Health Technol. (2014) 4:27–30
DOI 10.1007/s12553-013-0069-0

ORIGINAL PAPER

Identification of tumor-immune system via recurrent neural network

Arash Pourhashemi · Sara Haghighatnia · Reihaneh Kardehi Moghaddam

Received: 30 May 2013 / Accepted: 12 December 2013 / Published online: 21 December 2013

Abstract Cancer immunotherapy is an emerging therapy for cancer disease treatment which stimulates immune systems to fight against tumor cells. In this paper, a back propagation neural network with some feedbacks from hidden layer is used as a method of identification for one validated mathematical model. Since it is not possible to model complex system due to void of information and knowledge to model all complexity of complex system, identification methods are effective tools for modeling ill-defined system. Afterward, it is possible to perform control methods on the estimated model to reach the clinical goals. The simulation results have shown the correctness of the identification process.

Keywords Identification · Multi-layer perceptron · Artificial neural network · Immune system

1 Introduction

Cancer diseases are one of the main causes of death in the world. In spite of the fact that a lot of researches have done to overcome cancer diseases the number of people who dies are numerous.

There are different kinds of model which all have shown the tumor growth system in a framework. According to the advantages of immune therapy [1–3], we selected tumor-immune model to describe the tumor immune system. Tumor immune system is one of the most complex systems that it is in charge to fight against all type of potentially dangerous agent which breaks the anatomic barriers of the host organism [4]. This model has been used in different researches [4]. A lot of researches have done to conquer these dangerous diseases.

One way to considering the problem is modeling system. For the aim, we need to have much more knowledge about the system which makes the possibility of investigating system in a frame work. Another way to model system is based on experimental knowledge and assuming the system as a black box which there is no knowledge about the parameters and details of system [2,4,5].

Neural networks are a model simulating human neural system through computer algorithm. What is more, it is a powerful tool that is able to capture and represent complex input/output relationships. That is to say, it can perform the mapping between input signals and output signals.

Identification of systems can be found in various applications and these methods have become popular tools of identification of plants [6,7]. Information on the local data structure and the function approximation is sensitive to the training data [8]. There are different kinds of neural networks, such as multi-layer perceptron [9], Hopfield neural network, back propagation neural network and so on. [10–12]. A typical back-propagation consists of input layers, hidden layers, and output layers [13,14]. A typical back-propagation consists of input layers, hidden layers, and output layers.

In recent years, there has been considerable interest in the application of neural networks to dynamic system identification and control. Identification is necessary if sufficient information about the system being modeled is not available. Neural networks can be classified as feed forward neural networks (FNNs) and recurrent neural networks (RNNs). There are only feed forward connections in the FNNs but both feed forward and feedback connections in the RNNs.

A. Pourhashemi (✉)
Department of Biomedical Engineering, Mashhad Branch, Islamic Azad University, Mashhad, Iran
e-mail: arash.poorhashemi@gmail.com

S. Haghighatnia · R. K. Moghaddam
Department of Electrical Engineering, Mashhad Branch, Islamic Azad University, Mashhad, Iran

S. Haghighatnia
e-mail: sara.haghighatnia@gmail.com

R. K. Moghaddam
e-mail: rkardehi_moghaddam@yahoo.com

Various kinds of neural networks have been used for modeling dynamic systems and a more suitable one to represent dynamics systems is the recurrent neural network which has the inherent format to internally represent the autoregressive aspect if dynamic systems [15,16]. Recurrent neural networks with constant inputs have been proposed in [17]. A recurrent multilayer perceptron architecture consisting of several layers has been proposed in [18]. The recurrent multilayer perceptron architecture covers both the FNN and the single layer fully RNN.

According to the fact that one of the critical stages in control system design is the development of a mathematical model of the system, in this paper we propose an identification based method for modeling of tumor immune system in order to cover complexity and uncertainties. In addition, the identified system is prepared to be implemented by different controlling methods. Therefore, identification of mathematical tumor-immune interaction model is done by multi-layer perceptron neural network with some feedback from hidden layer to its inputs.

The rest of this paper is organized as follows. Section 2 presents the mathematical tumor-immune model. Section 3 we introduce a brief explanation about artificial neural network and system identification and finally the conclusion is represented in section 4.

2 Mathematical model

Tumor immune interaction models have been provided to explain the interaction between tumor cells and immune cells. Ordinary deferential equations (ODE) are used to represent concentrations or populations of cells. In this paper, we use the ODE model which shows the interactions between cells as follows:

$$H = a_0 + c_0 D\left[d_0 H\left(1 - \frac{H}{f_0}\right) - b_0 H \tag{1}$$

$$C = a_1 + c_1 I(M+D)\left[d_1 C\left(1 - \frac{C}{f_1}\right) - b_1 C \tag{2}$$

$$M = \left[d_2 M\left(1 - \frac{M}{f_2}\right)\right] - e_2 MC \tag{3}$$

$$\dot{D} = -e_3 DC \tag{4}$$

$$\dot{I} = a_4 DH - c_4 IC - e_4 I \tag{5}$$

Table 1 Parameters of the model in (1–5) from [19]

Name	Description	value-units(⋆)
a_0	birth of CD4 T	$10^{-4}\ c\ d^{-1}\ mm^{-3}$
b_0	death of CD4 T	$0.02\ d^{-1}$
c_0	max prolif of CD4 T	10
d_0	1/2 satur const of CD4 T	$10^{-2}\ c^{-1}\ d^{-1}\ mm^3$
f_0	carrying capacity of CD4 T	$1\ c\ mm^{-3}$
a_1	birth of CD8 T	$10^{-4}\ c\ d^{-1}\ mm^{-3}$
b_1	death of CD8 T	$0.02\ d^{-1}$
c_1	max prolif of CD8 T	10
d_1	1/2 satur cont of CD8 T	$10^{-2}\ c^{-1}\ d^{-1}\ mm^3$
f_1	carrying capacity of CD8 T	$1\ c\ mm^{-3}$
d_2	1/2 satur const of tumor	$0.02\ d^{-1}$
e_2	killing by CD8 of tumor	$0.1\ c^{-1}\ d^{-1}\ mm^3$
f_2	carrying capacity of tumor	$1\ c\ mm^{-3}$
e_3	CD8 T killing of DC	$0.1\ c^{-1}\ d^{-1}\ mm^3$
a_4	production by CD4 T	$10^{-2}\ c^{-1}\ d^{-1}\ mm^3$
c_4	IL-2 uptake by CD4 T	$10^{-7}\ c^{-1}\ d^{-1}\ mm^3$
e_4	degration rate	$10^{-2}\ d^{-1}\ mm^{-3}$

Where H are the tumor-specific CD4 T helper cells, C are the tumor-specific CD + 8 T cells, M are cancer cells which expose the TAA, D are the mature dendritic cells which are loaded with the TAA (which expose tumor peptides on HLA molecule) and I is the IL-2 secreted by H and responsible for T cell growth [19,20].

3 Artificial neural network

A typical three-layer back propagation neural network with the input layer, hidden layer and output layer is suitable for identification systems. In this paper, the back propagation neural network is used with five feedbacks from hidden layer as its inputs. It has the sigmoid activation functions in the hidden layer and linear activation function in output with sufficient number of neurons in the hidden. In this neural network, the weights are updated as follows:

$$\begin{aligned} W_{bh}(t+\Delta t) &= W_{bh}(t) + \Delta W_{bh}, \\ \Delta W_{bh} &= -\gamma \frac{\partial E}{\partial W_{bh}}, \end{aligned} \tag{6}$$

$$\begin{aligned} W_{ha}(t+\Delta t) &= W_{ha}(t) + \Delta W_{ha}, \\ \Delta W_{ha} &= -\gamma \frac{\partial E}{\partial W_{ha}}, \end{aligned} \tag{7}$$

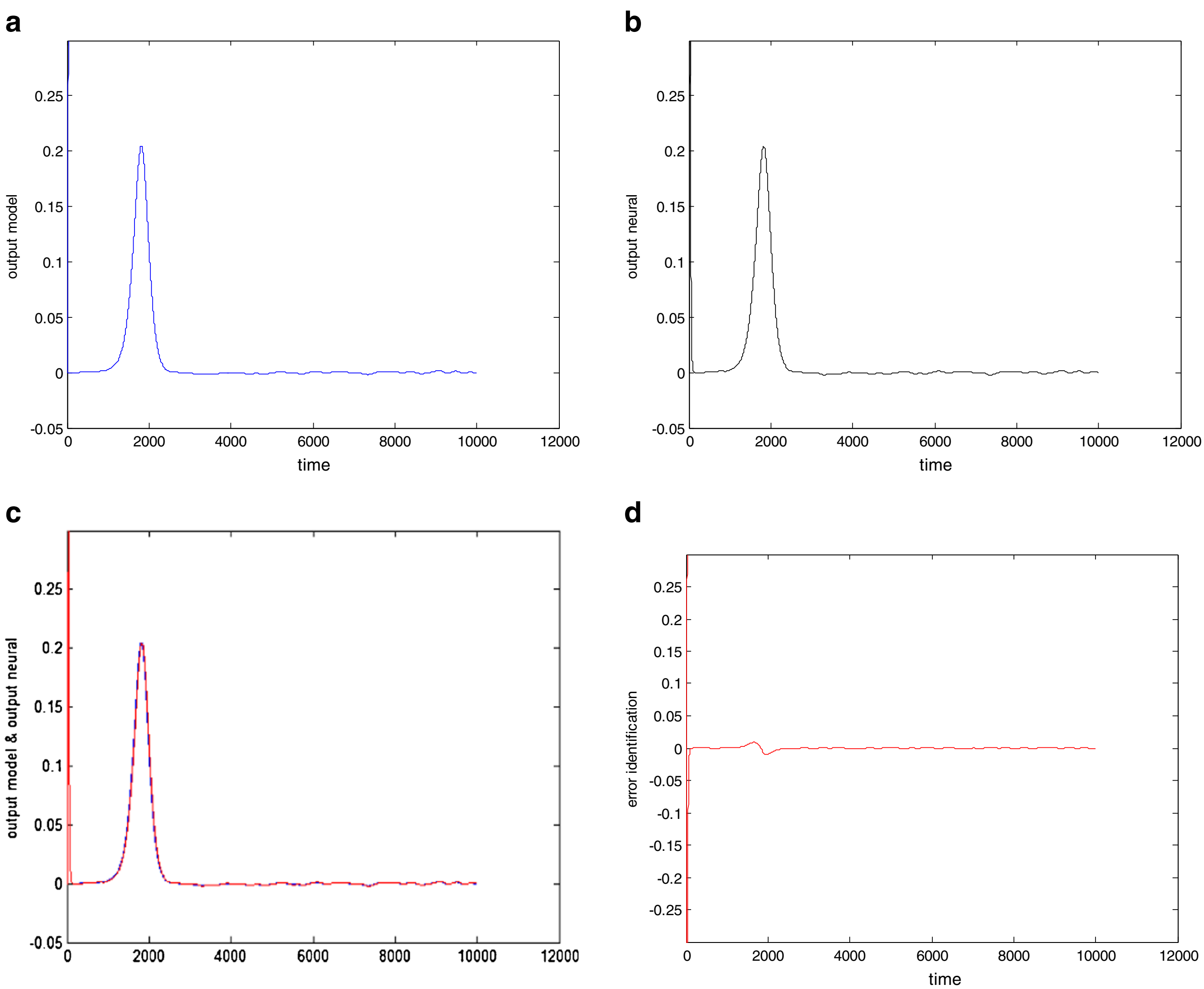

Fig. 1 **a** is Input signal, **b** is Output of the plant, **c** both output neural and output model and **d** is error of identification

Where, W_{yh} is the weight between output layer and hidden layer, and W_{hx} is the weigh between hidden layer and input layer,the coefficient γ is the learnig rate and E is the error which is obtained as follows:

$$E = (y - y_d)^2 \tag{8}$$

Where y is the output of the neural network and y_d is the desired output.

4 Results

The result of identification of system (1–3) with parameter value of Table 1 from [19] are shown in Fig. 1. For system (1–3), the mentioned neural network is used and the feedback is taken from hidden layer. The output of the neural network model and the plant for a random signal (Fig. 1a and b), both output model and output neural (Fig. 1c) and the error identification(Fig. 1d) are shown in Fig. 1c to show the efficacy of identification process.

5 Conclusion

In this paper, we used a tumor-immune model as a complex system with assumption that there is no information about the system as a black box. Afterward,a neural network with five feedback from hidden layer, is used for identification of tumor-immune system. We have proven that a neural network can identify tumor immune model properly if the number of layer and neuron choosed properly.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Pillis et al. Mixed immunotherapy and chemotherapy of tumors: Modeling, applications and biological interpretations. In Elsevier Science 2005.
2. Pillis LG, Radunskaya AE, Wiseman CL. A validated mathematical model of cell-mediated immune response to tumor growth. Cancer Res. 2005;65(17):7950–8.
3. Pappalardo F et al. Vaccine protocols optimization: in silico experiences. Biotechnol Adv. 2010;28:82–93.
4. Sarkar RR, Banerjee S. Cancer self remission and tumor stability—a stochastic approach. Math Biosci. 2005;196:65–81.
5. Merola A, Cosentino C, Amato F. An insight into tumor dormancy equilibrium via the analysis of its domain of attraction. Biomedical signal processing and control. 2008;3:212–219.
6. Kalogirou SA. Applications of arti®cial neural-networks for energy systems. 2000;67:17–35.
7. Gulliford SL et al. Use of artificial neural networks to predict biological outcomes for patients receiving radical radiotherapy of the prostate. Radiother Oncol. 2004;71:3–12.
8. Parlos AG, Menon SK, Atiya AF. An algorithm approach to adaptive state filtering using recurrent neural network. IEEE Trans Neural Netw. 2001;12(6):1411–32.
9. ZHANG W. System identification based on generalized ADALINE neural network. Int J Intell Control Sys. 2006;11(1):17–25.
10. Alexander IG. Neural networks theory. New York: Springer; 2010.
11. David MS. Building neural networks. Boston: ACM Press; 1996.
12. Eberhard RC, Dobbins RW. Neural Network PC Tools: A Practical Guide. A Practical Guide. Academic Press, San Diego, pp: 414, 1990.
13. Weerasooriya et al. Identification and control of a DC motor using back-propagation neural networks. IEEE Power Energy Soc. 1991; 6:663–669.
14. Narendra KS, Parthasarathy K. Identification and control of dynamical systems using neural networks. IEEE Comput Intell Soc. 1990;1(1):4–27.
15. Gparlos A, Chong KT, Atiya AF. Application of the reccurent multilayer perceptron in modeling complex process dynamics. IEEE Trans. 1994;5(neural network):255–266
16. Obradovic D. On-line training of recurrent neural networks with continuos topology adaptation. IEEE Trans. 1996;7(neural networks):222–228.
17. Pineda F. Generalization of backpropagation to recurren neural networks. 1987;59(19):2229–2232.
18. Puskorius GV, Feldkamp LA. Neurocontrol of nonlinear dynamical systems with Kalman filter-trained recurrent networks. IEEE Trans Neural Netw. 1994;5(2):279–97.
19. Castiglione F, Piccoli B. Optimal control in a model of dendritic cell transfection cancer immunotherapy. Bull Math Biol. 2006;68:255–74.
20. Castiglione F, Piccoli B. Cancer immunotherapy, mathematical modeling and optimal control. J Theor Biol. 2007;247(4):723–32.