International Journal of Medical, Medicine and Health Sciences
ISSN: 2517-9969
Vol:13, No:1, 2019

A Recommendation to Oncologists for Cancer Treatment by Immunotherapy: Quantitative and Qualitative Analysis

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***Abstract*—**Today, the treatment of cancer, in a relatively short period, with minimum adverse effects is a great concern for oncologists. In this paper, based on a recently used mathematical model for cancer, a guideline has been proposed for the amount and duration of drug doses for cancer treatment by immunotherapy. Dynamically speaking, the mathematical ordinary differential equation (ODE) model of cancer has different equilibrium points; one of them is unstable, which is called the no tumor equilibrium point. In this paper, based on the number of tumor cells an intelligent soft computing controller (a combination of fuzzy logic controller and genetic algorithm), decides regarding the amount and duration of drug doses, to eliminate the tumor cells and stabilize the unstable point in a relatively short time. Two different immunotherapy approaches; active and adoptive, have been studied and presented. It is shown that the rate of decay of tumor cells is faster and the doses of drug are lower in comparison with the result of some other literatures. It is also shown that the period of treatment and the doses of drug in adoptive immunotherapy are significantly less than the active method. A recommendation to oncologists has also been presented.

***Keywords*—**Tumor, immunotherapy, fuzzy controller, Genetic algorithm, mathematical model.

I. Introduction

IN the recent decades, the issue of modeling, diagnosis, and treatment of cancer is not only in the focus of attention of clinicians and biology researchers but also is in interest of scientists, including mathematicians and control engineers. Cancer is the second leading cause of death globally after heart disease According to a report, which was published in 1994 in Britain, one out of three persons will get cancer during his or her lifetime [1]. Experimental methods for treatment of cancers are malefic and with exorbitant expense, whereas cancer modeling can predict the result of treatment at no cost. As a result, cancer modeling has absorbed attractions of many scientists in various majors. In [2], [3], examples of modeling of cancer growth in ODE equations and in [4], [5] the partial differential equations (PDE) have been studied.

Different methods for cancer treatments have been devised such as chemotherapy, immunotherapy, surgery and radiotherapy. One of them is used based on patient condition. Cancer treatment has two essential obligations. First, the destruction of tumor cells should be completely done by the treatment. Second, healthy cells should be preserved, and they should be distinguished from tumor cells. For instance, the chemotherapy approach is not a complete appropriate method because it damages healthy cells, whereas the immunotherapy is an appropriate method because of possessing both obligations [6].

Immunotherapy is alimentation of normal immune system against tumor cells, which is done with vaccine therapy. In this method, the immune system is activated to destroy tumor cells. Here the word of vaccine has some curing features against its usual use as a preventing method. The importance of immune system for extirpating cancer has been demonstrated by clinical data in many articles such as [7], [8].

In Section II, a simplified model proposed in [6] will be studied. This model presents the battle between tumor cells and the important parts of immune system. It is assumed that the patient has a metastatic cancer. It also considers two types of immunotherapy, active immunotherapy and adoptive immunotherapy. In adoptive immunotherapy, activated T lymphocyte cells are injected to a person who has the metastatic cancer. These cells move through tissues and when encounter tumor cells; they are activated by the recognition of tumor cell antigens [9]. In active immunotherapy, the weakened tumor cells with their antigens are injected to the patients and it activated the helper T lymphocyte cells and immune system.

In Section III, the dynamic of the system, the equilibrium point and the stability of system are studied. In the next section the fuzzy controller is applied to the system, the advantages of fuzzy controller will be discussed later. Since the closed loop systems are more reliable and more accurate, the closed loop system is used here. For example, in [10] the open loop system is used for the treatment of cancer. Consequently, one of the two patients had died. In [11] the closed loop system is used and both of the patients are cured. Therefore, in this paper, the fuzzy closed loop controller system has been designed and by the use of that an immunotherapy protocol has been proposed. The unknown parameters of membership functions are acquired by the use of genetic algorithm.

II. Mathematical Model and Its Stability

Many mathematical models are proposed to show confrontation of immune system and tumor cells until now. A

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brief history of them is mentioned in [12].

The immune system mechanisms are different against diseases. However, they are divided to the two main branches; the innate immune system and the adaptive immune system. They are the most important aspects of an immune system.

The innate immune system contains proteins and cells, which always exist in a body. Its tasks are to fight and destroy the microbes. However, unfortunately, some of these microbes escape and overcome the innate immune system, so that they activate the adaptive immune system. Therefore, responsibility of adaptive immune system clarifies here; it should fight with these escapee microbes and destroy them. The natural killer cells are a part of innate system. The IL-2 and IFN6 cytokines activate the NK cells, and cause the natural killer cells change to LAK cells (lymphokine-activated killer cell). TNF (tumor necrosis factor) that is produced by LAK cells is more effective than NK cells. Therefore, the model consists of the interaction among NK cells, LAK cells and T helper cells with tumor cells, which is proposed in [6]. This model is simple and consists of the most important factors, which are involved in interaction of tumor cells and immune system. In addition, two different considered immunotherapies can be compared to each other easily. All of the system parameters are estimated in Table I and according to [6] they are considered in peripheral blood. The goal of this part is finding the equilibrium point and its stability.

According to the adoptive immunotherapy, the simplified equations of the model will be [6]:

$$\dot{T} = a_1 T - \alpha_1 TK - \beta_1 TL \tag{1}$$

$$\dot{K} = s_2 - dK - \alpha KH + \beta_2 T \tag{2}$$

$$\dot{L} = -dL + \alpha KH \tag{3}$$

$$\dot{H} = s_4 - d_4 H + \alpha_4 H\left[\mathrm{T} - q_4 T^2\right] + v \tag{4}$$

Also with the active immunotherapy, the equations are [6]:

$$\dot{T} = a_1 T - \alpha_1 TK - \beta_1 TL \tag{5}$$

$$\dot{K} = s_2 - dK - \alpha KH + \beta_2 T \tag{6}$$

$$\dot{L} = -dL + \alpha KH \tag{7}$$

$$\dot{H} = s_4 - d_4 H + \alpha_4 H\left[\mathrm{T} - q_4 T^2\right] + \beta_4 HV \tag{8}$$

$$\dot{\mathrm{V}} = s_7 - d_7 V \tag{9}$$

- No treatment condition: In this condition, we consider that there is no immunotherapy treatment. So the equations change as;

$$\dot{T} = a_1 T - \alpha_1 TK - \beta_1 TL \tag{10}$$

$$\dot{K} = s_2 - dK - \alpha KH + \beta_2 T \tag{11}$$

$$\dot{L} = -dL + \alpha KH \tag{12}$$

$$\dot{H} = s_4 - d_4 H + \alpha_4 H\left[\mathrm{T} - q_4 T^2\right] \tag{13}$$

- The equilibrium point: To find the equilibrium points, (10)-(13) should be equaled to zero. Therefore, the no tumor equilibrium point is:

$$E_0 = \left(0, \frac{s_2}{d + \frac{\alpha s_4}{d_4}}, \frac{\alpha s_4 s_2}{dd_4\left(d + \frac{\alpha s_4}{d_4}\right)}, \frac{s_4}{d_4}\right) \tag{14}$$

The stability of this point has a high importance. If the system changes a little from equilibrium condition, it will move back to its equilibrium point. First, the system around this equilibrium point with Jacobian matrix is linearized as:

$$A = \begin{bmatrix} a_1 - \alpha_1 K - \beta_1 L & 0 & 0 & 0 \\ \beta_2 & -d & 0 & -\alpha H \\ 0 & \alpha H & -d & 0 \\ \alpha_4 H & 0 & 0 & -d_4 \end{bmatrix} \rightarrow$$

$$A_{E_0} = \begin{bmatrix} a_1 - \alpha_1 K_0 - \beta_1 L_0 & 0 & 0 & 0 \\ \beta_2 & -d & 0 & a_{24} \\ 0 & a_{32} & -d & 0 \\ a_{41} & 0 & 0 & -d_4 \end{bmatrix}$$

$$a_{11} = a_1 - \frac{\alpha_1 s_2}{d + \frac{\alpha s_4}{d_4}} - \frac{\beta_1 \alpha s_4 s_2}{dd_4(d + \frac{\alpha s_4}{d_4})}, a_{24} = \frac{-\alpha s_2}{d + \frac{\alpha s_4}{d_4}},$$

$$a_{32} = \frac{\alpha s_2}{d + \frac{\alpha s_4}{d_4}}, a_{41} = \frac{\alpha_4 s_4}{d_4}$$

Now the eigenvalues of this matrix are found as:

$$\begin{cases} \lambda_1 = a_{11} = a_1 - \dfrac{\alpha_1 s_2}{d + \dfrac{\alpha s_4}{d_4}} - \dfrac{\beta_1 \alpha s_4 s_2}{dd_4(d + \dfrac{\alpha s_4}{d_4})} \\ \lambda_2 = -d \\ \lambda_3 = -d \\ \lambda_4 = -d_4 \end{cases}$$

For stability, all of the eigenvalues must be negative. The parameters d and d_4 are always positive. So the eigenvalues

$\lambda_2, \lambda_3, \lambda_4$ are always negative. The value of λ_1 must be lower than zero because of stability. So the stability boundary is as:

$$\lambda_1 = a_1 - \frac{\alpha_1 s_2}{d + \frac{\alpha s_4}{d_4}} - \frac{\beta_1 \alpha s_4 s_2}{dd_4(d + \frac{\alpha s_4}{d_4})} < 0 \rightarrow a_1 < \frac{\alpha_1 s_2 dd_4 + \beta_1 \alpha s_4 s_2}{d + \frac{\alpha s_4}{d_4}} \quad (15)$$

Equation (15) shows the stability boundary. By considering Table I this equilibrium point is unstable which is shown in Fig. 1 (a), it shows that in the same initial conditions, a little change in amount of a_1 causes the system becomes unstable. Fig. 1 (b) shows that system is sensitive with initial conditions. If the initial tumor cells changed to 10 numbers and all of the other initial conditions were the same, the system would be unstable.

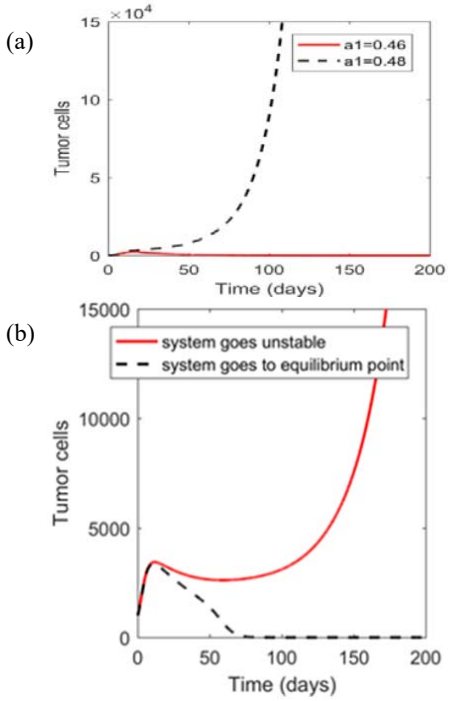


Fig. 1 (a) With the initial conditions of K=500, L=1, H=700, T=1000 the system is stable. However, if the number of tumor cells increase to 1010, system becomes unstable. (b) A little change in amount of a_1 causes the system becomes unstable. All of the parameters are from Table I

III. Fuzzy-Genetic Controller for Immunotherapy

In this part, the fuzzy logic controller is used to stabilize the unstable equilibrium point. The fuzzy controllers have some advantages in comparison with common ones. For example, they can be designed with the wide bounds of inputs and outputs. They are easy to understand and flexible. The inaccuracy of data has a little effect on the system controller and they are suitable for nonlinear systems. The common controllers linearized the nonlinear systems so that their results can be unreliable [8]. The input of fuzzy controller system is the tumor cells, which is the output of model. And the output of fuzzy controller is the doses of vaccine, which is the input of model. The range of the input controller is considered from 0 to 4000 and the range of the output is considered from 0 to 1000. The membership functions are assumed as a Gaussian membership function. It is defined as:

$$gaussian(x, c, \sigma) = e^{\frac{1}{2}\left(\frac{x-c}{\sigma}\right)^2}$$

The parameter c shows the position of center and σ is the width of the membership function. For finding these parameters, the Genetic algorithm (GA) is used. The cost function is defined as:

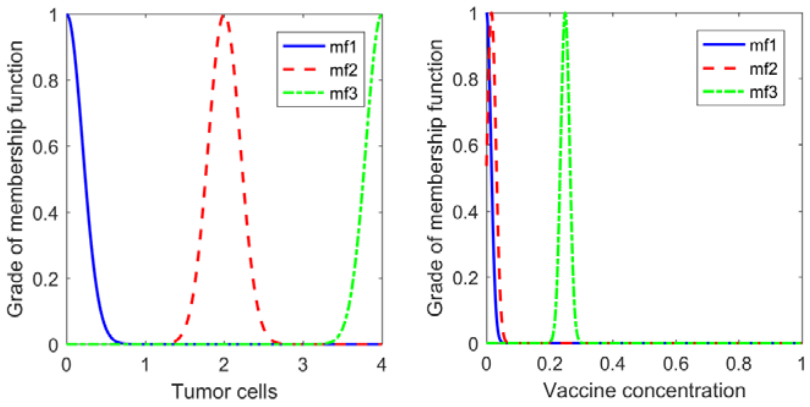
$$J = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(y_i - t_i)^2}$$

y_i is the output of model and t_i is the desired output. Here t_i should be zero because the number of tumor cells should go toward zero. The parameters of membership functions are unknown in fuzzy controller and the bound of output and input is certain. The GA finds these unknown parameters for cost function, which means that the tumor cells become zero. The Roulette Selection with uniform crossover has been used, the mutation rate is 0.01 and the maximum generation is equal to 150.

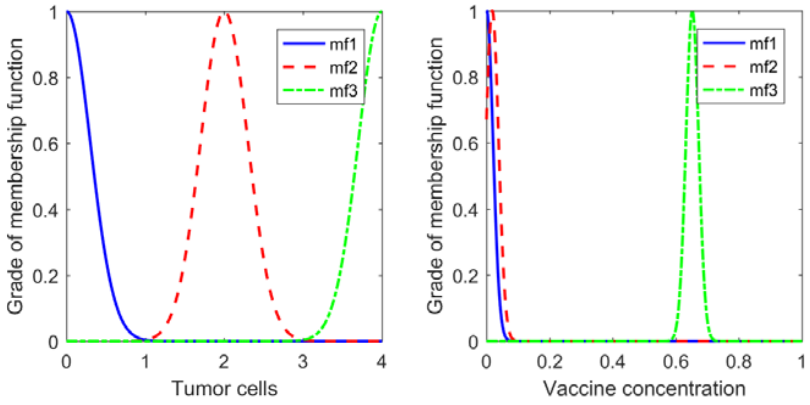
IV. Analysis and Results

The normalized membership function of input and output of fuzzy controller is shown in Fig. 2. Their parameters have been gained with genetic algorithm. The value of Gaussian membership functions parameters is inserted in Table II. The changes of tumor cells, natural killer cells, LAK cells and T helper cells with the fuzzy genetic controller, are as Fig. 3 and the doses of the vaccine which are required for treatment are shown in Fig. 4.

According to Fig. 4, the adoptive immunotherapy can kill the tumor cells faster and also causes the fast raising in T helper cells, with consequence of activating the immune system faster. Period of treatment in active immunotherapy is longer than adoptive immunotherapy. Also according to Fig. 4 the doses of drug in adoptive immunotherapy is lower than active immunotherapy. In both kinds of immunotherapies with fuzzy-genetic controller, the tumor cells will be killed less than 70 days. For example, in [13] this time is 250 days, 200 in [14] and 150 in [15], also the doses of immunotherapy drug have been decreased from the drug doses of other references [e.g. 16], which can reduce the side effects of high doses drugs.



(a)



(b)

Fig. 2 The membership functions of fuzzy controller's output and input (a) The Gaussian membership functions of adoptive immunotherapy's input and output, which GA founds the parameters and uses Selection Roulette and uniform crossover. (b) The Gaussian membership functions of active immune therapy and the values of parameters are shown in Table II

V. A Recommendation to Oncologists

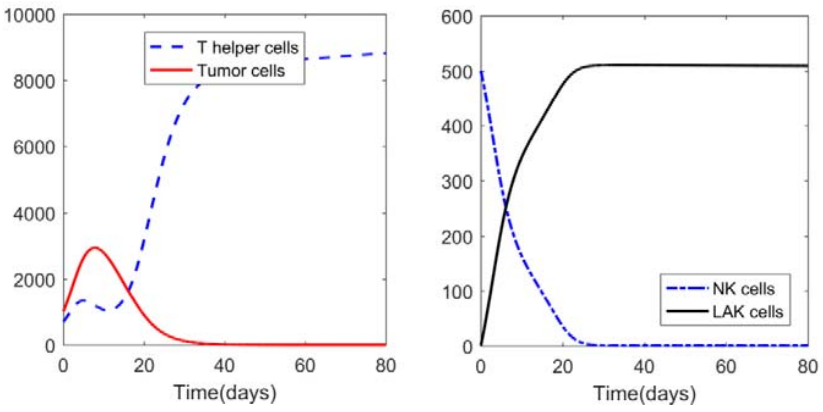
So the oncologists' recommendation for both methods is expressed as: On one hand, according to protocol in Fig. 4 (a), if the oncologists employ adoptive immunotherapy; first, they should apply 45 doses of vaccine in first 15 days. Secondly, they decrease the doses to 29 in second 15 days until the 30th day. Finally, in next ten days, until the day of 40th, the doses of the drug decline to 13.5 whereas, the tumor cells will be decreased to zero and the patient will be cured, as well. It is according to Fig. 4 (a). The total doses of drug will be 1254 in adoptive immunotherapy. On the other hand, if the oncologist uses the active immunotherapy; first, the doses of vaccine in the first 15 days should be 140 doses. Secondly, in the next 15 days, until the day of 30th, the doses of vaccine reduce to 45. Thirdly, there is a decline to 23.7 doses in next fifteenth day until the day of 45th. Fourthly, for days of 45 until 60 the doses of the drug go down to 13.6 units. Eventually, for last 10 days, until the day of seventieth, the doses of vaccine is 10, and according to Fig. 4 (b) the patient will be treated. The usage of drug is 34345 doses in 70 days.

TABLE I
Estimated Parameters

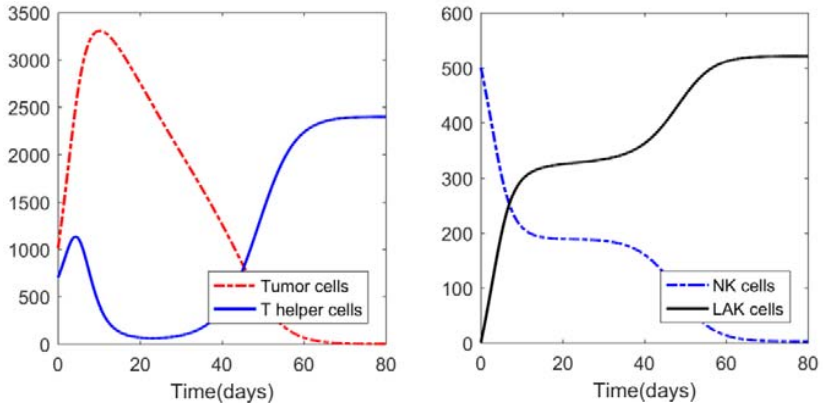
Parameter	Estimated Value	Source	Parameter	Estimated Value	Source
a_1	0.3,0.35	[6]	α	0.0001	[6]
d_4	0.00055	[6]	β_2	0.00025	[6]
α_1	0.00001	[6]	S_4	0.38	[6]
β_1	0.001	[6]	α_4	0.00025	[6]
S_2	0.68	[6]	q_4	0.0004	[6]
d	0.0014	[6]	β_4	0.001	estimated

TABLE II
Parameters of Membership Functions

	Input parameters		Output parameters			Input parameters		Output parameters	
Adoptive immunotherapy	C	σ	C	σ	Active immunotherapy	C	σ	C	σ
	0.2026	0	0.02029	0.0003931		0.2998	0	0.01411	0
	0.2026	2	0.02029	0.01811		0.2998	2	0.01411	0.01577
	0.2026	4	0.02029	0.6522		0.2998	4	0.01411	0.2493



(a)



(b)

Fig. 3 Changes of system against vaccine therapy. (a) tumor cells, T helper cells, NK cells and LAK cells with initial conditions of 1010 ,700, 500, 1 during adoptive immunotherapy and Fuzzy-Genetic controller. (b) Changes of system when active immunotherapy with fuzzy-genetic controller is applied to system

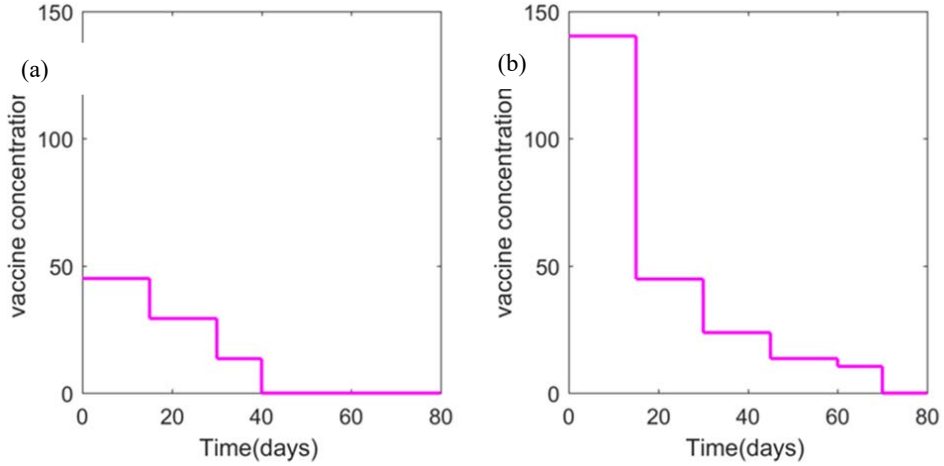


Fig. 4 Doses of drug (a) the adoptive immunotherapy (b) the active immunotherapy

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