Extracting Mutual Interaction Rules Using Fuzzy Structured Agent-based Model of Tumor-Immune System Interactions

Allahverdy A.[1,2], Rahbar S.[1,2], Mirzaei H. R.[3], Ajami M.[4], Namdar A.[5], Habibi S.[6], Hadjati J.[7], Jafari A. H.[8,9]*

ABSTRACT

Background: There are many studies to investigate the effects of each interacting component of tumor-immune system interactions. In all these studies, the distinct effect of each component was investigated. As the interaction of tumor-immune system has feedback and is complex, the alternation of each component may affect other components indirectly.

Objective: Because of the complexities of tumor-immune system interactions, it is important to determine the mutual behavior of such components. We need a careful observation to extract these mutual interactions. Achieving these observations using experiments is costly and time-consuming.

Material and Methods: In this experimental and based on mathematical modeling study, to achieve these observations, we presented a fuzzy structured agent-based model of tumor-immune system interactions. In this study, we consider the confronting of the effector cells of the adaptive immune system in the presence of the cytokines of interleukin-2 (IL-2) and transforming growth factor-beta (TGF-β) as a fuzzy structured model. Using the experimental data of murine models of B16F10 cell line of melanoma cancer cells, we optimized the parameters of the model.

Results: Using the output of this model, we determined the rules which could occur. As we optimized the parameters of the model using escape state of the tumor and then the rules which we obtained, are the rules of tumor escape.

Conclusion: The results showed that using fuzzy structured agent-based model, we are able to show different output of the tumor-immune system interactions, which are caused by the stochastic behavior of each cell. But different output of the model just follow the predetermined behavior, and using this behavior, we can achieve the rules of interactions.

Introduction

The contribution of biologists and mathematicians made the biological modelling as a new field of research, and tumor growth modelling is one of the branches of this field. The aim of this modelling is to facilitate the advances in cancer immunology [1]. There are many approaches to model tumor growth, among them are spatial [2-7] and non-spatial models [5]. Spatial models investigate the morphology

[1]PhD Candidate, Department of Medical Physics & Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]PhD Candidate, Research Center for Biomedical Technologies and Robotics (RCBTR), Tehran University of Medical Sciences, Tehran, Iran
[3]PhD Candidate, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[4]PhD Candidate, Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[5]PhD, Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[6]MSc, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[7]PhD, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[8]PhD, Department of Medical Physics & Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[9]PhD, Research Center for Biomedical Technologies and Robotics (RCBTR), Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author:
A. H. Jafari
Department of Medical Physics & Biomedical Engineering, School of Medicine & Research Center for Biomedical Technologies and Robotics (RCBTR), Tehran University of Medical Sciences, Tehran, Iran
E-mail: h_jafari@tums.ac.ir

and dispersion of cells, both in the normal host cells and tumor micro-environment and non-spatial models investigate the overall population of cells, which may include tumor cells, immune cells and cytokines. Anther classification of tumor growth model is based on the mathematical approach used for modelling; these approaches include partial differential equations (PDE) [6], cellular automata (CA) [7], ordinary differential equation (ODE) [8] and agent-based modelling (ABM) [9]. Each of these models have advantages and defects, which force the researchers to improve them. In this study, we will develop a non-spatial model of tumor-immune system interaction. Early studies to model tumor growth as non-spatial behavior, described the growth pattern of tumor cells [10]. Gradualy, these models developed and extended by considering immune cells [11, 12], host normal cells [13], innate and adaptive immune system [14] and cytokines [15]. Most of these models were based on ODE, which do not consist spatial features, but they made an easy and user friendly framework to model the dynamics of tumor immune system interactions, which can be used to probe the interactions between components of tumor immunology. But ODE models just follow the average behavior of the system and cannot predict random noises or uncertainties of real systems. To overcome this deficiency of ODE models, fuzzy models [16], stochastic models [17] and ABM [1] can be used.

Agent-based models are used for modelling the tumor-immune system with spatial [18] and/or non-spatial [1] features. As a non-spatial approach, ABM is an alternative to ODE models to consider the memory and the emerging properties of tumor-immune system interactions, which were not considered in ODE models. On the other hand, in comparison with stochastic approaches for modelling tumor-immune interactions, the ABM's emergent behaviors can show more patterns of system, which were not discovered by stochastic models [17].

The main goal of this study is to extract the rules, which the components of the tumor immune system show as mutual interactions. For this aim first, we should present a non-spatial model to simulate the interactions between tumor cells and the immune system. This model must comprise the uncertainty of the immunological rules to show the variation of the output of the model. Fuzzy systems are famous models to comport the uncertainties. By the fuzzy rule-base and overlapping membership functions to contain the uncertainties, the fuzzy system may be a suitable choice for an inference unit of our model. On the other hand, the experimental data are noisy affecting the values of data as stochastic behavior. To overcome the noises of experimental data, we will use an ABM which uses the outcome of fuzzy system to generate the population of cells as a stochastic manner. The present model has two separated levels, containing fuzzy system and stochastic ABM. At each execution of the model, we can obtain different output, which follow the overall behavior of the system. Therefore, we are able to obtain an infinite number of the observations, which follow the overall trend of the model. Using such output, we will be able to determine which rule has occurred.

In the following, we will introduce the experimental data gathering, then we will present the model and describe the components of the model. Next the results of the model will be explained and using these results, the rules of mutual interaction will be extracted. Finally, the outcome of these rules will be discussed.

Material and Methods

Experimental Data

In this experimental and based on mathematical modeling study, for evaluating the outcome of the presented model, we used experimental data from 35 tumor bearing C57BL6 mice. For tumor inoculation, 5×10^5 cells of B16-F10 melanoma cancer cell line

in 200μL of incomplete culture medium were subcutaneously injected to the right flank of mice. The experiment duration was 24 days. On the first day, tumor cells were injected into the mice. Since 8th day, with 4-day intervals, 7 mice were sacrificed to investigate the features of the tumor micro-environment including; tumor size (tumor area), number of cytotoxic T-cell lymphocytes (CTLs), gene expression of interleukin-2 (IL-2) cytokine and gene expression of transforming growth factor-β (TGF-β). For numbering CTLs, we used the immuno-histochemistry image of tumor sections and for calculating the gene expression level of cytokines, real time PCR technique was used. Figure 1 shows the procedure and timing of experiments and data gathering.

Fuzzy-Structured ABM

The presented ABM is contained into agents and two components as environments. The agents are tumor cells and immune effector cells, which show the oppositional behaviors. The environment contains cytokine of transforming growth factor-β (TGF-β) and interleukin-2 (IL-2). In general, TGF-β is beneficial for tumor cells and detrimental to the immune system. On the other hand, IL-2 is beneficial for the immune system. The model has two separat levels including the population level and cellular level. The structure of the model is shown in Figure 2.
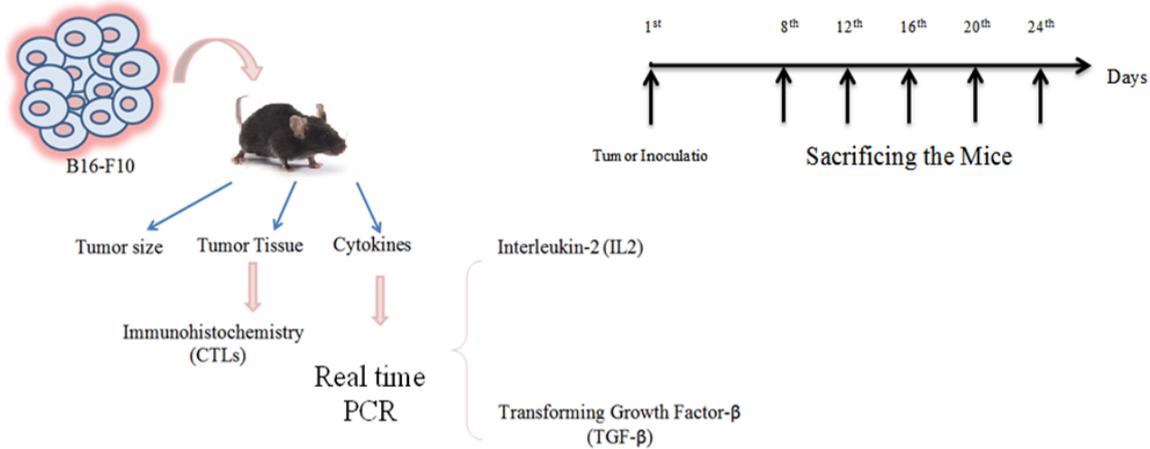

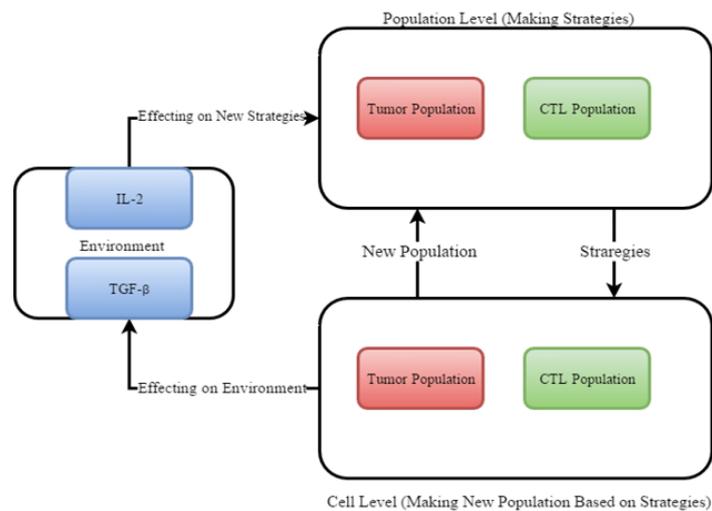**Figure 1:** Data Gathering Procedure and Timing

Figure 2: The Structure of the Model

Our model will be structured by biological considerations and tumor immunology. For this purpose, first we explain the tumor immunology of the interactions between agents and environment of our model. The actions of each part of our model are highlighted as follows.

Tumor cells as agents do four following actions:

i)   Proliferation: Tumor cells proliferate as an autonomous behavior. If the total number of tumor cells are low, the rate of proliferation will be high and vice versa. Therefore, the total number of tumor cells has a negative effect on tumor proliferation ratio.

ii) Recruitment of CTLs: Tumor presented antigens force CTLs to migrate to the tumor microenvironment; therefore, the total number of tumor cells has a positive effect on CTLs recruitment.

iii) Producing TGF-β: Tumor cells can produce and elevate the level of TGF-β concentrations in tumor microenvironment [19], in other words, the total number of tumor cells has a positive effect on TGF-β producing.

iv) Killing CTLs: CTLs may be killed in a challenge with tumor cells; therefore, the total number of tumor cells plays a positive role in killing the CTLs.

CTLs are the second agent of our model, which show three following actions:

i)   Tumor killing: CTLs have a cytotoxic effect on tumor cells and can kill tumor cells, in other words, CTLs have a positive effect on tumor killing.

ii) Apoptosis: CTLs have a program to die and will die as an autonomous behavior.

iii) Producing IL-2: CTLs can produce IL-2 and a large number of CTLs cause more IL-2 productions, in other words, the number of CTLs has a positive effect on IL-2 production.

IL-2, as an environment component, can elevate the CTLs recruitment and cytotoxicity;

therefore, this cytokine plays a positive role in recruitment and cytotoxicity of CTL. TGF-β is another component of the model environment which has a positive effect on the proliferation rate of tumor cells.

As described above, our model structurally contains a fuzzy block and the stochastic ABM block. The fuzzy block will determine the overall behavior of the model, and the stochastic ABM block will use the overall behavior which is determined by the fuzzy block to behave. More generally, the model contains two levels: 1) Population level and 2) Cellular level. The population level is fuzzy block and the cellular level is stochastic level. The schematic of the model is illustrated in Figure 2.

As the model works based on stochastic approach, the fuzzy level should generate the probabilities for the behavior of each agent. Tumor cells use two probabilities including: 1) Probability of tumor proliferation and 2) Probability of tumor death which is induced by CTLs. CTLs also use two probabilities including: 1) Probability of CTLs death, which is induced to CTLs in challenge with tumor cell and 2) Probability of CTLs apoptosis, also the CTLs use the rate of recruitments. These probabilities and rates depend on the parameters of model, which have positive and negative effects on them. The fuzzy system considers these parameters to estimate each probability and rate. The fuzzy system uses three triangular membership functions including "*Low*", "*Middle*" and "*High*" which are illustrated in Figure 3.

For the rule based on fuzzy systems, the model uses two types of rules which depend on the effect of input parameters of the model on the output of fuzzy systems. Assuming x as the parameter of the model (input of fuzzy system) and y as the output of fuzzy system. If x has a positive effect on y, we will have the following rules:

i)   *If x is Low, then y is Low*
ii) *If x is Middle, then y is Middle*
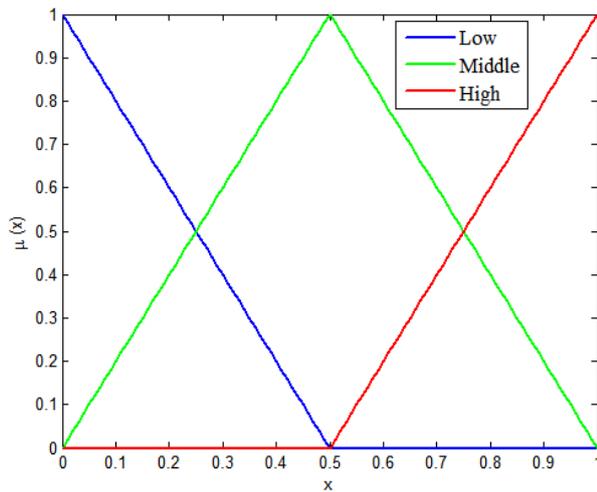iii) *If x is High, then y is High*

Figure 3: Membership Function of Fuzzy System

In contrast, if x has a negative effect on y, we will have the following rules:

i) *If x is Low, then y is High*
ii) *If x is Middle, then y is Middle*
iii) *If x is High, then y is Low*

According to the above descriptions, the fuzzy block of the model produces three probabilities which include the probabilities of tumor proliferation, tumor killing by CTLs and CTLs killing in challenge with tumor. Also, the fuzzy block produces the rate of CTLs recruitment. It should be noted that in this model, we use a constant value as the probability of CTLs apoptosis. These probabilities and rates will be calculated by equations 1-4.

$$T_p(n)=aT_{p1}(T(n))T_{p2}(TGF\text{-}\beta(n)) \quad (1)$$
$$T_c(n)=\gamma T_{c1}(C(n))T_{c2}(IL\text{-}2(n)) \quad (2)$$
$$C_r(n)=\tau C_{r1}(T(n))C_{r2}(IL\text{-}2(n)) \quad (3)$$
$$C_d(n)=\mu C_{d1}(T(n)) \quad (4)$$

Where T_p is the probability of tumor proliferation, T_{p1} is the probability of tumor proliferation as a function of the total number of tumor cells, T_{p2} is the probability of tumor proliferation as a function of TGF-β. T_c is the probability of tumor killing by CTLs, T_{c1} is the probability of tumor killing as a function of the total number of CTLs, T_{c2} is the probability of tumor killing by CTLs which is related to the concentrations of IL-2. C_r is the prob-

ability of CTLs recruitment, C_{r1} is the probability of CTLs recruitment as a function of the total number of tumor cells and C_{r2} is the probability of CTLs recruitment as a function of IL-2 concentration. C_d is the probability of CTLs death and C_{d1} is the probability of CTLs death as a function of the total number of tumor cells. The coefficients of these equations are described below:

a: The maximum rate of tumor proliferation
γ: The initial cytotoxicity of CTLs.
τ: The maximum speed of CTLs recruitment.
μ: The maximum rate of CTLs death.

Therefore, there are seven fuzzy inference systems for T_{p1}, T_{p2}, T_{c1}, T_{c2}, C_{r1}, C_{r2} and C_{d1} in the fuzzy block of the model. Moreover, there is a probability of CTLs apoptosis, which is defined by *d*.

At the cellular level of the model for tumor cells and CTLs, we have considered numerical arrays with length of total number of each cell type. These arrays contain uniform random numbers from zero to one. Each number is interpreted as the probability of its behavior. For example, if the random number assigned to a tumor cell is less than the proliferation probability of the tumor cells, this cell will be duplicated and if the random number is in the range of death, this cell will be eliminated. In other words, cellular level of the model receives the probabilities and rates from population level and uses them to generate a new population of tumor cells and CTLs. The output of this level is first fed into the environment to determine the new concentrations of IL-2 and TGF-β. The concentrations of these cytokines are modelled through equations 5 and 6.

$$IL(n+1)=IL(n)+\varepsilon_I C(n)-u_I IL(n) \quad (5)$$
$$S(n+1)=S(n)+\varepsilon_S T(n)-u_S S(n) \quad (6)$$

where *IL* is the concentration of IL-2, *C* is the number of CTLs, ε_I is the IL-2 production coefficient, u_I is the IL-2 utilization coefficient, *S* is the concentration of TGF-β, *T* is the number of tumor cells, ε_S is the TGF-β production coefficient and u_S is the TGF-β utilization coefficient.

Extracting Mutual Rules

Using the presented model at each execution, the model will present different output which follow the overall behavior of the tumor-immune system interaction. Therefore, we can obtain an infinite observation of the model. Moreover, using this model, we have access to the probabilities of tumor proliferation, tumor killing, effector cells death and the ratio of effector recruitment. To extract mutual rules, we will investigate the effect of each impressive component on the probabilities and ratios. In Table 1, the impressive component on each probability and ratio are illustrated. The rules must be expressed as fuzzy rules. Therefore, we defined three membership functions for each feature and component of the model as Figure 3. To determine which rule occurs at each time step, we will investigate the level of membership of each component and feature to each membership function. The strongest membership will show the occurred rule.

Table 1: Impressive Component on the Features of the Model

Feature	Impressive Components
Probability of Tumor Profileartion	Number of Tumor Cells
	Concentration of TGF-β
Probability of Tumor Killing	Number of Effector Cells
	Concentration of IL-2
Ratio of Effector Cells Recruitment	Number of Tumor Cells
	Concentration of IL-2

TGF-β: Transforming growth factor-beta

Results

To execute the model, according to [20] we have assumed melanoma cells as circular shape with radius in 10μm size. Therefore, each mm² of tumor contains 3200 tumor cells. Other agents of the model are dimensionless. The first step is to optimize the coefficients of

population level of model to follow the experimental data. For this purpose, we used genetic algorithm (GA) and optimized these parameters. The values of these parameters are as follows: $a = 1.0932$, $\gamma = 0.1082$, $\tau = 0.3386$, $\mu = 0.3031$, $d = 0.2023$, $\varepsilon_I = 1.0294$, $\mu_I = 0.2758$, $\varepsilon_s = 0.1122$ and $\mu_s = 0.0413$. The results of this part of the model are illustrated in Figure 4.

After optimizing the coefficients of the population level, we executed the whole model. At the first time point, the population level used the tumor size, CTLs number, concentration of IL-2 and TGF-β as input to determine the probabilities for cellular level. At the cellular level, random values of each cell were compared with these probabilities and death, proliferation or no action was chosen for that cell, the overall choices of all cells generated the new population and effects on the environments and population level were seen. This cycle continues to the final time point. As the arrays of cells consisting the random number in [0,1], each execution of model may cause different results. In Figure 5, we showed the result of 100 times execution of the whole model.

As it is illustrated in Figure 5, the execution of this model can consist of all data in a determined range, and using this model we can comport the alternations of experimental data and uncertainty in the knowledge for modelling the behavior or any other uncertainties. In other words, using this model we will be able to make numerous virtual experiments, which can offer more information than experiments containing the features of the model which is listed in Table 1.

The next step of this study is extracting the fuzzy rule-base which maps the components of the model with the features of the model. For mapping the number of tumor cells and concentration of TGF-β to the probability of the tumor proliferation, considering three membership functions, there are 27 possible rules. In the same way, there are 27 possible rules to map the number of effector cells and
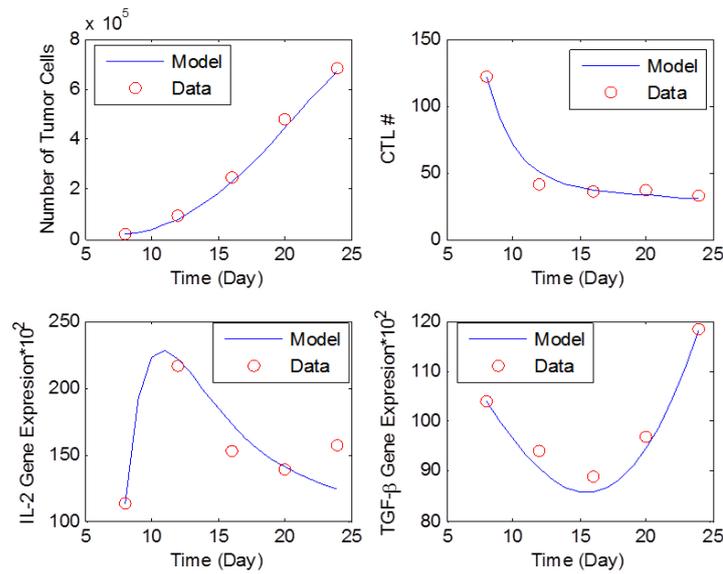
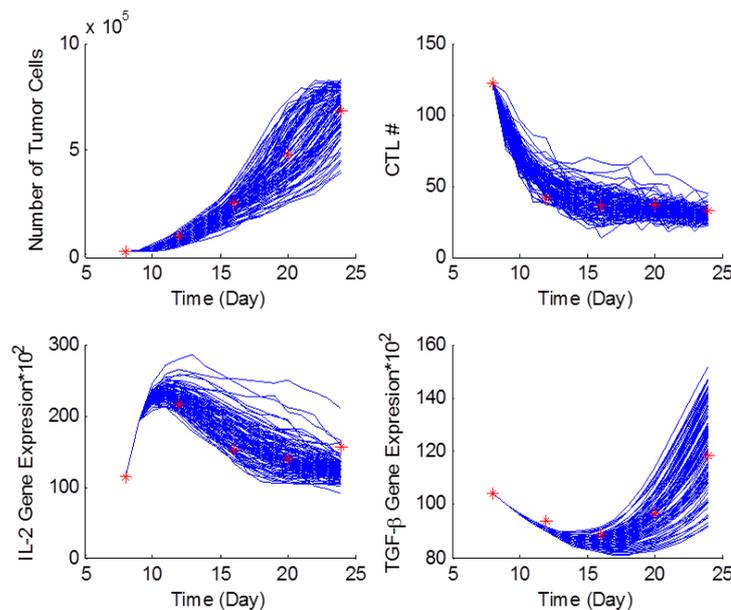**Figure 4:** Average Result of the Model

Figure 5: Output of 100 Times Execution of the Model

concentration of IL-2 to the probability of the tumor killing and 27 possible rules to map the number of tumor cells and concentration of the IL-2 to the ratio of effector cell recruitment. To determine that, which rules are fired, we calculated the frequency of each rule firing. In Figures 6-8, we illustrated the frequency of fired rules.

In Tables 2-4, we illustrated the firing probabilities of each rule.

Discussion

In this study, we developed a new fuzzy-structured agent-based model of tumor-immune system interactions. This model contained two separate levels; the population level and cellular level. The population level is structured based on biological evidence and a fuzzy inference system. In fuzzy inference systems, we considered three triangular membership functions for input and output of the fuzzy
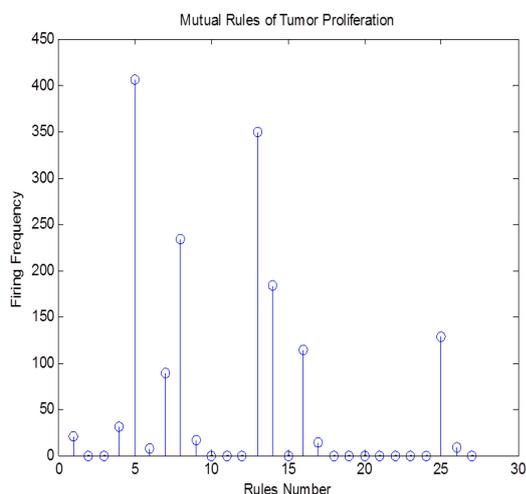
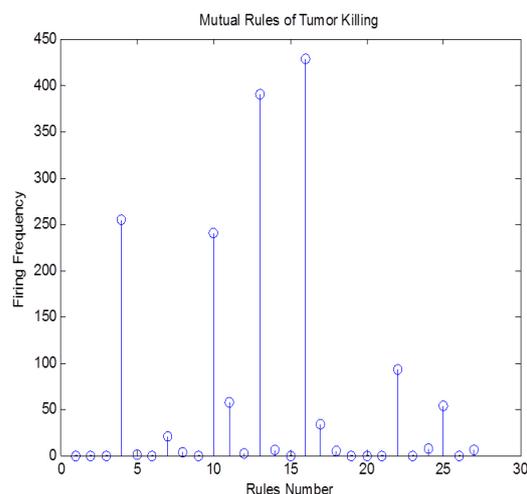**Figure 6:** Number of Firings of Each Rule for Tumor Proliferation

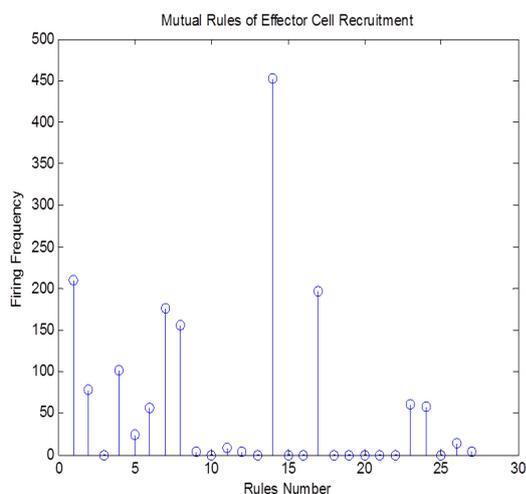**Figure 7:** Number of Firings of Each Rule for Tumor Killing

Figure 8: Number of Firings of Each Rule for Effector Cell Recruitment

inference systems including;"*Low*", "*Middle*" and "*High*". If the input had a positive effect on the output, the rules were increasing and if the input had a negative effect on the output, the rules were decreasing. Using the fuzzy inference system in this model, we could bear the uncertainty of the immunological actions, which were pre-defined in immunology literature. Comporting these uncertainties can make us able to gain more insight on actions of each component in the tumor microenvironment and have a better immunological decision to treat the tumor. The second level of the model was cellular level, which is constructed as a stochastic agent-based model. This level of the model used the probabilities, which were defined by population level of the model to

Table 2: Firing Probability of Each Rule of Tumor Proliferation Probability.

		Number of Tumor Cells		
		Low (%)	Middle (%)	High (%)
Concentration of transforming growth factor-beta (TGF-β)	High	Low (29.3)	Low (96)	Low (98)
		Middle (67.2)	Middle (4)	Middle (2)
		High (3.5)		
	Middle	Low (12.3)	Low (72.3)	Not Occured
		Middle (87.7)	Middle (27.7)	
	Low	Not Occured	Low (100)	Not Occured

Table 3: Firing Probability of Each Rule of Tumor Killing Probability

		Number of Effector Cells		
		Low (%)	Middle (%)	High (%)
Concentration of IL-2	High	Low (100)	Low (51.1) Middle (48.9)	Low (77.5) Middle (18) High (4.5)
	Middle	Low (100)	Low (100)	Low (92) Middle (8)
	Low	Not Ocurred	Low (95) Middle (5)	Not Ocurred

Table 4: Firing Probability of Each Rule of Effector Death Probability

		Number of Tumor Cells		
		Low (%)	Middle (%)	High (%)
Concentration of IL-2	High	Low (55) M (43.2) H (1.8)	Middle (100)	Middle (87.5) High (12.5)
	Middle	Low (60) Middle (10) H (30)	Middle (100)	Middle (78.8) High (21.2)
	Low	Low (83.4) M (16.6)	Middle (100)	High (100)

behave, the outcome of this level was the new population of tumor cells and CTLs and new concentrations of the IL-2 and TGF-β.

For optimizing the parameters of population level of the model, we used the experimental data which were gathered from murine model. The murine model consisted of 35 tumor bearing mice, which were inoculated by B16-F10 cell line of melanoma cancer. For data gathering, the tumor size was measured and the number of CTLs was calculated by immunohistochemistry technique and the concentrations of IL-2 and TGF-β were measured by Real time PCR technique. Using these data which were extracted from murine model, we optimized the parameters of the population level of the

model using genetic algorithm.

Using the optimized population level of the model, we executed the whole model. In this execution, the population level determined the probabilities then, the cellular level used these probabilities as a stochastic behavior to generate the new populations. These new populations affected the environments and determined the new concentrations of cytokines. Finally, these new populations and new concentrations affected the population level of the model. This cycle continued to reach the final time step. We executed the model 100 times and the result showed that the model could create the uncertainty region to enclasp the experimental data. Using this model, we

could show the uncertainty of data gathering and any uncertainty of biological evidence. Moreover, as the model could show different results at each execution in the uncertainty region; therefore, this model made an ability to generate the virtual experiments, which relied on real experiments. Using these virtual experiments, we could get some information which were unreachable in real experiments. Finally, using these information of virtual experiments, we extracted the mutual interaction rules of each component of the model. In Figures 6-8, we showed the firing frequency of each rule and in Tables 3 and 4, we showed the probability of firing of the rules. In Figures 9-11, we showed the surface of these rules.

As we expected, in Figure 9, some number of tumor cells have a negative effect on tumor proliferation and TGF-β has a positive effect on tumor proliferation. On the other hand, we expected that the number of effector cells and concentration of IL-2 have a positive effect on tumor killing; also, Figure 10 shows this fact, but in this figure the concentration of IL-2
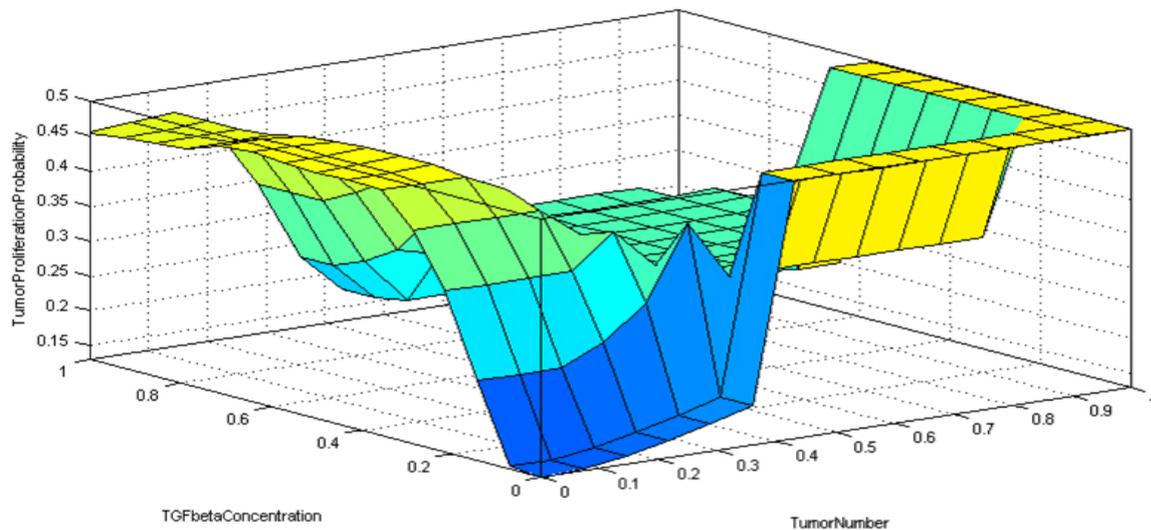

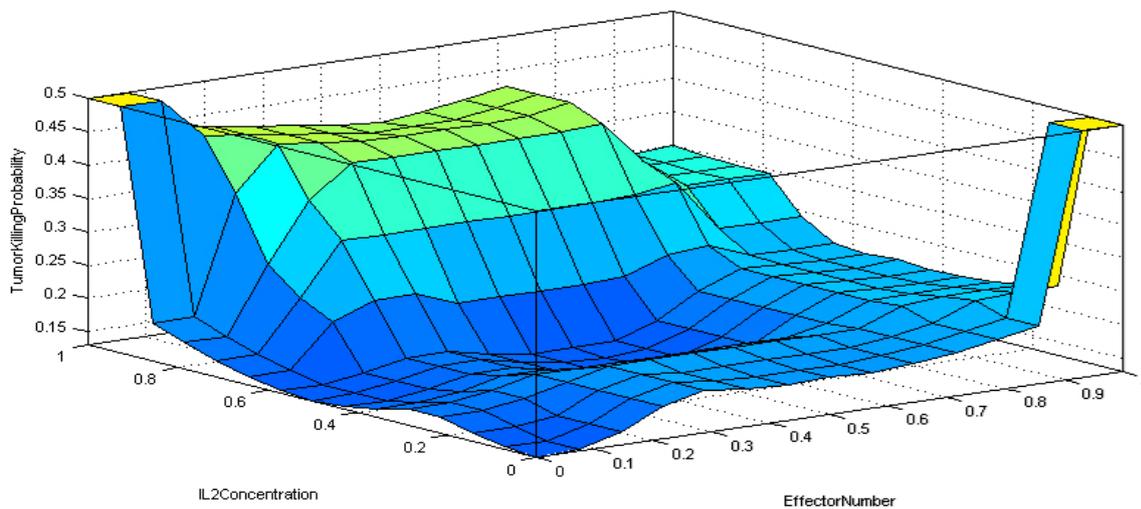**Figure 9:** Rules Surface of Tumor Proliferation

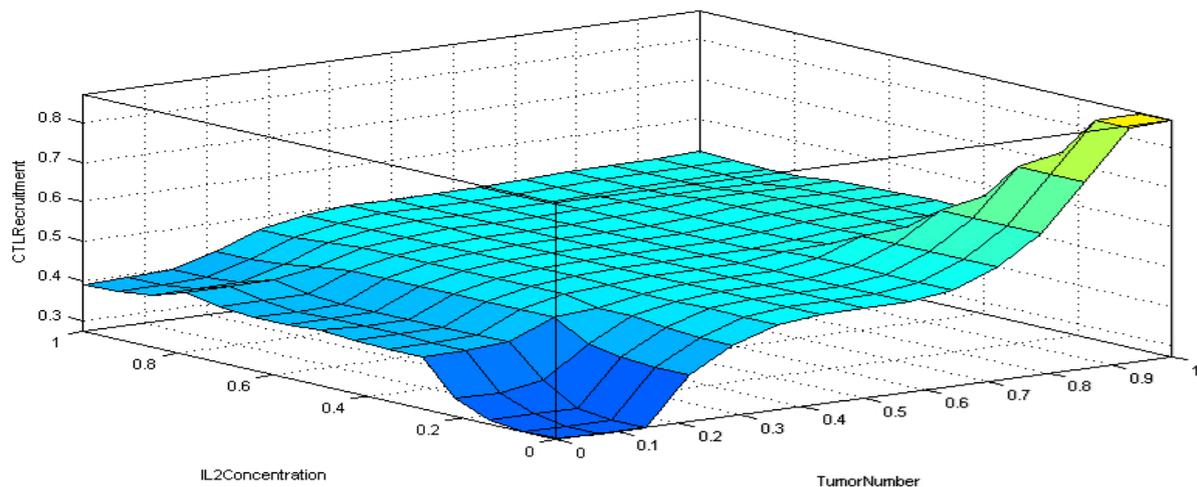**Figure 10:** Rules Surface of Tumor Killing

Figure 11: Rules Surface Effector Cell Recruitment

shows more significant effect on the probability of tumor killing. Moreover, we expected that tumor number and concentration of IL-2 have a positive effect on the ratio of effector cell recruitment. Figure 11 shows this fact but in this figure, the number of tumor cells has a more significant effect on this ratio.

In this model, we considered tumor cell, cytotoxic T-lymphocytes (CTL) as agents and IL-2 and TGF-β as cytokines, which made the environment. Using more cells (like regulatory T-cells, Myeloid-derived suppressor cells, etc.) and molecules (like IL-10, IFN-γ, etc.) as components of the model, this model would be more precise.

Conclusion

A fuzzy structured agent-based model of tumor-immune system interaction was constructed. In this model, tumor cells confronted by effector cells in presence of interleukin-2 and transforming growth factor-beta. This model modified by experimental data of murine models of B16F10 cell line of melanoma cancer cells.

Using this model, linguistic rules of tumor-immune system interaction were extracted for escape state of tumor. Results illustrated that, fuzzy agent-based model are able to introduce linguistic rules of different states of tumor-im-

mune system interaction.

Conflict of Interest

None

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