Original Article

A Predictive Approach for the Tumor-Immune System Interactions Based on an Agent Based Modeling

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A B S T R A C T

Purpose- The goal of this study is to introduce a quantified feature for investigating the quality manner and interaction between the immune system and tumor cell.

Methods- For this purpose, we introduced an agent based model which uses two agents consisting tumor cell and CD8+ cells and the environment which consists IL-2 and TGF-β cytokines. This model works using a variety of ratios. The most important ratio of this model is the tumor's proliferation ratio.

Results- We investigated this ratio in three states of tumor-immune system interaction consisting elimination, equilibrium and escape using a raw model, then this ratio was investigated using models which were optimized by experimental data.

Conclusion- The results showed that if the model is leaning to the elimination state, this ratio falls faster and if is leaning to the escape state, this ratio will reduce slowly. The result was proved by models which used experimental data for optimizing. Therefore, using this ratio we can compare different manners of tumor-immune system interactions.

1. Introduction

Cancer is the boundless proliferation of cells [1, 2]. It is one of the most difficult diseases to treat and one of the main causes of mortality in the world. The lack of knowledge about cancer make it hard to understand and treat. Despite the wide range of research about cancer, the mortalities caused by it are numerous.

In order to achieve a relatively good knowledge about real world consisting biological phenomena, mathematical models were developed. These may show an approximated manner of real world and can make some extra experiments which may be hard, expensive and dangerous or non-ethic to do in practice. On the other hand, they may make some new knowledge about the real world. Biological sciences, especially cancer research field is a capable field of making mathematical models. The joint work of immunologists and mathematicians made some advances in cancer immunology [1-3]. The main concern of cancer modeling researchers

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is to find a reliable model which is able to act as a real interactive manner of tumor and the immune system. Sufficient models may cause a prespective and predictive way for the tumor manner [4].

There are many advances in research about tumor-immune interactions based on ordinary differential equation models (ODE) and these models are very popular among cancer modeling researchers [5]. However, these models are not able to show sub-state manners, memory and selecting strategies by the cells and emerging properties of molecules which are important characteristics of these interactions. Agent based models (ABM) of tumor-immune interaction is one of the alternatives of ODE which can show a more realistic manner and present more hidden information about these interactions. The ABM is a type of system simulation modeling which is a set of approaches to mimic the real manner of system [6, 7]. Using ABM, systems can be modeled as object oriented, employing autonomous agents which interact together [8-10]. The interactions between agents were defined by the rules which determine the relation of agents. The outcomes of these models illustrate the overall behavior of the system that arise from the interaction of each agent with other agents and environments.

Kirsches and Panetta [3] describe the interaction between the effector cell, tumor cell, and IL-2. They illustrated the effect of adoptive cellular immunotherapy and the tumor cells. Wilson and Levy propose an ODE model related to immunotherapy using TGF-β [11]. They analyzed the effect of TGF-β as a treatment for tumor growth. The ODE models are very useful to describe the biological phenomena but have several limitations. For example, they are not capable of representing individual behavior and emerging properties over the simulation course [12, 13]. Scholl [14] tries to describe the strength and weakness of ODE and ABMS. Pourdehnad [15] compared the two methods and the conceptual framework for ODE and ABMS to a model group learning to compare methods in order to propose their use in a complementary way. Lorenz [16] compared ABM and ODE from 3 different points of view: structure, behavior and emergence. Grazziela [17] obtained equivalent agent-based modeling from ODE formulation and compared outcomes. He confirmed that ABM is useful as the toolkit for assisting immune studies.

There are a few studies which used ABM approach for cancer research, but plenty examples showed agent based modeling and simulation can lead to a better comprehension of the trend for cancer growth in patients.

The agent based models are used for modeling the tumor-immune system with spatial [18] and/or non-spatial [17] features. As a non-spatial approach, the ABM is an alternative to ODE models to consider the memory and emerging properties of tumor-immune system interactions, which were not considered in ODE models. On the other hand, in comparison with stochastic approaches for modeling the tumor-immune interactions, the ABM's emergent behaviors can show more patterns of the system, which were not discovered by stochastic models [19]. Moreover, using agent based models, we can obtain an insight into the new knowledge which can not be obtained using other structures of modeling. For example, using agent based model for tumor-immune system interactions, it would be possible to extract the rules which accured [20].

Agent based modeling consists of agents, an environment and a framework for simulating agent behaviors and interactions with each other, and also with their environments. Agents are autonomous decision making units with diverse characteristics. The environment is defined by the region in which agents behave and interact.

One of the advantages of ABM is a simplification of complex processes to understand and apply by the biology researchers. These models can show the interactions as simple as possible for the biologists.

In this study, we intend to present an agent based model of tumor-immune interaction and investigate the sub-states of tumor as important features, which can describe the overall manner of the system. This model will contain four compartments, two of them are agents containing tumor cells and two of them are environment components which include TGF-β and IL-2 cytokines.

In the following, the considered model will be introduced first, then the parameters of the raw model will be changed to achieve three overall state

of tumor-immune interaction system containing Elimination, Equilibrium and Escape. Then, the ratio functions of tumor death and proliferation will be obtained. Finally, using experimental data which were gathered from two cancerous groups of mice models, one treated and the other one not, we will optimize the model and the ratio function of tumor death and proliferation will be compared.

2. Methods and Materials

As previously described, the considered model is a rational ABM which derived from an ODE model. This model contains four compartments which include tumor cells, effector cells, TGF-β and IL-2 cytokines. This model should be optimized using the experimental data which were gathered from two groups of mice models. In the following, the considered model and optimizing approach will be introduced first, then the experimental data acquisition will be described.

2.1. Agent Based Model

The considered ABM is based on an ODE model in order to make a rational approach to model the tumor-immune system interactions. This model was implemented with MATLAB simulation software (2013). The basic ODE model contains tumor cells, effector cells, TGF-β and IL-2 cytokines and is based on a mathematical model which was introduced by Arciero *et al* [1] as follows:

$$\frac{dT}{dt} = aT\left(1 - \frac{T}{K}\right) - \frac{a_a ET}{g_2 + T} + \frac{p_2 ST}{g_3 + S} \quad (1)$$

$$\frac{dE}{dt} = \frac{cT}{1 + \gamma S} - \mu_1 E + \left(\frac{p_1 EI}{g_1 + I}\right)\left(p_1 - \frac{q_1 S}{q_2 + S}\right) \quad (2)$$

$$\frac{dI}{dt} = \frac{p_3 ET}{(g_4 + T)(1 + \alpha S)} - \mu_2 I \quad (3)$$

$$\frac{dS}{dt} = \frac{p_4 T^2}{\theta^2 + T^2} - \mu_3 S \quad (4)$$

Where T is tumor size, E is the number of effector cells, I is the concentration level of IL-2, S is the concentration level of TGF-β, K shows the maximum population of tumor cells and θ shows the maximum level of the TGF-β concentration.

The first item of equation 1 corresponds with the growth of tumor cells, the second one corresponds with the effector induced death of tumor and the third one corresponds with the tumor growth stimulation derived by TGF-β. In equation 2, the first item corresponds with the effector cell recruitment which was stimulated by tumor immunogenecity and suppressed by TGF-β. The second one introduces the apoptosis of effector cells and the third one is corresponding with the effector cell proliferation which was stimulated by IL-2 and suppressed by TGF-β. In equation 3, the first item shows IL-2 producing which was stimulated by the interaction of effector cells and tumor cells and suppressed by TGF-β and the second one shows the IL-2 utilization. Finally, in equation 4, the first item shows the TGF-β production and the second one is corresponding with the TGF-β utilization.

The considered ABM uses a ratio and messages for modeling these interactions as follows:

$$T(n+1) = T(n) + T(n)(r_1(n) - r_2(n) + r_3(n)) \quad (5)$$

$$E(n+1) = E(n) + E(n)\left(-r_4(n) + r_5(n)\right) + m_1(n) \quad (6)$$

$$I(n+1) = I(n) - r_6(n)I(n) + m_2(n) \quad (7)$$

$$S(n+1) = S(n) - S(n)r_7(n) + m_3(n) \quad (8)$$

Where T(n) is the tumor size at n-th step time, E(n) is the number of effector cells at n-th step time, I(n) is the concentration level of IL-2 at n-th step time and S(n) is the concentration level of TGF-β and r_1 is the ratio of tumor proliferation, r_2 is the ratio of effector induced death of the tumor, r_3 is the ratio of TGF-β stimulated tumor growth, r_4 is apoptosis ratio of effector cells, r_5 is effector proliferation which was stimulated by IL-2 and suppressed by TGF-β, r_6 is IL-2 utilization ratio and r_7 TGF-β utilization ratio. In addition to these ratios, there are some messages which have an effect on each compartment independently, including m_1 which is a message from tumor to stimulating recruitment of effector cells, m_2 which is a message from effector cells for producing IL-2 and m_3 which is a message from tumor cells to producing TGF-β. These ratios and message descriptions are presented in Table 1.

Table 1. The description of ABM's ratios.

Component name	Value name	Description	Definition
Tumor	r_1	Tumor Proliferation	$a\left(1-\frac{T}{K}\right)$
	r_2	Tumor Killing by Effector Cells	$\frac{a_a E}{g_2+T}$
	r_3	Tumor Proliferation Stimulated by TGF-β	$\frac{p_2 S}{g_3+S}$
Effector	r_4	Effector Apoptosis	μ_1
	r_5	Effector Proliferation Stimulated by IL-2	$\left(\frac{p_1 E}{g_1+I}\right)\left(p_1-\frac{q_1 S}{q_2+S}\right)$
	m_1	Effector Recruitment	$\frac{cT}{1+\gamma S}$
IL-2	r_6	IL-2 Utilization	μ_2
	m_2	IL-2 Production by Effector Cells	$\frac{p_3 ET}{(g_4+T)(1+\alpha S)}$
TGF-β	r_7	TGF-β Utilization	μ_3
	m_3	TGF-β Production by Tumor Cells	$\frac{p_4 T^2}{\theta^2+T^2}$

The main aim of this study is to investigate the growth and death ratio of tumor. The growth ratio is equal to the sum of tumor proliferation ratio (r_1) and the ratio of tumor proliferation stimulated by TGF-β (r_3).

After constructing the model, we will use a genetic algorithm for optimizing the model. The Genetic Algorithm (GA) is an adaptive heuristic search algorithm based on simplifications of natural evolutionary processes. This algorithm was first introduced by Holland [21]. As such, they represent an intelligent exploitation of a random search used to solve optimization problems. The basic techniques of the GA are designed to simulate processes in natural systems necessary for evolution. Since in nature, the competition among individuals for scanty resources results in the fittest individuals dominating over the weaker ones.

2.2. Data Acquisition

In this section, we presented the in vivo experiment carried on 2 mice groups (balb/c). The experiment duration was 20 days. Mice were divided into two groups, one for the control untreated group and the other one was the test group. The experiments were performed by using a mouse cell line of breast cancer (4T1). 106 4T1 cells, which were purchased from Pasteur Institute of Iran, were incubated at 37°C and 5% CO2 in air atmosphere in a 25 mL flask with 7 ml of complete culture medium (containing 10% FBS and 1% glutamine). The control group contained 15 mice without any treatmentand the test group contained 15 mice which were treated by 50mg/kg fluoracil (5-FU) from the 5th day (when the tumor was tangible for the first time) by 3 days interval. The time and description of these two groups are shown in Table 2.

Table 2. The description of mice groups.

Group's Name	5-FU Injection Time (day)	Experiment Time (day)	The Number of Mice
A_1	5^{th}	8^{th}	3
A_2	5^{th}, 8^{th}	11^{th}	3
A_3	5^{th}, 8^{th}, 11^{th}	14^{th}	3
A_4	5^{th}, 8^{th}, 11^{th}, 14^{th}	17^{th}	3
A5	5^{th}, 8^{th}, 11^{th}, 14^{th}, 17^{th}	20^{th}	3
Control	Without threat	Three mice for each test group	15

For tumor inoculation, 7×105 cells of 4T1 breast cancer cell line in 200 µL of incomplete culture medium subcutaneous were injected to the right flank of mice, after the 5th day the tumor was tangible for all mice. In this study, we measured the tumor size and the number of tumor infiltrating CD8+ cells. For measuring the tumor size we used caliper and measured the big (a) and small diameters of tumor. Using the equation 9, we estimated the tumor size in mm^3.

$$Tumor\ Size = \frac{1}{6}\pi ab^2 \quad (9)$$

For numbering the tumor infiltrating CD8+ cell at each experiment time, we extracted the tumor from mice and using Immunohistochemistry (IHC) the number of tumor infiltrating were counted. For using the IHC, the formalin-fixed, paraffin-embedded tumor section (with 4 µm thickness) were pasted on 3-aminopropyltiethoxysilane (APTS) coated glass slides. Then, these sections were deparaffinised by xylene for 7 minutes and in the next step, sections were placed in 70% ethanol for 5 minutes. Then, the section surface were embrocated by 0.3% H2O2. At antigen retrieval step, the sections were placed by Tris-EDTA buffer (pH=9) for 11 minutes in autoclave at 100° centigrade. Then the sections were embrocated with distilled water and placed in phosphate buffer. After that, the primary antibody with 1:200 fraction was added to the sections for 1 hour, again the section embrocated with distilled water and placed in phosphate buffer, then the secondary with 1:200 fraction was added to the sections for half of an hour. The DAB chromogen were then added to sections for 5 minutes and sections were placed in hematoxylin for 2 minutes. Finally, sections were placed in xylene for 2 minutes and three times. A sample of IHC images of these sections is shown in Figure 1. For counting the number of tumor infiltrating CD8+ cells using IHC images, an image of each sample was captured from the section with 50µm×50µm area. The image processing toolbox of MATLAB (2013) was used for counting the tumor infiltrating CD8+ cells.

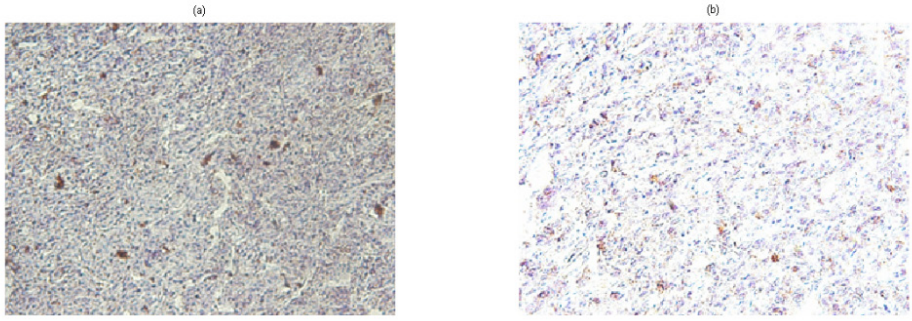

Figure 1. A sample of histological section of tumor infiltrating CD8+ (brown dots) (a) Control group, (b) Test group.

3. Results

As mentioned previously, the introduced ABM will be used in two parts. In the first part, without using any experimental data, the model will be executed and some parameters will be changed to simulate the different overall manner of tumor-immune system interactions and the ratios of tumor growth and death over the time will be investigated. In the second part, using the experimental data, the model will be optimized and their tumor growth and tumor death ratios will be investigated.

In order to achieve the first part of our results, the values of the model's parameters were obtained from [5] (Table 3). For obtaining the states of the model (Elimination, Equilibrium and Escape) a value of the model's parameter, which may be interpreted as a consequent of immunogenicity of tumor cells and cytotoxicity of effector cells (c), was changed between 0.005, 0.05 and 0.5. The lower value of c may lead the model's outcome to the Escape state and the higher value may lead the model's outcome to the Ellimination (Figure 2).

Table 3. Parameter values of the model **[17]**.

Parameters	Values	Parameters	Values
A	0.18	μ3	10
Aa	1	p1	0.1245
Alpha	0.001	p2	0.27
g1	20000000	p3	5
g2	100000	p4	2.84
g3	20000000	q1	10
g4	1000	q2	0.1121
Gamma	10	Theta	1000000
μ1	0.03	K	10000000000
μ2	10		

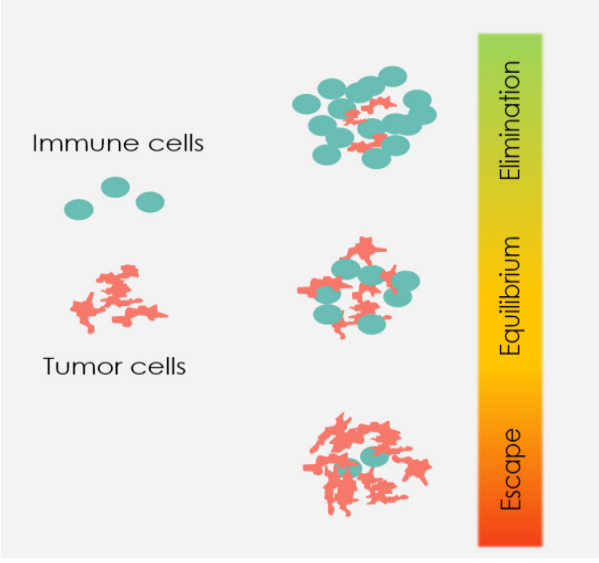

Figure 2. The EEE states of tumor-immune system interactions

By changing the c in the model, we simulated the EEE as follows and the outputs of the model which contain tumor size, number of effector cells, concentration of IL-2 and TGF-β were obtained as illustrated in Figure 3 to 5.

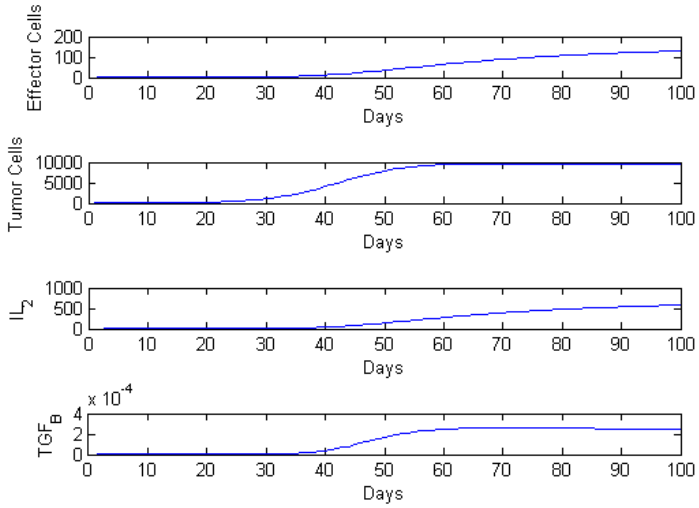

Figure 3. The outputs of the model for the escape state (c=0. 005).

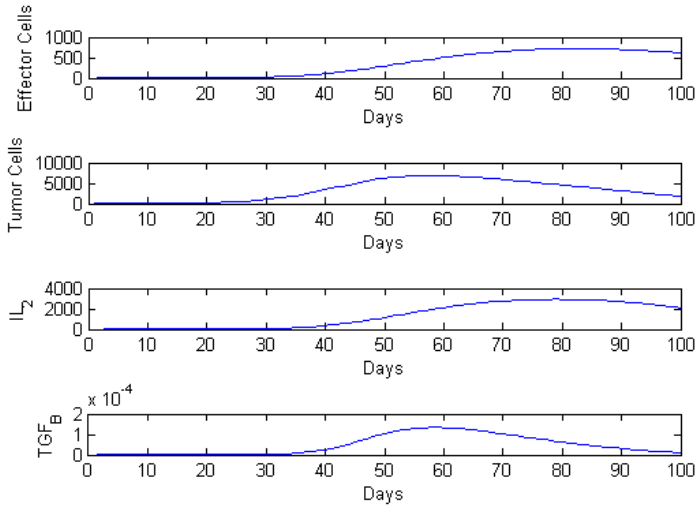

Figure 4. The outputs of the model for the equilibrium state (c=0.05).

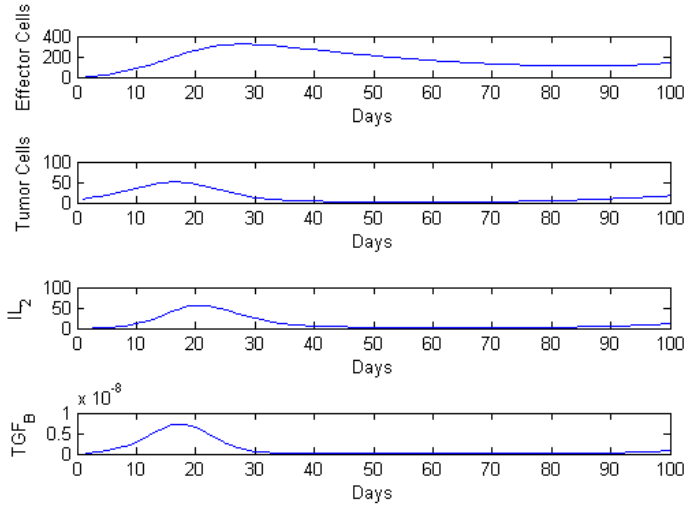

Figure 5. The outputs of the model for elimination state (c=0.5).

As illustrated in Figure 3 to 5, at escape state, tumor cells were grown indefinitely and the final number of these cells achieved to 104 cells. At equilibrium state, the number of tumor cells, achieved to the maximum number at the 60th day and slowly decreased in the next days. In other words, the effector cells tried to overcome the tumor cells and at the elimination state, tumor cells failed to grow and effector cells overcame the tumor cells. As these descriptions are presented, the differences of tumor-immune systems are sunjective and presented as qualities. For investigating these differences as quantities and making these descriptions more objective, the tumor proliferation and death ratios used and these ratios have been shown in Figure 6 to 8.

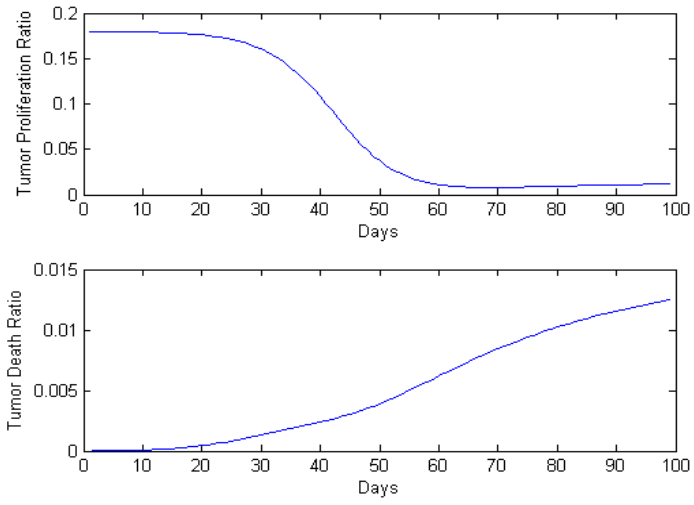

Figure 6. The ratios of tumor proliferation and death in escape state.

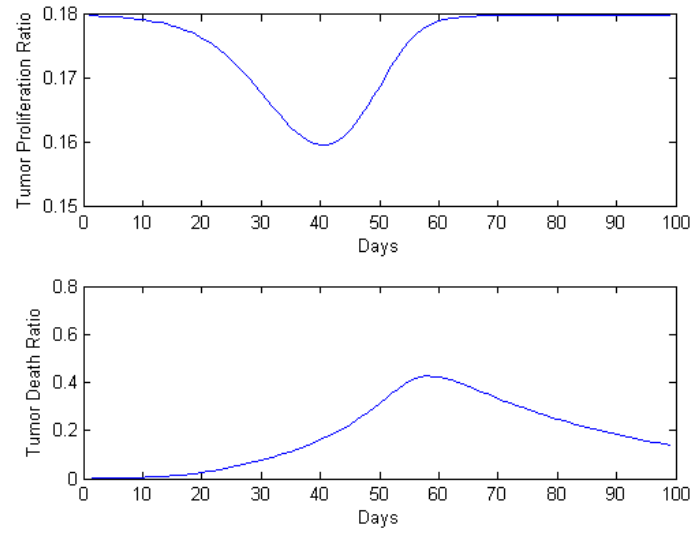

Figure 7. The ratios of tumor proliferation and death in equilibrium state.

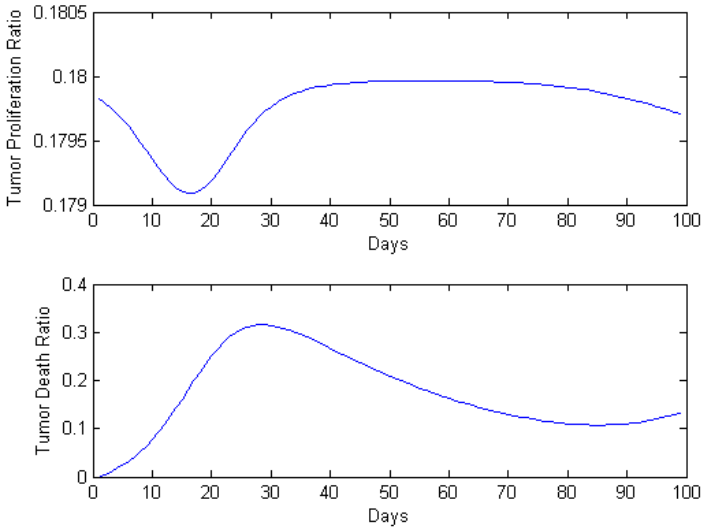

Figure 8. The ratios of tumor proliferation and death in elimination state.

As illustrated by ratios of tumor proliferation in EEE states, if the tendency of tumor-immune system interaction is to the escape, the tumor proliferation ratio will reduce later and if its tendency is to the elimination state, this ratio will reduce early. In other words, an early reduction in the tumor proliferation ratio may be equal to the better progression of the immune system and more destruction of tumor cells. For investigating this theorem, the model parameters were optimized to meet the experimental data which were described in methods and materials section. For obtaining this optimization, the parameters of the model which contributes to the tumor site were optimized to achieve the best matching between the experimental data, which contains tumor size and number of CD8+ cells, and the other values of parameters obtained from table 3. We used Genetic algorithm for optimizing the parameter values.

For using the GA, a fitness function must be defined. Therefore, the sum of Mean Square Error between the real size of tumor and the simulated one and the Mean Square Error between the real number of CD8+ cells and the simulated one was used in equation 10.

$$FF = \frac{1}{N}\sum_{i=1}^{N}(TS_i - \widehat{TS}_i)^2 + \frac{1}{N}\sum_{j=1}^{N}(CD_j - \widehat{CD}_j)^2 \quad (10)$$

Where FF is the value of the fitness function, N is the number of the data sample, TS is the real size of the tumor, $\widehat{TS}$ is the simulated size of the tumor, CD is the real number of CD8+ cells and $\widehat{CD}$ is the simulated number of CD8+ cells.

The outputs of the model and experimental data from two groups of mice are illustrated in Figure 9 and 10.

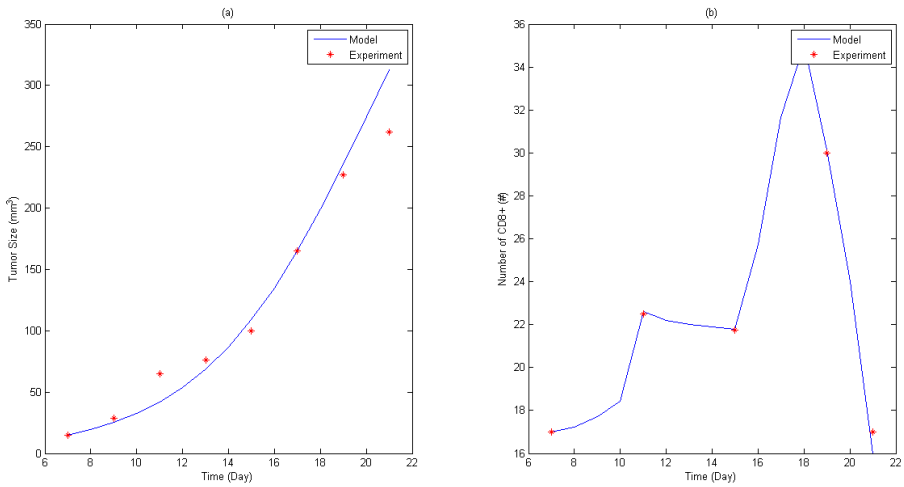

Figure 9. Optimizing the model's parameters for the control group. (a) Tumor size, (b) Number of CD8+.

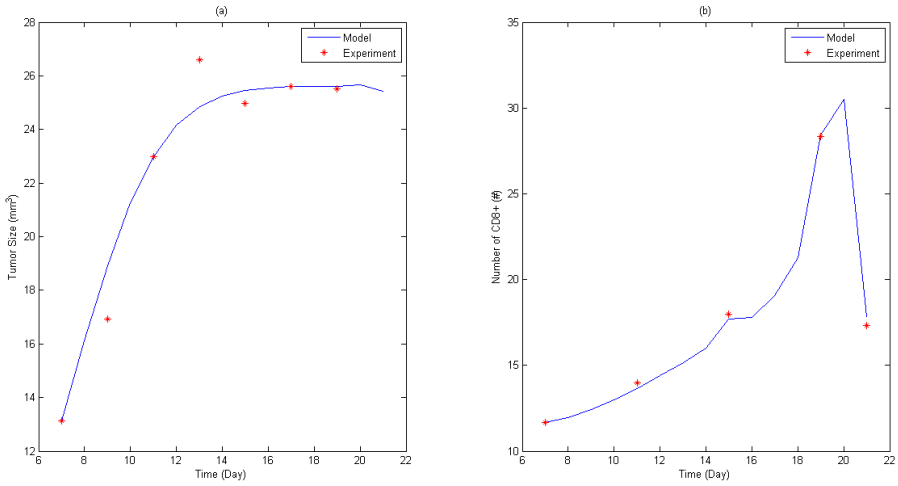

Figure 10. Optimizing the model's parameters for the test group. (a) Tumor size, (b) Number of CD8+.

The values of parameters which were obtained from optimizing the model for each two groups are illustrated in Table 4 and other parameters are the same as Table 3.

Table 4. The values of model's parameters which obtained for each group.

	A	Aa	g2	p2	g3	k
Control Group	0.3088	0.5081	3150	0.4775	$10^6 \times 2.6993$	50000
Test Group	0.494	2.7785	3150	0.4962	$10^6 \times 2.5789$	2654

It is obvious from Figure 9 and 10 that the test group showed a lower growth of tumor cells. In other words, injecting a low dosage 5-FU prevented the overgrowth of tumor cells which was approximately a sufficient treatment in comparison with the control group which has no treatment. Therefore, according to the theorem which was presented previously, we expected that the proliferation ratio of tumor cells in the test group is reduced faster than the control group. For testing this expectation, we ran these two models for 120 days duration and investigated the proliferation ratio of each model. These ratios are illustrated in Figure 11.

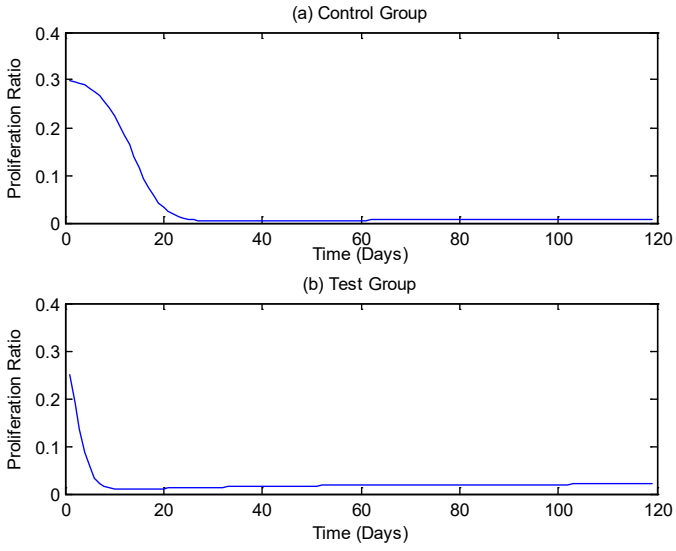

Figure 11. Proliferation ratio of (a) control group, (b) test group.

As we expected, the proliferation ration of the test group reduces faster than the control group. This result can prove the theorem which is presented above. For investigating the impact of stochastic variation in parameters on the fall time of proliferation ratios in these two models, we changed the parameters of each model randomly with 0.1 variations of each parameter's value and computed the proliferation ratios. In other words, we varied the parameters of the model for the control and test group randomly with a range of 0.1 of parameters for 40 times and computed the proliferation rate for these 40 times variations to investigate the robustness of the model. These ratios are illustrated in Figure 12.

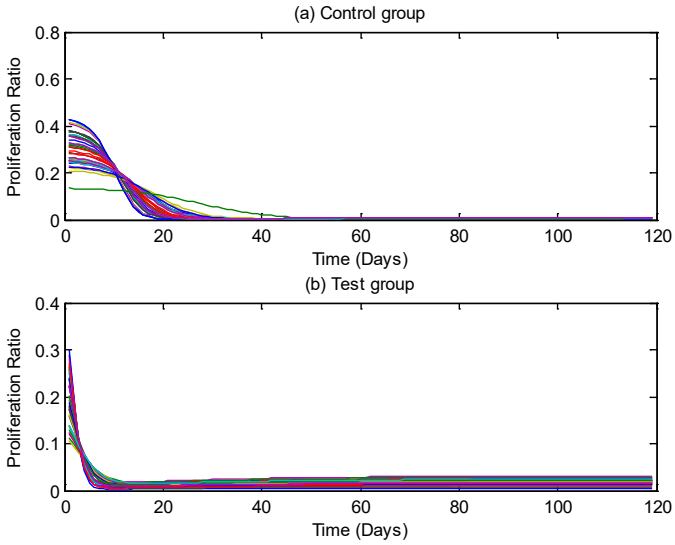

Figure 12. Impact of stochastic variation of parameters in proliferation ratio (a) control group, (b) test group.

It is obvious that despite the stochastic variation in parameters, the proliferation ratio of the test group reduces faster than the control group. For a more precise investigation of this discrepancy, the fall times of each group are illustrated in Figure 13. Fall time is determined as when the proliferation ratio is reduced to half of its maximum value.

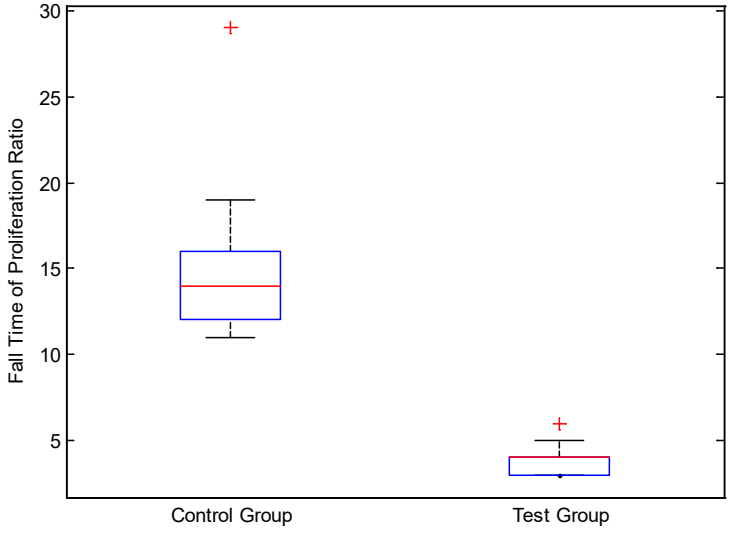

Figure 13. Proliferation ratio of control and test group with parameter variation.

As it can be seen in Figure 13, there is a significant discrepancy between fall times of groups. This result shows the robustness of proliferation ratio as a feature which can distinguish the two groups with two different treatments.

4. Discussion

In this study, we presented an agent based model of the immune system and tumor cell interaction which used two agents consisting tumor cells and CD8+ cells and an environment consists IL-2 and TGF-β cytokines. This model used ratios for execution. The most important ratio of this model was tumor proliferation ratio, which can describe the trend of the immune system and tumor cell interaction. In other words, using this ratio, we can predict the final states of tumor, which consists of elimination, equilibrium and escape. The other application of this ratio will be comparing two different treatments and scoring their ability of eliminating tumor.

At the first step we used the raw model and changed the cytotoxicity of CD8+ cells in the model for achieving three different states of tumor cell (EEE), then we obtained the tumor proliferation ratio in each state. The results in this section showed that if the immune system-tumor cell interaction is leaning to the elimination state, this ratio reduces faster and if is leaning to the escape state, this ratio reduces slowly. This result purposes a theorem which can describe the final state of the immune system-tumor cell interaction. This theorem maintains that if the fall time of tumor proliferation ratio is low, the tumor will be eliminated and if is high, the tumor will escape. For investigating this theorem, we used two groups of experimental data. Both groups consisted 15 C57 mice which received 5×105 initial cells of B16F10 cell line of melanoma. The first group received no treatment (control group) and second group received a low dosage 5-FU (50mg/kg) for eliminating MDSC (test group). Using experimental data which were obtained from these two mice groups, the model was optimized for each group and we achieved two models: the first was the model of the control group and the second was the test group. S the ratio of tumor proliferation of each model was obtained. This ratio falls faster in the test group which proved our theorem. Using this ratio, we can compare groups which received treatments or drugs and score them. In the future works, we can use multi-treatments and compare them.

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