Local Optimal Control Based on Neural Network Observer States

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Abstract. Immunotherapy refers to the use of natural and synthetic substances to stimulate the immune response. This paper provides a description for an adaptive locally optimal control design for immunotherapy cancer treatment mathematical model, where all state vector is considered to be not on-line available. The control strategy is suggested in two stages: the first one deals with the state estimation process using differential neural networks technique. The second part introduces the construction for a locally optimal control function based on the DNN mathematical representation. This technique was successfully applied in the tracking process for immunotherapy dosage control.

1. Introduction

1.1. Neural Networks with Differential Representation

The increasing demand of technology requires different approaches to solve control and identification problems of nonlinear systems. The neural networks (NN) promise better solutions in some problems. The control applications of NN are motivated for the necessity to treat more complex systems, to find new adaptive control methods and to regulate systems affected by external uncertainties. Roughly speaking, the NN can be classified as follows: *static* one, using mainly the back-propagation technique [1], and *dynamic (or recurrent) neural networks* which applies differential learning laws or dynamic (recurrent) ones [2]. Nowadays the neural networks employment in several science fields, as pattern recognition, image processing, industrial process, biological systems and automatic control engineering, has increase the interest to develop new approaches that could improve the results obtained until today. One of these new kinds of dynamic neural networks is the differential neural networks (DNN) which has been applied successfully in many identification, estimation and control techniques, such as non-parametric estimation for diabetes mellitus illness [3], fermentative process [4], [5] and Human Immunodeficiency Virus dynamics as well [4]. This approach permits to avoid many problems related to global extreme search converting the learning (training) process to an adequate state feedback design. The DNN-approach provides an effective instrument to attack a wide spectrum of problems such as identification, state estimation, trajectories tracking, if the mathematical model of a considered process is incomplete or partially known, [1]. Considering all these previous papers and the well studied identification and control theory developed in [7], a novel cancer treatment control technique is suggested in order to obtain a slightly improvement in the illness evolution.

1.2. A brief review on robust output feedback control

Research on adaptive output feedback control of uncertain non-linear dynamic systems is of paramount importance today, particularly considering the growing interest in the use of unconventional control devices such as chemical sensors, piezoelectric actuators, etc. In a large number of practical problems there are important disturbances, uncertainties or several parameter variations. In these situations, a solution of the control problem is given by the, so-called, unconventional adaptive control supplied by a mechanism to adjust the controller's parameters. In the case of only one single output measurement, the existing works show semi-global results for a class of systems whose non-linearities depend on the unmeasured variable, [8] and [9]. If the non-linearity depends on output measured variables, the published papers suggest a mechanism which can achieve global results only for a class of parametric output-feedback systems. By the adaptive observer backstepping technique, a self-adjusted output feedback controller can be designed for a class of parametric output-feedback form [10] guarantying asymptotic tracking of the reference signal while keeping bounded all signals (states and control). The observer based-control is a way to solve the output feedback control problem that imposes a restriction in the possibility to use all the states directly for feedback control design. Still for linear systems, this allows to discompose the problem in two sub-problems that can be solved separately: a) by designing a state observer and b) by designing a controller based on the on-line state estimates. This approach is known as the *Separation Principle*. However, in non-linear systems, this principle is not well justified [11].

In the context of the non-linear systems, adaptive controllers that ensure good tracking performance (and disturbance rejection) of signals that corresponds to bounded solutions of known non-linear time variant systems are not clearly established. The suggested solutions for this problem are based on the internal model principle wherein the "dynamics" of the reference signal (and disturbances) are incorporated in the plant dynamics via an adequate chosen pre-filter or pre-compensator. For this study, such pre-filter going to be design as a "internal" differential neural network whose states ($\tilde{x}_t$) will be used by the controller structure to reproduce the non-linear system dynamics (represented by the supplied differential neural network observer) and then to "adjust" the control function in order to follow the reference trajectories. Using the following definitions: x_t is the current state of an uncertain system, $\hat{x}_t^{\circ}$ is the current state estimation generated by DNN observer (DNNO) which is shown to be close to x_t (that is, $x_t \sim \hat{x}_t$ by means of a special Lyapunov-like function), $\tilde{x}_t$ is the internal model state of the neural controller which is closed to $\hat{x}_t^{\circ}$ (that is, $\hat{x}_t^{\circ} \sim \tilde{x}_t$) and x_t^{*} is the state of a reference model. In this paper, the following fact going to be demonstrated: $x_t \sim \hat{x}_t^{\circ} \sim \tilde{x}_t \sim x_t^{*}$. This means that the application of a control, which solves the problem $\left(\tilde{x}_t \sim x_t^*\right)$, for an initial uncertain system with states x_t at the same time guarantees that $x_t \sim x_t^*$.

2. System description and basic assumptions

Let's consider the class of perturbed non-linear systems with incomplete information (not all the state vector is assumed to be available) described by the set of ordinary differential equations

$$\dot{x}_t = f\left(x_t, u_t^*, t\right) + \xi_{1,t}, \quad y_t = Cx_t + \xi_{2,t} \tag{1}$$

where $x_t \in \Re^n$ is the system state vector, $y_t \in \Re^p$ is the system output vector, $u_t^* \in \Re^m$ is the control action belonging to a specific admissible set U^{adm} that will be define below, $C \in \Re^{p \times n}$ is an *a* priory known output matrix. The uncertain vectors $\xi_{1,t}$ and $\xi_{2,t}$ represent the state and output deterministic external bounded (unmeasurable) disturbances $\left(\left\|\xi_{j,t}\right\|_{\Lambda_{\xi_j}}^2 \le \Upsilon_j, \Lambda_{\xi_j} > 0,\ j = 1,2\right)$. Hereafter it is supposed the non-linear function in (1) satisfies the Lipschitz property (uniform on t and for all possible systems belonging to the non-linear systems class given above):

$$\begin{gathered}\left\|f\left(x,u^*,t\right) - f\left(z,v^*,t\right)\right\| \le L_1\left\|x - z\right\| + L_2\left\|u^* - v^*\right\| \\ \left\|f(0,0,t)\right\|^2 \le C_1;\quad 0 \le L_1, L_2 < \infty;\quad x, y \in \Re^n;\ u^*, v^* \in \Re^m\end{gathered} \tag{2}$$

The last assumption automatically implies the ODE solution existence and uniqueness and, obviously, the following property $\left\|f\left(x_t,u_t^*,t\right)\right\|^2 \le C_1 + C_2\left\|x_t\right\|^2 + C_3\left\|u_t^*\right\|^2$ that is valid for any x, u and t. Besides the unperturbed $\left(\xi_{1,t} = \xi_{2,t} = 0\right)$ non-linear system (1) is assumed to be stable, that is, there exists a Lyapunov function $\bar{V}\left(x_t\right)$ fulfilling the following inequality $\left\|\frac{d}{dx_t}\bar{V}\left(x_t\right)\right\| \le -\lambda$ and using (2) then the next expression is valid $\frac{d}{dt}\bar{V}\left(x_t\right) \le -\lambda\left[\bar{\upsilon} + \bar{C}_2\left\|x_t\right\|^2\right]$. Notice that (1) "always" could be rearranged as

$$\begin{aligned}\dot{x}_t &= f_0\left(x_t, u_t^*, t \mid \Theta(t)\right) + \tilde{f}_{1,t} + \xi_{1,t} \\ \tilde{f}_{1,t} &:= f\left(x_t, u_t^*, t\right) - f_0\left(x, u^*, t \mid \Theta(t)\right)\end{aligned} \tag{3}$$

where $f_0(x,u^*,t \mid \Theta(t))$ will be referred like "*nominal dynamics*" that can be selected according to designer desires; and $\tilde{f}_t$ is a vector defined like the "*no modelled dynamics*". Here, the set of parameters $\Theta(t)$ are subjected to adjustment (this is the so-called training process) in order to obtain the best possible accuracy in the nominal representation (a DNN representation, for example). According to DNN approach [1], the nominal dynamics is defined by

$$f_0(x,u^*,t \mid \Theta) = A^* x + W_{1,t}^* \sigma(x) + W_{2,t}^* \varphi(x) u^*,\ \Theta := A^*, W_{1,t}^*, W_{2,t}^* \in \Re^{n \times n}$$
$$W_{1,t}^* \in \Re^{n \times l}, \sigma(\cdot) \in \Re^{l \times 1},\ W_{2,t}^* \in \Re^{n \times s}, \varphi(\cdot) \in \Re^{s \times m} \tag{4}$$

The admissible control set for u_t^* (at least for the estimation process, without any feedback control design) is supposed to be bounded:

$$U^{adm} := \left\{ u^* : \left\| u^* \right\|_{\Lambda_u}^2 \le v_0^2 \right\}\ \Lambda_u = \Lambda_u^T > 0 \tag{5}$$

The activation vector-functions $\sigma(\cdot) := [\sigma_j(\cdot)]_{j=\overline{1,l}}^T$, $\varphi(\cdot) := [\varphi_{jk}(\cdot)]_{j=\overline{1,n};\,k=\overline{1,s}}^T$, are usually composed with smooth monotonically growing functions. As usual, the selected activation functions are sigmoid ones:

$$\sigma_i^{-1}(x) := a_{\sigma i}^{-1}\left(1 + b_{\sigma i} \exp\left(-\sum_{j=1}^{n} c_{\sigma i} x_i\right)\right)$$
$$\varphi_j^{-1}(x) := a_{\varphi j}^{-1}\left(1 + b_{\varphi j} \exp\left(-\sum_{j=1}^{n} c_{\varphi j} x_j\right)\right) \tag{6}$$

It is easy to proof they satisfy the sector conditions $\left\| \sigma(x) - \sigma(x') \right\|^2 \le l_\sigma \left\| x - x' \right\|^2$ and $\left\| (\varphi(x) - \varphi(x')) u \right\|^2 \le l_\varphi \left\| x - x' \right\|^2 v_o^2$. In view of (2) the following upper bound for the no modelled dynamics $\tilde{f}_{1,t}$ takes place:

$$\left\| \tilde{f}_{1,t} \right\|_{\Lambda_f}^2 \le \tilde{f}_{1,0} + \tilde{f}_{1,1} \left\| x_t \right\|_{\Lambda_{\tilde{f}}}^2,\ \Lambda_f = \Lambda_f^T > 0, \Lambda_{\tilde{f}} = \Lambda_{\tilde{f}}^T > 0 \tag{7}$$

3. DNN training algorithm

The training process for the DNN algorithm is associated with the off-line best possible selection (before the begging of the state estimation) of the nominal parameters $\Theta := [A^*, W_{1,t}^*, W_{2,t}^*]$ using experimental data (x_{t_k}, u_{t_k}). Notice that the corresponding rate-vectors $\dot{x}_t$ are not available. In view of the nominal dynamics selection, the following procedure could be applied in order to define the parameter which going to be used in the non-linear output feedback controller design.

DNN trainer. In order to define the training process, all the vector state and the control action (x_{t_k}, u_{t_k}) could be measurable in specific times t_k (by direct experimentation), but the exact mathematical structure about the vector field $f(x_t, u_t^*, t)$ is partially unknown (the order of the system and its stability properties are *a* priory assumed). A special nonparametric identifier (based on DNN properties) will be applied to derive an approximation of this non-linear model. The mathematical description of this neural trainer is given by:

$$\frac{d}{dt}\hat{x}_t = A\hat{x}_t + W_{1,t}\sigma(\hat{x}) + W_{2,t}\varphi(\hat{x})u_t^* + K_1\Delta_t + K_2\frac{\Delta_t}{\|\Delta_t\|}. \tag{8}$$

Here $\Delta_t = \hat{x}_t - \bar{x}_t \in \Re^n$ is the identification error between the system states to be identified and the corresponding DNN variables, $\hat{x}_t \in \Re^n$ is the state of the neural network, $\bar{x}_t$ are reconstructed versions of x_{t_k} and u_{t_k} respectively using classical interpolation algorithms [12], $A \in \Re^{n\times n}$ is a stable matrix (maybe diagonal or upper triangular) which elements going to be selected below, $W_{1,t} \in \Re^{n\times k}$ is the weight matrix for non-linear "state feedback" and $W_{2,t} \in \Re^{n\times r}$ is the "input" weight matrix; both matrices will be adjusted using a special learning law described by matrix differential equations. The vector field $\sigma(x_t): \Re^n \to \Re^k$ and the matrix function $\varphi(\cdot)$ have the same meaning and structure that (6). In view of the neural network structure (8), it can be classified as a Hopfield-type [1]. K_1 and K_2 are constants matrices which have the same function like correction terms in observers structure [13]. These two additional terms were added following the results derived in [11] where a significant reduction in the upper bound for the convergence process was obtained. Taking into account that the elements of $\sigma(\cdot)$ and $\varphi(\cdot)$ are chosen as sigmoid functions, the following assumption are easily fulfilled.

As.1: The functions $\sigma(\cdot)$ and $\varphi(\cdot)$ satisfy the Lipschitz condition:

$$\begin{gathered}\tilde{\sigma}_t^T \Lambda_\sigma \sigma_t \le \Delta_t^T D_\sigma \Delta_t,\ \ \sigma_t^T Z_\sigma \sigma_t \le x_t^T C_\sigma x_t \\ (u_t^*)^T \tilde{\varphi}_t^T \Lambda_\varphi \tilde{\varphi}_t u_t^* \le v_0^2 \Delta_t^T D_\varphi \Delta_t,\ \ (u_t^*)^T \tilde{\varphi}_t^T Z_\varphi \tilde{\varphi}_t u_t^* \le v_0^2 x_t^T C_\varphi x_t \\ \tilde{\sigma}_t := \sigma(\hat{x}_t) - \sigma(x_t),\ \tilde{\phi}_t := \phi(\hat{x}_t) - \phi(x_t)\end{gathered} \tag{9}$$

and $\Lambda_\sigma, \Lambda_\phi, D_\sigma, D_\phi, Z_\sigma, Z_\phi, C_\sigma, C_\phi$ are know positive definite matrices. The identifier design requires the next important assumption:

As.2. There exist a strictly positive defined matrix Q_0 *such that the Riccati equation*

$$A^T P + PA + PRP + Q = 0 \tag{10}$$

has a positive solution $P = P^T > 0$, where $R = \Lambda_f^{-1} + W_{1,t}^{\bullet}\Lambda_\sigma^{-1}\left(W_{1,t}^{\bullet}\right)^T$ + $W_{2,t}^{\bullet}\Lambda_\varphi^{-1}\left(W_{2,t}^{\bullet}\right)^? + K_1\Lambda_1^{-1}K_1^? + K_2\Lambda_2^{-1}K_2^? + \Lambda_{\xi 1}^{-1}$ and $Q = D_\sigma + v_0 D_\varphi + \Lambda_1 + Q_0$. If the algebraic Riccati equation has positive definite solution, the weights $W_{j,t}$, $j = 1,2$ are adjusted by

$$\frac{d}{dt}\tilde{W}_{j,t} = \frac{d}{dt}W_{j,t} = -K_j P \Delta_t \Omega_j^? \\ \Omega_1 := \sigma(\hat{x}_t),\ \Omega_2 := \varphi(\hat{x}_t)u_t^{\bullet},\ K_j > 0,\ \tilde{W}_{j,t} = W_{j,t} - W_{j,t}^{\bullet} \tag{11}$$

The training process could be abstracted in the following:

Theorem 1. Let 's consider the partially unknown non-linear system (1) and a model matching neural network (8) whose weights are adjusted by the matrix differential equations (11), and also the assumptions *As.1* and *As.2* hold, then the upper bound (in average sense) for the identification (training) error is described by

$$\overline{\lim_{T\to\infty}} \tfrac{1}{T}\int_{t=0}^{T}\left\|\Delta_t\right\|_P dt \le \frac{\rho_T}{\alpha_{Q,T}} \\ \alpha_{Q,T} = \lambda_{\min}\left(P^{-1/2}Q_0P^{-1/2}\right) > 0,\ \rho_T := \tilde{f}_{1,0} + n\left\|\Lambda_2\right\| + \Upsilon_1 \tag{12}$$

The identification error sign term in (8) is introduced to apply the robustness settings on sliding mode approach, especially those that can help to solve the parameter uncertainties in the problem description. This important behaviour could be useful in this new kind of identifier because in DNN the most difficult problem is to select the matrix A. That is why the simultaneous application of DNN and sliding mode technique seems to be a promising solution to solve the problem to be tackled in this report.

4. Output feedback DNN controller

Once the DNN has been trained the automatic feedback controller for uncertain nonlinear system, affected by external perturbations could be designed in two stages, the first one deals with the state estimator develop using a special class of DNN, considering the control action as a function depending on the state estimated. The second section is related with the adaptive control suggestion; in this work three different methods are applied to solve this problem.

4.1. DNN Non-Parametric State Estimator

The observer design is going to be maddened using the ideas developed on [11]. So, let define DNN observer as follows

$$\frac{d}{dt}\hat{x}_t^{\circ} = A\hat{x}_t^{\circ} + W_{1,t}^{\circ}\sigma(\hat{x}_t^{\circ}) + W_{2,t}^{\circ}\varphi(\hat{x}_t^{\circ})u_t + K_1^{\circ}(y_t - C\hat{x}_t^{\circ}) + K_2^{\circ}\frac{y_t - C\hat{x}_t^{\circ}}{\|y_t - C\hat{x}_t^{\circ}\|} \quad (13)$$
$$\hat{y}_t^{\circ} = C\hat{x}_t^{\circ}$$

Here $\hat{x}_t^{\circ} \in \Re^n$ is the state of the neural network observer, $W_{1,t}^{\bullet} \in \Re^{m\times k}$ and $W_{2,t}^{\bullet} \in \Re^{m\times r}$ are the corresponding weight matrices for this observer adjusted by the special *updating* (learning) law for the estimation process

$$\frac{d}{dt}\widetilde{W}_{j,t}^{\bullet} = -K_j\left(P_2\hat{x}_t^{\bullet} + P_1N_\delta\left(C^Te_t + \Pi_jN_\delta P_1\overline{W}_{j,t}\chi_j\right)\right)\chi_j^T$$
$$\chi_1 := \sigma(\hat{x}_t),\ \chi_2 := \varphi(\hat{x}_t)u_t,\ k_{wj} > 0 \quad (14)$$
$$\Pi_j := C^T\Lambda_{\xi_{2,t}}C + \Lambda_j^{-1},\ \Lambda_j > 0;\ N_\delta := \left(CC^T + \delta I_{n\times n}\right)^{-1},\ j = 1,2$$

$P_1 = P_1^T > 0$ and $P_2 = P_2^? > 0$ are positive definite solutions (if they exist) of the following Riccati equations

$$P_h\widetilde{A}_h + \left(\widetilde{A}_h\right)^T P_h + P_hR_hP_h + Q_h = 0,\quad h = 1,2 \quad (15)$$

whose parameters are defined by

$$\widetilde{A}_1 := \left(A - K_1^{\bullet}C\right),\quad \widetilde{A}_2 := A$$
$$Q_1 := \delta^2\Lambda_1 + \delta^2\Lambda_2 + \delta k\upsilon I_{n\times n} + D_\sigma + 2\Xi\nabla_2\Lambda_u^1 + \Xi_1\nabla_2\Lambda_u^1 + 2\mathcal{J}_{1,1}\Lambda_{\mathcal{J}} + \Lambda_3 + Q_0$$
$$R_1 := W_{1,t}^{\bullet}\Lambda_\sigma^{-1}\left(W_{1,t}^{\bullet}\right)^T + \left(W_{2,t}^{\bullet}\right)\Lambda_\varphi^{-1}\left(W_{2,t}^{\bullet}\right)^T + K_1^{\bullet}\Lambda_{\xi_{2,t}}^{-1}\left(K_1^{\bullet}\right)^T + \Lambda_{\mathcal{J}_{1,t}} + \Lambda_{\xi_{1,t}} \quad (16)$$
$$Q_2 := Z_\sigma + 2\Xi\nabla_2\Lambda_u^1 + 2\mathcal{J}_{1,1}\Lambda_{\mathcal{J}} + \Xi\nabla_3\Lambda_u^2 + \nabla_3\Xi_1\Lambda_u^2 + \Xi_1\nabla_2\Lambda_u^1$$
$$R_2 := K_1^{\bullet}C\Lambda_3^{-1}C^T\left(K_1^{\bullet}\right)^T + K_1^{\bullet}\Lambda_{\xi_{2,t}}^{-1}\left(K_1^{\bullet}\right)^T + K_2^{\bullet}\Lambda_4\left[K_2^{\bullet}\right]^T + W_{1,t}^{\bullet}Z_\sigma^{-1}\left[W_{1,t}^{\bullet}\right]^T + W_{2,t}^{\bullet}Z_\varphi^{-1}\left[W_{2,t}^{\bullet}\right]^T$$

where $\overline{\Delta}_t := x_t - \hat{x}_t^{\circ}$. So, when $y_t = C\hat{x}_t^{\circ}$, ODE (13) should be attended as a differential inclusion. Such *robust adaptive observer* seems to be a more advanced device compared to one containing only a linear (Luenberger type) correction term since it possesses high sensibility within a zone with a small output error. Additionally

$\sigma(\cdot)$ *and* $\varphi(\cdot)$ were selected in the same way that (9). Once all the state is available using the state estimator (13), it is possible to implement the corresponding observed-state $\hat{x}_t$ neural identifier and DNN observer state $\hat{x}_t^\circ$, the admissible control set for $u_t(\tilde{x}_t)$ should be suggested as an element of the following set

$$U^{adm} := \left\{ u_t := \|u_t\|_{\Lambda_u}^2 = \tilde{v}_1 + \tilde{v}_2 \|x_t\|_{\Lambda_u^1}^2 + \tilde{v}_3 \|\hat{x}_t^\circ\|_{\Lambda_u^2}^2 \right\} \tag{17}$$

This selection for the admissible control allows the independent design for the controller and the observer (this is referred like a special form of the separation principle). The following theorem introduces the main result on state estimation procedure:

Theorem 2. If there exist positive definite matrices $\Lambda_{\tilde{f}}$, Λ_σ, Λ, Λ_1, $\Lambda_{\tilde{f}}$, Λ_{W_1}, Λ_{W_2}, Λ_{ξ_1}, Λ_{ξ_2}, Λ_u, Λ_D, $\tilde{Q}_0$, Q_0 and positive constants δ, k, v_1 such that the matrix Riccati equations (15) have positive definite solutions, then the DNN observer-identifier (11) with any matrix K_1 guarantying that the close-loop matrix $\tilde{A}^{(0)\bullet}$ is stable, that is, $\tilde{A}^{(0)\bullet} := \left(A^{(0)\bullet} + K_1 C\right)$ is Hurwitz (this is possible if and only if the pair (C, A) is observable) and $K_2 = \lambda P_1^{-1} C^?, \lambda > 0$ supplied by the learning laws (14) provides the following upper bound for the controlled-state estimation process:

$$\overline{\lim_{T\to\infty}} \frac{1}{T} \int_{t=0}^{T} \|\Delta_t\|_{P_1} dt \le \frac{\rho_s}{\lambda_{\min}\left(P_1^{-1/2} Q_0 P_1^{-1/2}\right)} \tag{18}$$
$$\rho_T := \tilde{f}_{1,0} + \tilde{v}_1(\Xi + \Xi_1) + 4k\sqrt{n}\|\xi_{2,t}\| + kv^{-1} + n\|\Lambda_4^{-1}\| + 4\Upsilon_2 + \Upsilon_1$$

Bringing together the two stages of control designing, which have been described above, the main result on the *neural- tracking-control* of a class of uncertain non-linear dynamic system subject to state and output external perturbation could be formulated. Due to the non-linear form on the cancer's dynamics, the lack of knowledge about the system structure and the uncertainties presence on the state and output signals, the control function design could be a slow and difficult process (sometimes impossible), specially if any performance index optimization or tracking error minimization are trying to be reached. The differential neural network "modelling" allows defining tracking controllers using the non-linear structure defined by (10). The next subsection gives some general solutions to control non-linear uncertain systems affected by external perturbations.

4.2. Model reference controllers

The control design using the estimated states requires the next definition. Let introduce the performance index describing the tracking quality as:

$$J_t = \lim_{T\to\infty} \sup \int_{t=0}^{T} \left(\left\| (x_t - \hat{x}_t) + (\hat{x}_t - x_t^*) \right\|_Q^2 + \|u_t\|_R^2 \right) dt \tag{19}$$

Using the inequality $\|a+b\|_M^2 \le (1+\varepsilon^{-1})\|a\|_M^2 + (1+\varepsilon)\|b\|_M^2$ in (19), the performance index could be presented as:

$$J_t \le (1+\varepsilon^{-1}) \overline{\lim_{T\to\infty}} \int_{t=0}^{T} \|(x_t - \hat{x}_t)\|_Q^2 dt + (1+\varepsilon) \overline{\lim_{T\to\infty}} \int_{t=0}^{T} \left(\|(\hat{x}_t - x_t^*)\|_Q^2 + \|u_t\|_R^2 \right) dt \tag{20}$$

In view of the last expression, the tracking controller could be described by the minimization (in any sense) of the third term, $\int_{t=0}^{T} \left(\|(\hat{x}_t - x_t^*)\|_Q^2 + \|u_t\|_R^2 \right) dt$. The optimization procedure was carried out as follows: Lets consider the non-linear system to be controlled as in (1) and consider, also, a reference model representing the normal conditions for a healthy patient $\dot{x}_t^* = \hat{f}(x_t^*, t)$, x_0^* is fixed where x_t^* is the state of the reference system, $\hat{f}$ is a non-linear function fulfilling the Lipschitz condition with the corresponding constant L^*. If the tracking process is going to be considered, the function $\hat{f}$ could be any which reachable set has a non empty intersection with that one of non-linear function [14], but if the studied case deals with regulation problem, the reference system must be purposed as $f = 0$, $x_0^* = c$, $c \in \Re^n$ is a vector composed by constant elements c_i, $i = \overline{1,n}$. To complete the control design, the control action (u_t) going to be made up by two parts $u_t = \left[W_{2,t}^\circ \varphi(\hat{x}_t^\circ)\right]^+ (u_{1,t} + u_{2,t})$ where $u_{1,t} \in \Re^m$ could be described as a direct linearization part, and $u_{2,t} \in \Re^n$ will act as a compensation of the tracking no modeled dynamics. In view of the reference model $\hat{f}(x_t^*, t), x_t^*$ structure, the first section in the control function is selected as: $u_{1,t} = -\left[F_0(\hat{x}_t, t) - \hat{f}(x_t^*, t)\right]$ where $F_0(\hat{x}_t, t)$ is obtained by the inverse model representation given for the DNN structure

$$\begin{gathered} \dot{\hat{x}}_t = F_0(\hat{x}_t, t) + F_1(\hat{x}_t, t) u_t \\ F_0(\hat{x}_t, t) = A\hat{x}_t^\circ + W_{1,t}^\circ \sigma(\hat{x}_t^\circ) + K_1^\circ (y_t - C\hat{x}_t^\circ) + K_2^\circ \frac{y_t - C\hat{x}_t^\circ}{\|y_t - C\hat{x}_t^\circ\|} \\ F_1(\hat{x}_t, t) = W_{2,t}^\circ \varphi(\hat{x}_t^\circ) \end{gathered} \tag{21}$$

and $u_{2,t}$ will be designed using the, so-called, Local Optimal Control. Unfortunately the weights $W_{1,t}^{\circ}$ and $W_{2,t}^{\circ}$ could be not bounded (at least this fact is unknown before the controller structure is applied). This fact is the main consideration to derive a inverse model control using an auxiliary dynamics $\tilde{x}_t$ constructed as $\frac{d}{dt}\tilde{x}_t = \tilde{F}_0(\tilde{x}_t,t)+\tilde{F}_1(\tilde{x}_t,t)u_t$ where $\tilde{F}_0(\tilde{x}_t,t)$ and $\tilde{F}_1(\tilde{x}_t,t)$ going to be described below. If this auxiliary dynamic vector converge fast to the DNNO structure, it is possible to use $\tilde{x}_t$ instead $\hat{x}_t$ in the control development (like in the well known adaptive control based on internal model). Let us define the tracking error between thisas "artificial" system ($\tilde{x}_t$) and the reference model (x_t^{*}) as $\delta_t = \tilde{x}_t - x_t^{*}$. From the previous definitions, the tracking error time derivative is described by $\dot{\delta}_t = \tilde{F}_0(\tilde{x}_t,t) - f(x_t^{*},t) + \tilde{F}_1(\tilde{x}_t,t)u_t$. Using this control function, the tracking error dynamics is presented as: $\dot{\delta}_t = A\delta_t + u_{2,t} + \tilde{f}$. If $u_{2,t}$ is able to compensate $\tilde{f}$, then the tracking error dynamics is asymptotically stable. The auxiliary dynamics is governed by the differential equation described (following the suggested DNNO structure) as

$$\frac{d}{dt}\tilde{x}_t = A\tilde{x}_t + V_{1,t}\sigma(\tilde{x}_t) + V_{2,t}\varphi(\tilde{x}_t)u_t + \bar{K}_1\Delta_t + \bar{K}_2 SIGN(\Delta_t) \tag{22}$$

where $\Delta_t := \hat{x}_t^{\circ} - \tilde{x}_t$, $\tilde{x}_t, \sigma(\cdot) \in \Re^n$, $\varphi(\tilde{x}_t), V_{1,t}, V_{2,t}, \bar{K}_1, \bar{K}_2 \in \Re^{n\times n}$. The parameters involved in this scheme are adjusted using the following matrix differential equations

$$\frac{d}{dt}\tilde{V}_{j,t} = -k_{Vj}\left(P_2\tilde{\Delta}_t^T + P_3\tilde{x}_t^T\right)\chi_j^T;\quad \chi_1 := \sigma(\tilde{x}_t), \chi_2 := \varphi(\tilde{x}_t)u_t, k_{Vj} > 0 \tag{23}$$

where P_2 and P_3 are the positive definite solution of the second Riccati equation in (13) and the following one $P_3\tilde{A} + \tilde{A}^? P + PR_3P + Q_3 = 0$. It easy to proof that $\hat{x}_t^{\circ} \sim \tilde{x}_t$ has a finite upper bound for the auxiliary error Δ_t. So the controller design could be abstracted by the following:

Theorem 3. *If the control function* u_t^{*} *is proposed as*

$$u_{t^*} = \left[F_1(\hat{x}_t,t)\right]^+\left(u_{0,t} + u_{1,t}\right),\quad u_{0,t} := F_0(\hat{x}_t,t) - \varphi(t,x_t^{*}) \tag{24}$$

and if $u_{1,t}$ *is suggested as* $u_{1,t} = -2R^{-1}P_c\delta_t$ *where* P_c *is solution for the*

Lyapunov function , *then* $\|\delta_t\|_{\bar{Q}}^2 + \|u_{2,t}\|_R^2 \leq \|\tilde{f}\|_{\Lambda^{\prime}Q,\Gamma^{\prime}}^2$ *where the semi-norm* $\|s_t\|_{\Pi}^2$ *is defined by* $\limsup_{T\to\infty}\frac{1}{T}\int_0^T s_t^{\top}\Pi s_t dt$.

Proof. The proof of this theorem is going to be described in [6].

5. Numerical Results

The cancer term corresponds more than one hundred of different illness. Each of they have particular characteristics, being able to consider itself independent illness, with their causes, evolution and specific treatment. The specific method of treatment used is determined by the cancer's type, stage, and location. There exist several treatments for this disease: chemotherapy, radiotherapy, surgery, etc. Although development of new technics of surgery and transplants, more effective drugs and better radiation methods, often some malignant cells survives to these therapies and disseminates into the organism (the so-called metastasis process). Recently, treatment efforts implementing immunotherapy are being investigated [15]. Although, the immunotherapy dynamics is difficult to be modeled (like many other biological processes), because it has many uncertainties in its description, it depends strongly on the input function, etc. One common solution for this problem is to consider this model as a black box, whereas only input and output information is supposed to be measurable. There are some theoretical studies that have been forcing into the order to modelling this particular cancer treatment method [16] The cancer model is based on the immunotherapy response describing the activated immune or effector cells (x_t), the tumor cells (y_t) and *IL-2* concentration (z_t) in the single tumor-site compartment

$$\begin{aligned}
\dot{x}_t &= cy_t - \mu_2 x_t + \frac{p_1 x_t z_t}{g_1 + z_t} + u_t s_1; \\
\dot{y}_t &= r_2 y_t (1 - b y_t) - \frac{a x_t y_t}{g_2 + y_t}; \\
\dot{z}_t &= \frac{p_2 x_t y_t}{g_3 + y_t} - \mu_3 z_t
\end{aligned} \tag{24}$$

Obviously the main result is devoted to adjust this function in order to reduce the tumour cells, considering the physiological restrictions given by the each patient under immunotherapy treatment.

5.1. Control Process results with incomplete information

The first stage in the controller developed is the DNN training process. This is carried out using some pattern data that usually are obtained using some real experiments or a database which contains some particular information about the nonlinear system to be controlled. Unfortunately, there are not on-line sensors that could measure any variable related with the immunotherapy treatment. As far as the authors known, there are not a database which contains the time evolution of the immunotherapy dynamics. That is the main reason to use an artificial mathematical model of the IL-2 interaction in patients which are assisted with immunotherapy, as a data generator to be used in the rest of the document. To guarantee the estimation error convergence "close" (depending on the perturbations values) to zero, training process for the DNN should be solved in order to obtain the best possible values for the free-design parameters in the identification design are adjusted using the learning laws described above. This adjustment procedure starts with the data set testing for the identifier structure. The data set is obtained using the mathematical description with a fixed initial condition. So if a bad performance in the error convergence is obtained, a new set of matrices is used to test again the identifier, and so on. Besides, the neural networks weights are adjusted using two matrix differential equations, so it is important the initial weights values selection.

The control problem for immunotherapy dosage is difficult because the designed controller should be restricted by real patient settings. In view of this, it is difficult to suggest any performance index to solve the corresponding optimization problem. In real situations, the health improvement for the patient is slow and progressive, so the controller must consider this important medical fact. Both elements recently mentioned implies the reference model should be designed in order to represent a slightly healthy condition for the patient. In order to solve the numerical example to evaluate the capabilities for this method, a modified parameter set for the DNNO corresponding to the healthy patient has been suggested [16]. The adaptive controller was designed using the local optimal control. Taking into account the obtained data in the estimation procedure; it is possible to apply the adaptive control function designed to make non-linear system dynamics (1) follows the corresponding reference trajectory. This sub-optimum controllers does not requires the trial and error method to obtain the previous matrix value. It is solved analytically which ensures there is positive solution for the Lyapunov equation selecting the implicated eigenvalues at $\lambda_1 = 2.56 \times 10^{-2}$, $\lambda_2 = 6.34 \times 10^{-2}$, $\lambda_3 = 3.42 \times 10^{-2}$. The next figure shows the performance for this observer based-controller considering there is not any mathematical model (this is true in principle because the same procedure using on-line information or a database containing such knowledge). It is important to note the total amount of tumour cells has a significative reduction once the controller was applied (upper right corner). However the effectors cells are not so affected by the immunotherapy dosage (upper left corner in). Another important fact in this controlled process is the important reduction on the IL-2 concentration in the body (lower left corner) diminishing a possible intoxication possibility. The control process quality could be evaluated using the performance index given by (), where the convergence between the immunotherapy model and the reference one is displayed. This element can be evaluated directly from the tracking figures. This approach could be used like a dosage predictor which is able to modify the immunotherapy strategy, this can be done using a computer with a friendly software which is ready to receive the current data on the IL-2 concentration and then to suggest the corresponding application period, i.e. if the dosage should be supplied or not. The last element in the previous figure shows the reference input that has demonstrated the best possible control action to diminish the cancer effects, and the control function generated by the DNN adaptive controller.

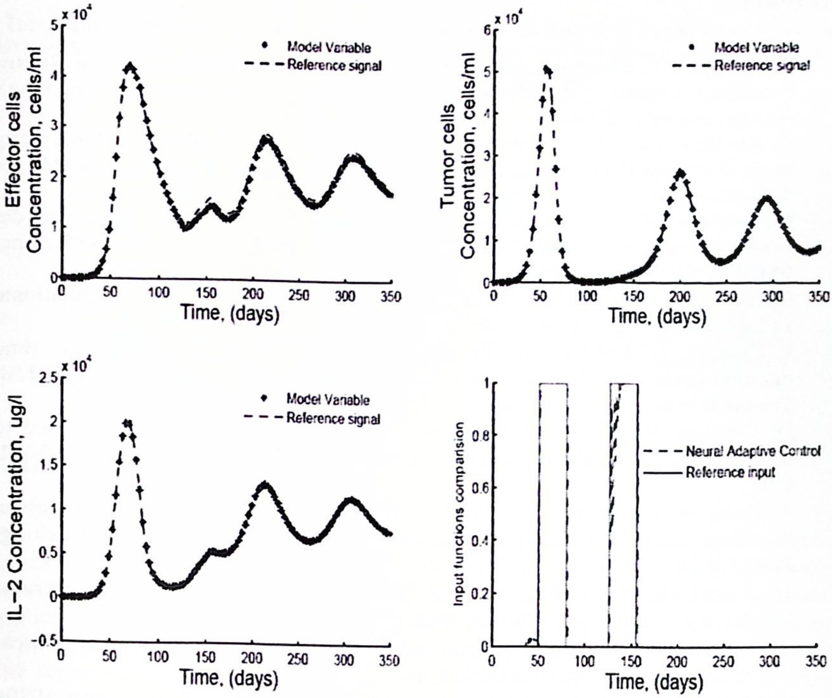

Figure 1. Adaptive Neural Control Process results. The figure at the upper right corner shows the effector cells tracking performance. It is important to note the close relationship between both variables. The same results can be attained for tummor cells and IL-2 concentrations. The last graph demonstrated the reference input (suggetsted by physician) estimation given by the DNNC.

6. Conclusions

In this paper a new model-free neural control is suggested and analyzed. It consists in robust approach application to control a simplified model of a differential neural network observer that represents a model of an uncertain non-linear system to be controlled. The upper bound for the averaged tracking error is established if the local optimal neural control be applied. The control of the real immunotherapy process for cancer treatment is considered. These results suggested the possible application in real medical procedures.

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