$$

where $\hat{x}_t \in \Re^n$ is the state vector of the DNN $u_t \in \Re^r$ is a measurable bounded control action, $A \in \Re^{n\times n}$ is a Hurwitz matrix, $W_{1,t} \in \Re^{n\times l}$ is the weight matrix for nonlinear state feedback and $W_{2,t} \in \Re^{n\times m}$ is the input weight matrix. The vector field $\sigma(\hat{x}_t): \Re^n \to \Re^l$ is designed to have elements with a monotonically increasing behavior just like sigmoid functions. The function $\varphi(\,)$ is the transformation from $\Re^r$ to $\Re^{n\times m}$ which is constructed by sigmoid activation functions in each element. The input function $u(\,)$ is assumed to be bounded as $\|u_t\|^2 \le \bar{u}$. The designed identifier requires the next technical fact: There

exists a positive defined matrix Q such that the Ricatti equation (4) has a positive solution $P = P^T > 0$.

$$A^T P + PA + PRP + Q = 0 \tag{4}$$

Theorem 1. Considering the nonlinear system (2) and a model matching neural network (3) whose weights are adjusted by the following matrix differential equations [17]:

$$\begin{aligned} \dot{W}_{1,t} &= -K_1 P \Delta_t \sigma(\hat{x}_t)^T \\ \dot{W}_{2,t} &= -K_2 P \Delta_t \gamma\left(u_t\right)^T \varphi(\hat{x}_t)^T \\ \Delta_t &:= x_t - \hat{x}_t \end{aligned} \tag{5}$$

where K_1 and K_2 are matrices with positive entries, and $P = P^T > 0$ is the solution of the algebraic Ricatti equation given by (4). Then the weights dynamics are bounded: $W_{1,t} \in L_\infty$ and $W_{2,t} \in L_\infty$ and they converge to their best possible values, i.e. $\lim_{t\to\infty} \dot{W}_{1,t} = 0$, $\lim_{t\to\infty} \dot{W}_{2,t} = 0$. Furthermore, it is possible to conclude that the identification process is asymptotically consistent, i.e., $\lim_{t\to\infty} \Delta_t = 0$.

The main element to construct the convergence proof in this scheme is by constructing a Lyapunov function in order to derive the learning laws. This Lyapunov function (6) was selected as:

$$\begin{aligned} V_t &= \Delta_t^T P \Delta_t + tr\left[\tilde{W}_{1,t}^T K_1^{-1} \tilde{W}_{1,t}\right] + tr\left[\tilde{W}_{2,t}^T K_1^{-1} \tilde{W}_{2,t}\right] \\ \tilde{W}_{j,t} &= W_{j,t} - W_{j,0}, \quad j = 1, n \end{aligned} \tag{6}$$

The training process was carried out just one time using the available data for a sick patient. This procedure generates the final values of the weights matrixes and allows the correct selection of the free parameter of the differential neural network as observer.

2.3. Procedure 2. Estimate Process

The estimate process gives us the necessary information required for controlling the HCV. The importance here is to create a system that responds the nearest possible to a real patient, considering different patients response to IFN $\alpha - 2b$ supply The nonlinear system representing the HCV dynamics is described by (2). Let's define a DNN observer as follows:

$$\begin{aligned} \frac{d}{dt}\hat{x}_t &= A^{(0)}\hat{x}_t + W_{1,t}\sigma(\hat{x}_t) + W_{2,t}\varphi(\hat{x}_t)u_t + K_1\left(y_t - C\hat{x}_t\right) + K_2 SIGN\left(y_t - C\hat{x}_t\right) \\ \hat{y}_t &= C\hat{x}_t \end{aligned} \tag{7}$$

This DNN structure is almost the same than the DNN identifier just by adding two new terms: the K_1 multiplied by the output error, which gives the Luenberger type observer and the K_2 multiplied by the sign of the error, which gives the sliding mode structure. The $SIGN(\cdot)$ function (8) is referred to:

$$SIGN(y_f) = \left(sgn(y_{1,f}), \ldots, sgn(y_{n,f})\right) \qquad SIGN(z) = \left(\frac{z_1}{|z_1|}, \ldots, \frac{z_n}{|z_n|}\right)$$
$$\forall x \in \Re^n, x_f \neq 0 \tag{8}$$

Hereinafter the following assumption is supposed to be validated: the matrixes pair (C, A) is observable. This nonlinear estimator is supplied with its own updating (learning) laws given by the nonlinear differential equations (9):

$$\begin{aligned}
\frac{d}{dt}\tilde{W}_{j,f} &= \Phi_{jw}\left(W_{j,f}, \hat{x}_f, y_f, u_f, t \,\middle|\, W_{j,*}^{(0)}\right) \\
\Phi_{jw}(\cdot) &:= -k_{wj} P_1 N_* \left(Ce_f + \frac{\Pi}{2} N_* P_1 \tilde{W}_{k,f} x_f\right) x_f^T \\
x_1 &:= \sigma(\hat{x}_f), \quad x_2 := \varphi(\hat{x}_f) u_f, \quad k_{wj} > 0 \\
\Lambda_j, \Pi_j &> 0, \quad W_{j,f} = W_{j,*} - W_{j,f} \\
\Pi_j &:= C^T \Lambda_{v_j} C + \Lambda_{W_j}^{-1} \\
N_* &:= \left(CC^T + \delta I_{n\times n}\right)^{-1}, \quad j = 1, 2
\end{aligned} \tag{9}$$

where $P = P^T > 0$ is the solution, if it exists, of the algebraic Ricatti equation given by (10).

$$\begin{aligned}
P_1 \tilde{A}_1^{(0)*} + \left(\tilde{A}_1^{(0)*}\right)^T P_1 + P_1 R_1 P_1 + Q_1 &= 0 \\
\tilde{A}_1^{(0)*} &:= \left(A^{(0)*} - K_1 C\right) \\
R_1 &:= \tilde{W}_1 + \tilde{W}_2 + \Lambda_f^{-1} + \Lambda_{v_1}^{-1} + K_2 \Lambda_{v_2}^{-1} K_2^T \\
Q_1 &:= I_n \Lambda_{v_0} + \Lambda^{-1} + 2\tilde{f}_1 \Lambda_f + \delta^2 \left(\Lambda_{W_1} + \Lambda_{W_2}\right) + Q_0, \quad Q_0 > 0
\end{aligned} \tag{10}$$

here $A^{(0)}$ is the "best" matrix possible value. This was obtained by the training process. In view of (7) structure, when $e_f = \hat{y}_f - C\hat{x}_f = 0$, the ODE (7) should be attended as a differential inclusion in Fillipov sense. This robust adaptive observer is a state estimator more advanced than one which only contains just one linear correction term like Luenberger type observer, since the observer proposed here possesses higher sensibility to external disturbances within a zone with a small estimation error upper bound. As a test of likeness between the mathematical model and a real patient,

different dose strategies have been given such as Gaussian, exponential and pulse dosages, checking in this way that the DNN presents robustness to entrance variations.

2.4. Procedure 3. Control by Hamilton Jacobi and Sliding Modes

With Hamilton Jacobi's Algorithm for the track of trajectory it is possible to simplify the computational spending since this control algorithm uses the estimated states obtained with a DNN. The system's behavior of prospective control is to displace the states such it is possible to make a track of a sign generated by some reference model given by (11).

$$\dot{x}_m = f_m(x_m, t) \tag{11}$$

Let's consider the following semi norm: $|z|_Q^2 = \limsup_{\tau \to \infty} \frac{1}{\tau} \int_0^{\tau} z^T(t) Q z(t) dt$ where $Q = Q^T > 0$. The track of trajectory can be formulated as (12).

$$J_{min} = \min_{u(t)} J, \qquad J = |x - x_m|_{Q_c}^2 + |u|_{\tilde{R}_c}^2 \tag{12}$$

Then, for any $\eta > 0$, we obtain (13):

$$J \le (1+\eta)|x - \hat{x}|_{Q_c}^2 + (1+\eta^{-1})|\hat{x} - x_m|_{Q_c}^2 + |u_t|_{\tilde{R}_c}^2 \tag{13}$$

The superior limit of the term $|x - \hat{x}|_{Q_c}^2$ has been reached by the corresponding states estimator. Selecting $\tilde{R}_c = (1+\eta^{-1})R_c$ we can formulate again the one control objective as follows, minimizing of being possible, the term 13. For this purpose, let us define the error of state trajectories as (14).

$$\Delta_m = \hat{x} - x_m \tag{14}$$

In agreement with 12, in order to carry out the pursuit of the system, the DNN as observer is presented as (15).

$$\dot{x} = F_0(x,t) + F_1(x,t)u \tag{15}$$

For the desire dynamics and well-known 11, the tracking trajectory is completed by the Hamilton Jacobi and Sliding Mode Control (HJSMC) described by (16).

$$u^{HJ} := F_1^{+}(x,t)[-\alpha \cdot SIGN(x - x_m) + (f_m(x_m,t) - F_0(x,t))] \tag{16}$$

where $\alpha > 0$. In this case, when considering the DNN as observer structure, we obtain: $F_0(\hat{x},t) = A\hat{x} + W_1\sigma(\hat{x}) + K_1(y_t - C\hat{x}_t) + K_2 SIGN(y_t - C\hat{x}_t)$ and $F_1(\hat{x},t) = W_2\varphi(\hat{x})$.

3. Numerical Simulation Results

In this section is presented the obtained simulation results, which are associated with the identification, estimation and control processes, showing the importance of computational programming in the study of hepatitis C viral dynamics.

3.1. Estimate Simulation Results

The following results show how the DNN estimator is able to track the trajectories in spite of the fact that the entry changes, which prove by this way the robustness about input variations. The first chart (Fig. 2) considers a dosage strategy called Gaussian which show to have similar way than the one were obtained when exponential dosage strategy were applied to the mathematical model.

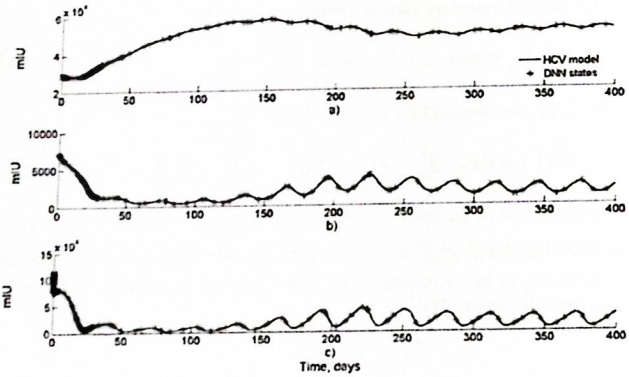

Fig. 2. Results when the treatment is considered as Gaussian signal. a) Target cells concentration, b) Infected cells concentration and c) Viral Load.

3.2. Control Simulation Results

The aim of this work is to control the viral load in a patient infected with HCV by means of the use and application of automatic control algorithms as HJT and SMA. These techniques are allowed to give the exact dose of IFN $\alpha - 2b$ that should be applied to the patient with this illness. In order to carry out this objective, it was necessary to have knowledge in their entirety HCV model. This complete knowledge was obtained by using a neuroobserver based on DNN. Once obtained that, is necessary to have a reference that is adapted to complete the goal, in this paper a reference model

was selected with the intention of eliminating all HCV and all infected cells of the patient's body in a few days as is shown in the figure 3.

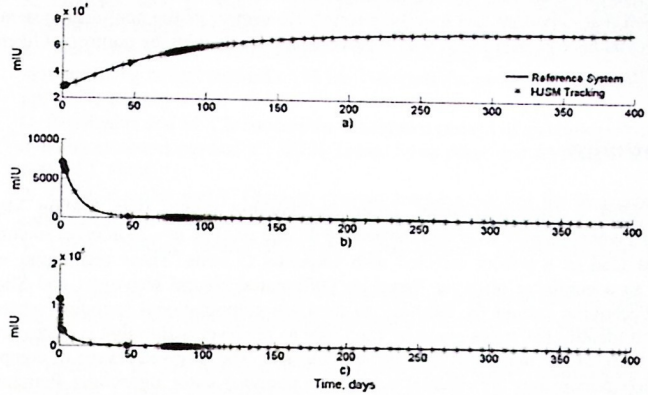

Fig. 3. Simulation results of the control process. a) Target cells concentration, b) Infected cells concentration and c) Viral Load.

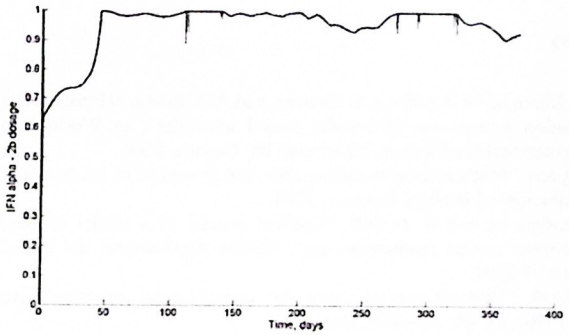

Fig. 4. IFN $\alpha - 2b$ dosage obtained by the HJSMC in order to eliminate the HCV.

The computational algorithms proposed in this paper have demonstrate to be able to control this nonlinear system, a prove of that is presented in figure 3 where it is evident that HJSMC can reconstruct the desire IFN $\alpha - 2b$ patients response eliminating in approximately 2 months more than 80% of HCV and infected productive cells.

To achieve that, the HJSMC provide the HCV model, which is supposed to have similar response than real patient, a strategy dosage the one that is shown in figure 4. This dosage has a maximum value around *25mIU*. This dosage would be the same to each patient provided they had similar response; nevertheless, in this work it has been considered that important fact into the interference vectors of the nonlinear system (2) these vectors have been selected with relatively high levels with the purpose of likening the reality.

4. Conclusion

In this work a Hamilton Jacobi Technique working jointly with Sliding Modes Approach was suggested to obtain the precise dosage on IFN $\alpha - 2b$ in order to control the viral load of a patient infected with Hepatitis C virus. These techniques were applied to a nonlinear observer based on Differential Neural Networks and Sliding Mode Technique getting by this way to diminish computational spending when no having to identify the states given by the DNN as observer action that is necessary to be able to check the nonlinear observer convergence. The received results of computer simulation demonstrate the efficient capacity of applying these algorithms. Perhaps, in a near future, this computational tools will be used in real medical procedures to be able to control, the, until now no controllable, hepatitis C, which has ended up being an important threat for the society.

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