Original Article

An Agent-based Model for Investigating the Effect of Myeloid-Derived Suppressor Cells and its Depletion on Tumor Immune Surveillance

Armin Allahverdy[1], Alireza Khorrami Moghaddam[2], Sarah Rahbar[2,3], Sadjad Shafiekhani[2,3], Hamid Reza Mirzaie[4], Saeid Amanpour[5], Yasaman Etemadi[6], Jamshid Hadjati[4], Amir Homayoun Jafari[2,3]

[1]Department of Radiology, Sari School of Allied Medical Sciences, Mazandaran University of Medical Sciences, [6]Department of Rehabilitation Science, Mazandaran University of Medical Sciences, Sari, Departments of [2]Medical Physics and Biomedical Engineering and [4]Immunology, School of Medicine, Tehran University of Medical Sciences, [3]Research Center for Biomedical Technologies and Robotics, Tehran University of Medical Sciences, [5]Cancer Institute, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: To predict the behavior of biological systems, mathematical models of biological systems have been shown to be useful. In particular, mathematical models of tumor-immune system interactions have demonstrated promising results in prediction of different behaviors of tumor against the immune system. **Methods:** This study aimed at the introduction of a new model of tumor-immune system interaction, which includes tumor and immune cells as well as myeloid-derived suppressor cells (MDSCs). MDSCs are immune suppressor cells that help the tumor cells to escape the immune system. The structure of this model is agent-based which makes possible to investigate each component as a separate agent. Moreover, in this model, the effect of low dose 5-fluorouracil (5-FU) on MDSCs depletion was considered. **Results:** Based on the findings of this study, MDSCs had suppressive effect on increment of immune cell number which consequently result in tumor cells escape the immune cells. It has also been demonstrated that low-dose 5-FU could help immune system eliminate the tumor cells through MDSCs depletion. **Conclusion:** Using this new agent-based model, multiple injection of low-dose 5-FU could eliminate MDSCs and therefore might have the potential to be considered in treatment of cancers.

Keywords: *5-fluorouracil, agent-based model, immune-tumor interaction, myeloid-derived suppressor cell*

Introduction

Functions of the immune system against the tumor cells are divided into three parts. First, the immune system suppresses the viral infection to protect the host from virus-induced tumors. Second, it causes the post-inflammatory environment to prevent the carcinogenicity. And third, it identifies the tumor cells and eliminates them.[1] The latest function was introduced in 1950s as immune-surveillance hypothesis which explains how immune system can eliminate the early stage tumor.[2,3] This hypothesis was the basis for the development of models to predict the tumor-immune system interactions using mathematical equations. Using this mathematical models, researchers can overcome the lack of knowledge about cancer and its interaction with immune system.[4,5]

The CD8+ T-cells are one type of immune cells which play principal role in anti-tumor response of immune system. Previous studies demonstrated that, in nude mice with CD8+ shortage, the immune system was not able to effectively inhibit the tumor cells.[6] The CD8+ cells have several pathways to detect and to eliminate the tumor cells.[7]

When immune system confronts a stranger, it suppresses itself to prevent perishing the host cells. It is possible that this suppression is mediated by cells such as regulatory T-cells (Treg) and myeloid-derived suppressor cells (MDSCs), or proteins such as transforming growth factor-beta (TGF-β).[8] Tumor cells use these approaches for immune evasion which may consequently result in tumor development. Therefore, elimination of immune suppressor factors such as MDSCs could be an effective approach to reinforce the immune system.

The low-dose 5-fluorouracil (5-FU) is able to selectively eliminate the MDSCs in tumor microenvironment.[9] In addition, many studies have investigated effects of other factors such as all-trans-retinoic acid (ATRA),[10] gemcitabine,[11] ATRA

How to cite this article: Allahverdy A, Moghaddam AK, Rahbar S, Shafiekhani S, Mirzaie HR, Amanpour S, *et al.* An agent-based model for investigating the effect of myeloid-derived suppressor cells and its depletion on tumor immune surveillance. J Med Signals Sens 2019;9:15-23.

Received: July, 2018. **Accepted:** October, 2018.

Address for correspondence:
Dr. Amir Homayoun Jafari, Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: h_jafari@tums.ac.ir

Website: www.jmss.mui.ac.ir
DOI: 10.4103/jmss.JMSS_33_18

and anti-CD25 antibody,[12] nitroaspirin derivative[13] and cisplatin[14] on MDSCs depletion.[15] All these factors resulted in better tumor prognosis.

Many studies have mathematically modeled the tumor-immune system interaction, and their results have provided insight about the activity of the immune system against the tumor cells. Many of these models investigated the spatial manner of tumor microenvironment based on partial differential equation or cellular automata.[16-20] Some studies only investigated the population of cells using temporal models. These models are based on ordinary differential equation (ODE) or agent-based modeling (ABM).[5,21] Primary temporal models investigated the interactions between tumor cells and effector cells such as natural killer cells (NK cells) and cytotoxic T-lymphocytes (CTLs).[22,23] Later studies, however, added cytokines such as TGF-β and interleukin-2 to this interaction[24] and investigated the immunotherapy.[25-28] These studies were mainly based on ODE and only few of them considered ABM.[5,29]

To control cancer, there are various therapeutic approaches such as chemotherapy,[19,30] radiotherapy,[31] bacteria-therapy,[32] combination therapy[33] and immune-therapy.[34] Although immune-therapy seems to be an effective approach for eliminating the tumor, however, presence of postinflammatory agents such as MDSCs may decrease positive therapeutic effects.[35] Hence, depletion of MDSCs would lead to more beneficial treatment.

ABM can consider properties of each cell and its memory.[36,37] An agent-based model of tumor-immune system interactions which contains agents and environment, each component having active behavior is considered as agent, and on the other hand, the components which have passive behavior are the environment.

To the authors' knowledge, no model has been developed to investigate the effect of immune suppressors such as MDSCs. Therefore, this study aimed to model and to simulate the effect of MDSCs on tumor-immune system interactions. In addition, since recent studies have demonstrated that the low dose of 5-FU can annihilate the effect of MDSCs on immune system suppression,[35] therefore, the effect of one and multiple dose of 5-FU were also evaluated in this model.

Materials and Methods

Immunologic definitions

In this model, three components will be considered including tumor cells, effector cells (CTLs) and MDSCs. Actions of these components, based on which the model was developed, were defined as below;

Action of tumor cells:

1. Proliferation: Tumor cells may proliferate based on their population
2. Proliferating the CTLs: The antigen presentation of tumor cells can cause the CTLs proliferation
3. Recruitment of MDSCs: the post-inflammatory condition in tumor microenvironment can cause the MDSCs recruitment.[15,38,39]

CTLs have two following actions:

1. Killing the tumor cells: The CTLs can cause the tumor cell cytotoxicity
2. Apoptosis: CTLs will be dying as programmed death.

MDSCs also show two actions:

1. Inhibiting the CTLs Proliferation: MDSCs as immune suppressor cells can inhibit the proliferation of CTLs
2. Apoptosis: MDSCs will be dying as programmed death.

Agent based model

As mentioned above, the agent-based model contains three components each of which has its own action. Each action was modeled as a mathematical equation. First, tumor cells proliferate as Eq. 1.

$$T_p(n) = \mathrm{aT}(n)\,(1 - \mathrm{bT}[n]) \quad (1)$$

In Eq. 1, $T_p(n)$ shows the number of proliferating tumor cells at n^{th} time point, $T(n)$ is number of tumor cells, a is proliferation rate and b is number of tumor cells limitation.

The second action of tumor cells is CTLs proliferating, which was modeled as Eq. 2.

$$E_p(n) = \mathrm{mT}(n) \quad (2)$$

Where, $E_p(n)$ is number of proliferating CTLs at n^{th} and m is CTLs proliferation rate.

The third action of tumor cells is MDSCs recruitment, which can be modeled as Eq. 3.

$$M_r(n) = \frac{xT(n)}{1 + yT(n)} \quad (3)$$

$M_r(n)$ is number of recruiting MDSCs at n^{th} time point, x is the rate of MDSCs recruitment and y is limitation factor.

There are also two actions for CTLs. First, they kill the tumor cells with a predefined cytotoxicity modeled as Eq. 4.

$$T_k(n) = j\mathrm{T}(n)\,E(n) \quad (4)$$

In this equation, $T_k(n)$, j and $E(n)$ demonstrate the number of killed tumor cells, cytotoxicity of CTLs and number of CTLs, respectively. CTLs also show that may be dying by apoptosis as Eq. 5.

$$E_d(n) = dE(n) \quad (5)$$

In this equation, $E_d(n)$ indicates the dead CTLs at n^{th} time point and d represents the CTL's apoptosis rate.

The final component of this model is MDSCs, which have two actions of inhibition of the CTL's proliferation and apoptosis and was modeled as Eqs. 6 and 7.

$$E_i(n) = \frac{1}{g + M(n)} \quad (6)$$

$$M_d(n) = \mu M(n) \quad (7)$$

$E_i(n)$ is CTL's proliferation inhibition factor, $M(n)$ is the number of MDSCs at n^{th} time point, $M_d(n)$ indicates number of died MDSCs at n^{th} time point and μ is MDSC's apoptosis rate.

Eqs. 8-10 represent the overall equations of this model which is also depicted in Figure 1.

$$T(n+1) = T(n) + T_p(n) - T_k(n) \quad (8)$$

$$E(n+1) = E(n) + E_p(n)\, E_i(n) - E_d(n) \quad (9)$$

$$M(n+1) = M(n) + M_r(n) - M_d(n) \quad (10)$$

Another purpose of this study was to investigate the effect of MDSCs depletion by 5-FU on response of immune system to tumor cells. To this end, effect of 5-FU on MDSCs depletion was modeled. Effect of 5-FU on leukocytes was investigated in[40] and also demonstrated in Figure 2. In this study, this effect of 5-FU on leukocyte was generalized to MDSCs and estimated by Rayleigh function as Eq. 11.

$$I_{5\text{-FU}} = \varepsilon t e^{-t^2/\sigma^2} \quad (11)$$

$I_{5\text{-}FU}$ indicates the impact of 5-FU on MDSC depletion, ε demonstrates the dosage power of 5FU and σ shows attenuation of 5-FU's impact through time.

Results

Simulation of tumor-immune system model will be described in this section. First, model was simulated without any intervention and then effects of 5-FU were considered. For model simulation, the values of coefficients were identified as Table 1. As other studies Allahverdy *et al.*,[29] used a constant rate as proliferation or recruitment, but in our study, this rate has been impressed by the number of MDSC's. Therefore, this model can be valid by this factors (cause all factors are same and recruitment rate just affected by the number of MDSC's).

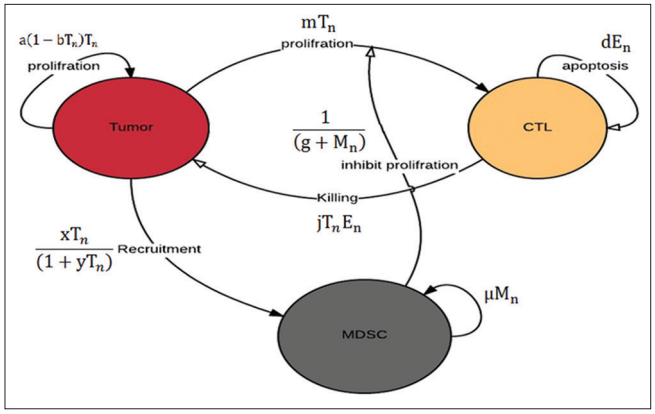


Figure 1: Graphical view of defined agent-based model

Initially, stability analysis of the model was conducted. As the effect of MDSCs population was considered in this study, for this aim, all coefficients were considered as constant, illustrated in Table 1, and "x" was the variable coefficient which has effective role on the stability analysis.

To start, fix points of Eqs. 8-10 were calculated as below:

$$T_p(n) - T_k(n) = 0 \quad (12)$$

$$E_p(n)\, E_i(n) - E_d(n) = 0 \quad (13)$$

$$M_r(n) - M_d(n) = 0 \quad (14)$$

By insertion of Eqs. 1-7 in Eqs. 12-14, the fix points were achieved.

Then, to evaluate the stability of the model, the Jacobian matrix of Eqs. 8-10 were computed as below:

$$J = \begin{bmatrix} a - 2bT & -jT & 0 \\ \dfrac{m}{g+m} & -d & \dfrac{-mT}{(g+m)^2} \\ \dfrac{x}{(1+yT)^2} & 0 & -\mu \end{bmatrix} \quad (15)$$

Table 1: The values of coefficients of tumor-immune system model

Coefficient	Value
a	1.05
b	0.0022
m	0.03
d	0.12
g	0.74
x	0.33
y	0.04
j	0.015
μ	0.03
ε	8.2
σ	3

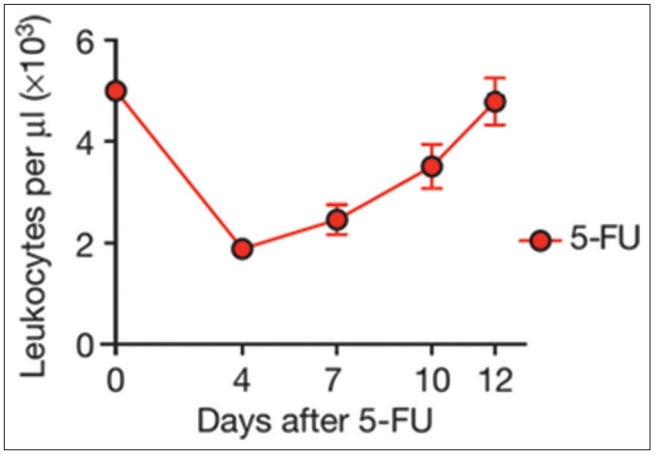


Figure 2: The leukocyte depletion impact of 5-fluorouracil

The attribute of eigenvalues of this matrix defines stability of the model. There are three types of stability including node, repellor, and saddle. If all eigenvalues have negative real part, the fix point will be node. If all eigenvalues have positive real part, the fixpoint is repellor and whether one or two eigenvalues have positive real part, the fixpoint will be saddle. Nonzero imaginary part will also define the spiral manner for each type of fixpoint. To evaluate the type of fix point, the value of "x" was set at 0.01–2 and then real and imaginary parts of eigenvalues evaluated. Figures 3 and 4 depict the real and imaginary parts of eigenvalues, respectively.

As Figure 3 demonstrates, all the eigenvalues have negative real part. Therefore, the fixpoint is node and in low "x" values the imaginary part of eigenvalues are nonzero and the spiral manner can be illustrated by fixpoint.

To illustrate the result of model's simulation, the two-dimensional view of tumor microenvironment and the number of cells in the tumor microenvironment over 51 days has been demonstrated in Figure 3. In this simulated model, the dark blue pixels are healthy tissue, live tumor cells, died tumor cells, CTLs (effector cells), and MDSCs have been marked in dark blue, bright blue, red and orange pixels, respectively. As depicted in Figure 5, through time MDSCs infiltrate the tumor microenvironmet and suppress the effector cells which consequently make the microenvironment suitable for tumor growth.

As illustrated in Figure 6, the number of effector cells tends to follow the number of tumor cells. However, this is prevented by the recruitment of MDSCs and as a result the tumor cells will escape the immune system.

According to Figure 6, at the beginning, effector cells tend to grow. However, more number of MDSCs would inhibit the increment of effector cells, and consequently, the tumor cells will grow.

For the next step and on day 5th, the one dose of 5-FU was administered which was simulated by Eq. 11. The MDSCs depletion effect of 5-FU is illustrated in Figure 7.

As illustrated, 5-FU had a considerable effect on MDSCs on day 7th and this effect lasted until day 15th. To investigate the effect of 5-FU injection on tumor microenvironment, this effect contributed by the model of tumor-immune system interaction. As Figure 8 demonstrates, on day 21th, the tumor size reduced. However, after that and through time, tumor size increased again. Which means one dose of 5-FU is not sufficient enough for sustainable effects.

Looking at Figure 9, number of MDSCs decreased on day 7th which in turn resulted in increase in number of effector cells and decrease in number of live tumor cells. However, this was a cross-sectional effect, and the number of MDSCs increased through time and tumor cells escaped the immune system.

As the third step, this model has been contributed by two dose injection of 5-FU. The first injection was on day 5th and the second one was on day 10th. Figure 10 demonstrates the effect of these injections on the tumor microenvironemt. According to figure, between day 21th and 31th, tumor decreased in size. However, on day 41th, the tumor grew again which again means two dose of 5-FU is not a effective yet.

Based on Figure 11, which depicts the number of each cells in the tumor microenvironemt, the immune system initially overcomes tumor cells, however, the size of tumor cells increased again on day 41th.

In the next phase, the third dose of 5-FU was administered. To avoid chemotherapy effect of 5-FU on tumor cells, this injection was simulated on day 20th. Change of tumor microenvironment through time has been depicted in Figure 12 which indicates third dose of 5-FU had

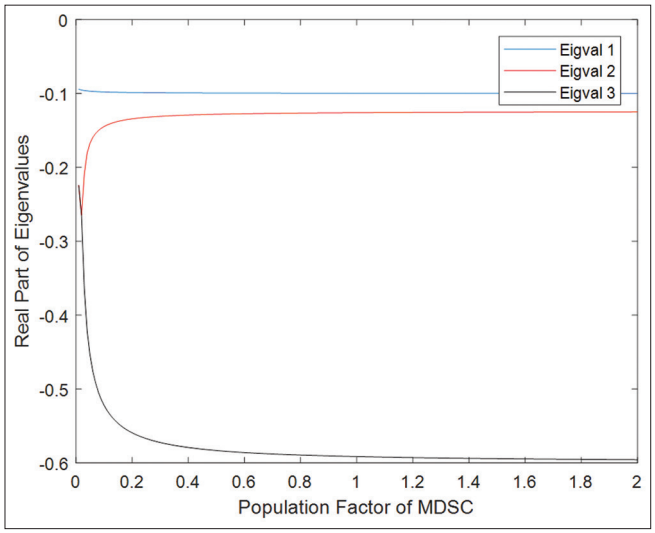


Figure 3: Real part of eigenvalues versus change "x"

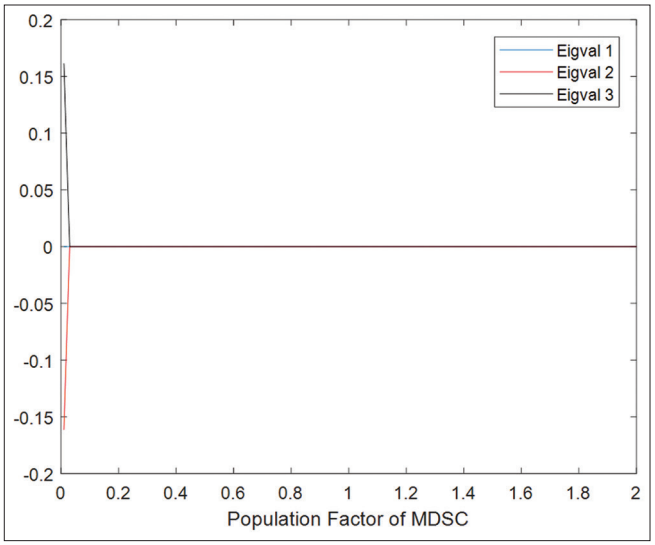


Figure 4: Imaginary part of eigenvalues versus change "x"

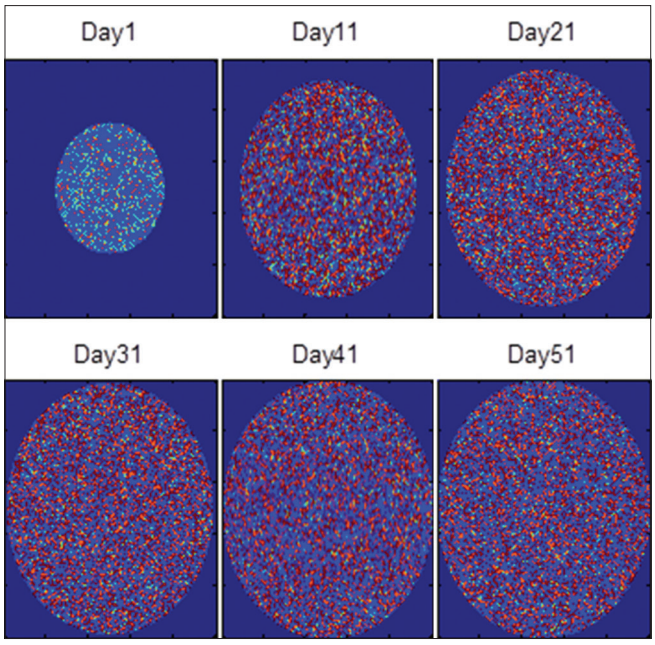


Figure 5: Tumor microenvironment over the time without any intervention

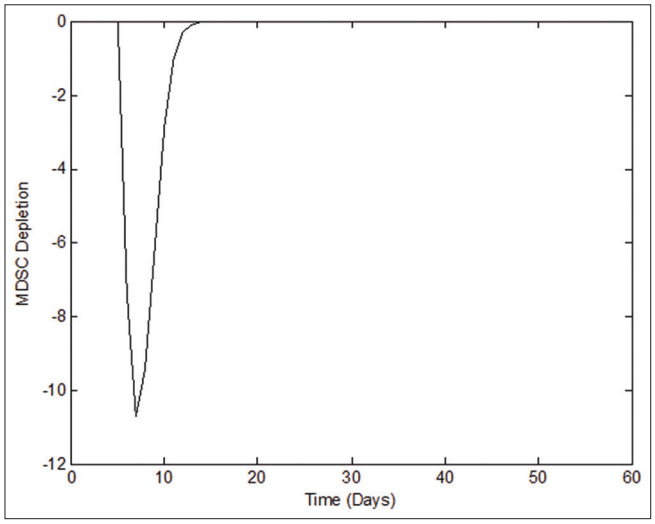


Figure 7: Myeloid-derived suppressor cells depletion with one dose injection of 5-fluorouracil

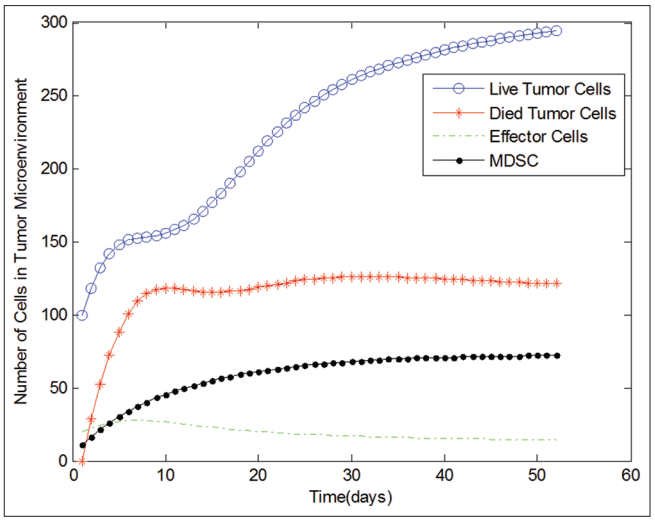


Figure 6: Number of cells in tumor microenvironment without any intervention

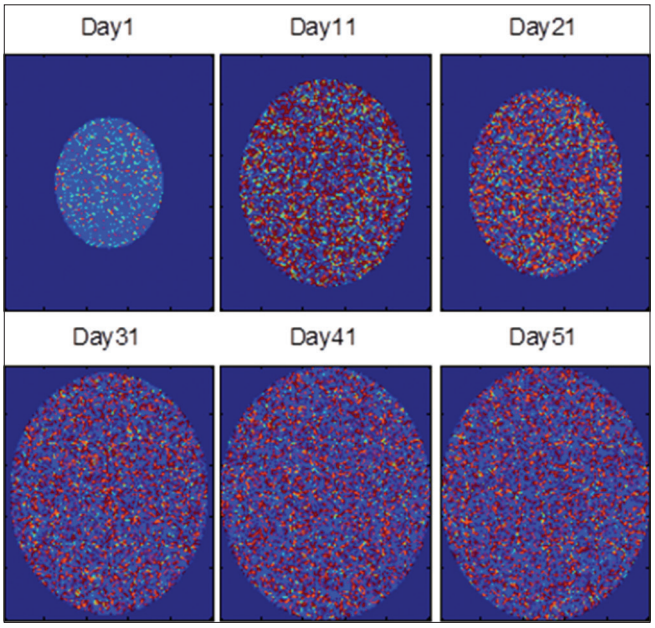


Figure 8: Tumor microenvironment modification by time pass with one dose injection of 5-fluorouracil

long-lasting suppressing effects on size of tumor cells that would make this intervention effective.

Figure 13 shows the change of each cell over the time. As it can be seen, the number of tumor cells reached and remained zero and immune system overcomes the tumor cells.

Discussion

Mathematical model of tumor-immune system interaction, which is time and cost-effective, is a useful method to gain insight about the interaction between components of the immune system and tumor cells. In addition, to investigate the effectiveness of interventions, application of these models might be beneficial. In this study, a new agent-based model was introduced that was based on interaction between tumor cells and effector cells. The effect of MDSCs, which suppress the proliferation of effector cells and cause the increment in number of tumor cells, was also considered in this model. To evaluate the effectiveness of intervention, the impact of low-dose 5-FU of MDSCs depletion was also simulated.

Simulation of this model was conducted in four steps. At the first step, simulation was done without any intervention. The results of this simulation showed recruitment of MDSCs prevents the increment of effector cells and creates a situation which allows the tumor cells to escape. At the second step, one dose of 5-FU was considered as an intervention.

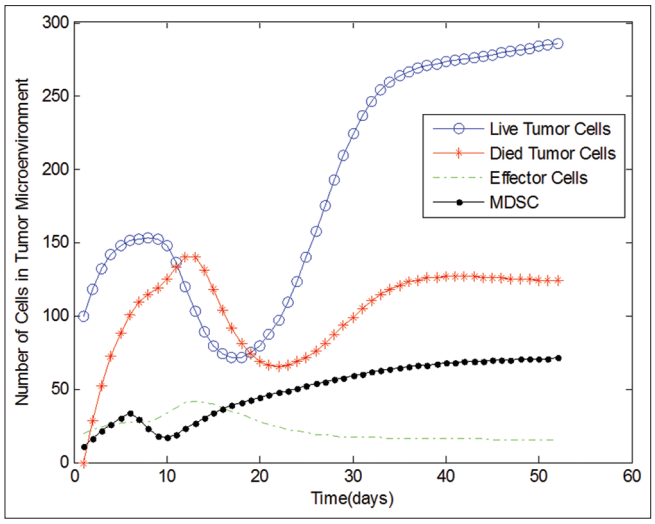


Figure 9: The effect of one dose injection of 5-fluorouracil on number of cells in tumor microenvironment

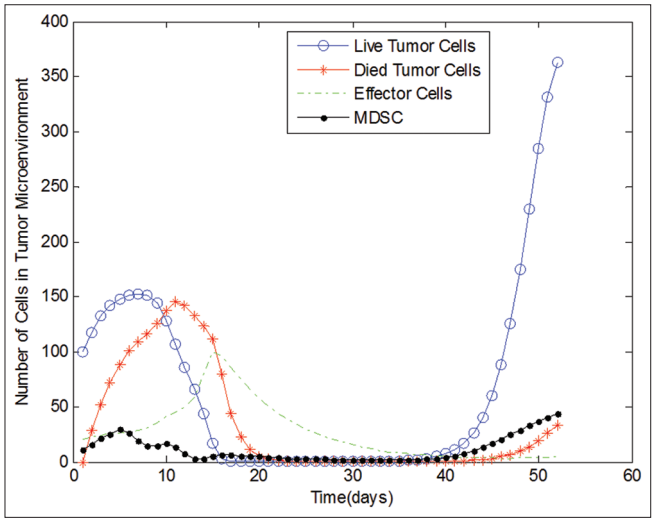


Figure 11: The effect of two dose injection of 5-fluorouracil on number of cells in tumor microenvironment

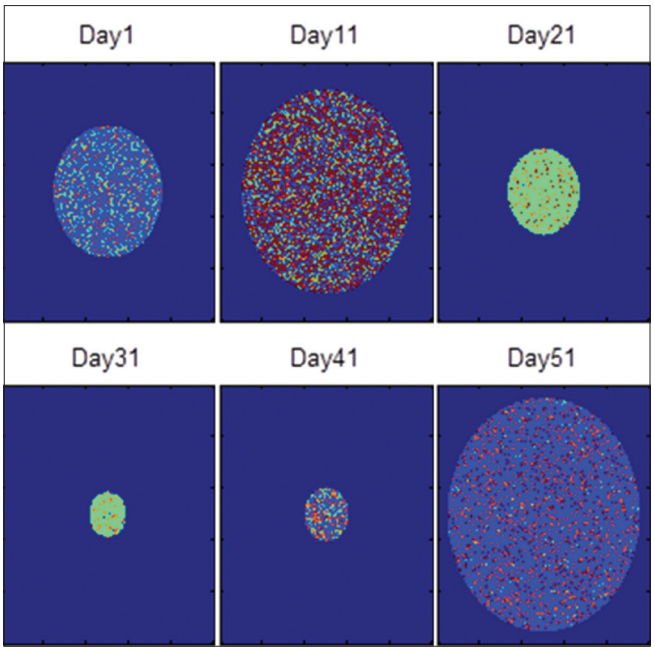


Figure 10: Tumor microenvironment modification by time pass with two dose injection of 5-fluorouracil

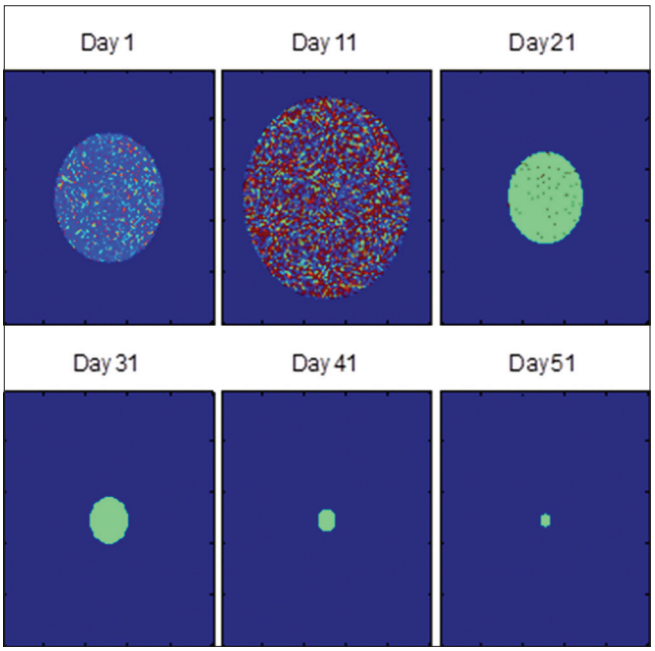


Figure 12: Tumor microenvironment modification by time pass with three dose injection of 5-fluorouracil

According to finding, 5-FU initially result in MDSCs depletion and decrement of the number of MDSCs in return led to increment of effector cells and consequently the decrement of the number of tumor cells. However, this effect was temporary and through time, the number of MDSC increased again. It was interpreted that the additional dose of 5-FU was required for more long-lasting effects. Hence, for the next step, the second dose of 5-FU was considered. As expected, this results in decrease in size of tumor cells which was transient again. At the final step, third dose of 5-FU was simulated this time all the tumor cells were eliminated and the immune system overcame the tumor cells. This finding was consistent with the results of the other similar study.[35] The first limitation of this study is low dose of 5-FU. Since 5-FU is a drug used in chemotherapy It is possible to act as a anti-tumor substance rather than MDSC's depletion. Number of 5-FU injection is the other limitation. If the dose of 5-FU precisely determined as low, but the number of injection increased or the injection interval decreased, the effect of injections may synergy and subsequently act as chemotherapy drug. Finally, this model only investigated a presumptive tumor. For further examination, this model must be retrofitted for every tumor cell lines like sarcoma, glioblastoma, melanoma and gastric cancer.

The immune system can fight the tumor cells in many pathways, therefore, adding more components of the

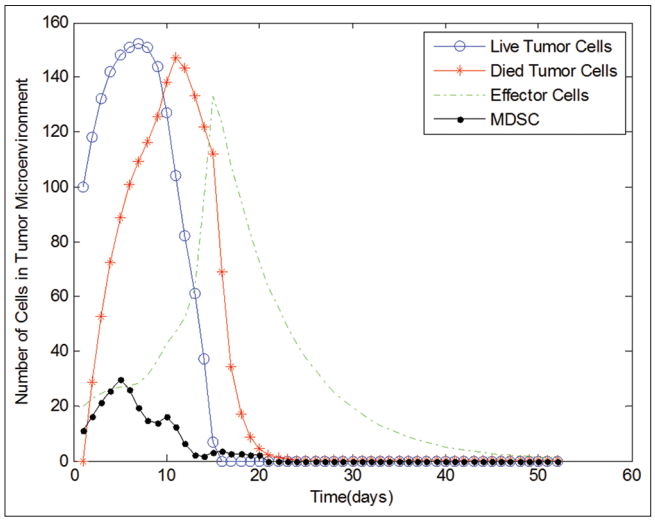


Figure 13: The effect of three dose injection of 5-fluorouracil on number of cells in tumor microenvironment

immune system to this model may be useful to gain more insight about the realistic behavior of tumor cells against the immune system. Moreover, tumor cells may have more strategies to escape the immune system and increasing their maintenance such as angiogenesis which can be contributed in this model.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

References

1. Corthay A. Does the immune system naturally protect against cancer? Front Immunol 2014;5:197.
2. Burnet M. Cancer; a biological approach. I. The processes of control. Br Med J 1957;1:779-86.
3. Burnet FM. Immunological aspects of malignant disease. Lancet 1967;1:1171-4.
4. Pourhasanzade F, Sabzpoushan SH, Alizadeh AM, Esmati E. An agent-based model of avascular tumor growth: Immune response tendency to prevent cancer development. Simulation 2017;93:641-57.
5. Jafari AH, Hadjati J, Allahverdy A, Zandi S, Mirzaei HR, Rahbar S, *et al*. A predictive approach for the tumor-immune system interactions based on an agent based modeling. Front Biomed Technol 2017;2:214-26.
6. Smyth MJ, Thia KY, Street SE, MacGregor D, Godfrey DI, Trapani JA. Perforin-mediated cytotoxicity is critical for surveillance of spontaneous lymphoma. J Exp Med 2000;192:755-60.
7. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology 2007;121:1-4.
8. Murphy K, Travers P, Walport M and Janeway C. Immunobiology. 7th. New York: Garland Science. 2008.
9. Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, *et al.* 5-fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res 2010;70:3052-61.
10. Kusmartsev S, Cheng F, Yu B, Nefedova Y, Sotomayor E, Lush R, *et al.* All-trans-retinoic acid eliminates immature myeloid cells from tumor-bearing mice and improves the effect of vaccination. Cancer Res 2003;63:4441-9.
11. Ishizaki H, Manuel ER, Song GY, Srivastava T, Sun S, Diamond DJ, *et al.* Modified vaccinia Ankara expressing survivin combined with gemcitabine generates specific antitumor effects in a murine pancreatic carcinoma model. Cancer Immunol Immunother 2011;60:99-109.
12. Weiss T, Vitacolonna M, Zöller M. The efficacy of an IL-1alpha vaccine depends on IL-1RI availability and concomitant myeloid-derived suppressor cell reduction. J Immunother 2009;32:552-64.
13. De Santo C, Serafini P, Marigo I, Dolcetti L, Bolla M, Del Soldato P, *et al.* Nitroaspirin corrects immune dysfunction in tumor-bearing hosts and promotes tumor eradication by cancer vaccination. Proc Natl Acad Sci U S A 2005;102:4185-90.
14. Tseng CW, Hung CF, Alvarez RD, Trimble C, Huh WK, Kim D, *et al.* Pretreatment with cisplatin enhances E7-specific CD8+ T-cell-mediated antitumor immunity induced by DNA vaccination. Clin Cancer Res 2008;14:3185-92.
15. Wesolowski R, Markowitz J, Carson WE 3rd. Myeloid derived suppressor cells – A new therapeutic target in the treatment of cancer. J Immunother Cancer 2013;1:10.
16. Araujo RP, McElwain DL. A history of the study of solid tumour growth: The contribution of mathematical modelling. Bull Math Biol 2004;66:1039-91.
17. Roose T, Chapman SJ, Maini PK. Mathematical models of avascular tumor growth. SIAM Rev 2007;49:179-208.
18. Martins M, Ferreira S, Vilela M. Multiscale models for the growth of avascular tumors. Phys Life Rev 2007;4:128-56.
19. Mazdeyasna S, Jafari AH, Hadjati J, Allahverdy A, Moghaddam MA. Modeling the effect of chemotherapy on melanoma B16F10 in mice using cellular automata and genetic algorithm in tapered dosage of fbs and cisplatin. Front Biomed Technol 2015;2:414-20.
20. d'Onofrio A. Metamodeling tumor-immune system interaction, tumor evasion and immunotherapy. Mathc Comput Model 2008;47:614-37.
21. Eftimie R, Bramson JL, Earn DJ. Interactions between the immune system and cancer: A brief review of non-spatial mathematical models. Bull Math Biol 2011;73:2-32.
22. Kuznetsov VA, Makalkin IA, Taylor MA, Perelson AS. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. Bull Math Biol 1994;56:295-321.
23. d'Onofrio A, Ciancio A. Simple biophysical model of tumor evasion from immune system control. Phys Rev E Stat Nonlin Soft Matter Phys 2011;84:031910.
24. Arciero J, Jackson T, Kirschner D. A mathematical model of tumor-immune evasion and siRNA treatment. Discrete Continuous Dyn Syst Ser B 2004;4:39-58.
25. Wilson S, Levy D. A mathematical model of the enhancement of tumor vaccine efficacy by immunotherapy. Bull Math Biol 2012;74:1485-500.
26. Kirschner D, Panetta JC. Modeling immunotherapy of the tumor-immune interaction. J Math Biol 1998;37:235-52.
27. d'Onofrio A, Ledzewicz U, Maurer H, Schättler H. On optimal delivery of combination therapy for tumors. Math Biosci 2009;222:13-26.
28. d'Onofrio A. A general framework for modeling tumor-immune system competition and immunotherapy: Mathematical analysis

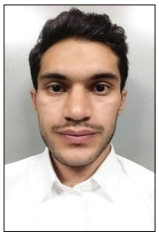
and biomedical inferences. Phys D 2005;208:220-35.
29. Allahverdy A, Rahbar S, Mirzaei RR, Ajami M, Namdar A, Habibi S, *et al*. Extracting mutual interaction rules using fuzzy structured agent-based model of tumor-immune system interactions. J Biomed Phys Eng 2016.
30. Dwek MR, Rixon L, Hurt C, Simon A, Newman S. Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health-related quality of life outcomes? A systematic review. Psychooncology 2017;26:1422-32.
31. Andersson KM, Dahlgren CV, Reizenstein J, Cao Y, Ahnesjö A, Thunberg P. CT Image Metal Artifacts in Proton Radiotherapy Treatment Planning: Evaluation of Two Commercial Correction Algorithms; 2018.
32. Hatzikirou H, López Alfonso JC, Leschner S, Weiss S, Meyer-Hermann M. Therapeutic potential of bacteria against solid tumors. Cancer Res 2017;77:1553-63.
33. Hatzikirou H, Alfonso JC, Mühle S, Stern C, Weiss S, Meyer-Hermann M. Cancer therapeutic potential of combinatorial immuno- and vasomodulatory interventions. J R Soc Interface 2015;12. pii: 20150439.
34. Banchereau J, Palucka K. Immunotherapy: Cancer vaccines on the move. Nat Rev Clin Oncol 2018;15:9-10.
35. Namdar A, Mirzaei HR, Jadidi-Niaragh F, Ashourpour M, Ajami M, Hadjati J, *et al.* Multiple low doses of 5-fluorouracil diminishes immunosuppression by myeloid derived suppressor cells in murine melanoma model. Iran J Immunol 2015;12:176-87.
36. Figueredo GP, Siebers PO, Aickelin U. Investigating mathematical models of immuno-interactions with early-stage cancer under an agent-based modelling perspective. BMC Bioinformatics 2013;14 Suppl 6:S6.
37. Figueredo GP, Siebers PO, Owen MR, Reps J, Aickelin U. Comparing stochastic differential equations and agent-based modelling and simulation for early-stage cancer. PLoS One 2014;9:e95150.
38. Umansky V, Sevko A, Gebhardt C, Utikal J. Myeloid-derived suppressor cells in malignant melanoma. J Dtsch Dermatol Ges 2014;12:1021-7.
39. Nagaraj S, Gabrilovich DI. Tumor escape mechanism governed by myeloid-derived suppressor cells. Cancer Res 2008;68:2561-3.
40. Busch K, Klapproth K, Barile M, Flossdorf M, Holland-Letz T, Schlenner SM, *et al.* Fundamental properties of unperturbed haematopoiesis from stem cells *in vivo*. Nature 2015;518:542-6.

BIOGRAPHIES

Armin Allahverdy is an Assistant Professor of Radiology Department of Mazandaran University of Medical Sciences. He has received his BSc in Biomedical Engineering from University of Isfahan, Isfahan, Iran in 2008. He also received his MSc in Biomedical Engineering from Shahed University, Tehran, Iran in 2011 and he received his Ph.D in Biomedical Engineering from Tehran University of Medical Sciences, Tehran, Iran in 2017. He is interested in modeling of biological systems.
Email: a.allahverdi@mazums.ac.ir

Alireza Khorrami Moghaddam is an Assistant Professor of Radiology Department of Mazandaran University of Medical Sciences. He has received his BSc in Physics from University of Urmia, Urmia, Iran in 2001. He also received his MSc in Medical Physics from Isfahan University of Medical Sciences, Isfahan, Iran in 2007 and he received his Ph.D in Medical Physics from Tehran University of Medical Sciences, Tehran, Iran in 2013. He passed IMRT fellowship in Ourish University, Germany and he also passed Therapeutical Radiopharmacutical fellowship in Julish University, Germany. He is interested in Radio Therapy, Nuclear Medicine and Molecular Imaging.
Email: ar.khorrami@gmail.com

Sarah Rahbar is a Ph.D. candidate in Physics and Biomedical Engineering department of Tehran University of Medical Sciences (TUMS). Her project is focused on optimizing combinational immunotherapy protocol by using Agent-based modeling of tumor and the immune system. Her interests are also the application of structural and interaction-based modeling techniques like Game Theory and PetriNets in biology. She loves spending time with her 6-year-old daughter playing with Lego bricks.
Email: sarahbar2002@yahoo.com



Sadjad Shafiekhani is a Ph.D student in Physics and Biomedical Engineering department of Tehran University of Medical Sciences(TUMS). His interests are mathematical and computational models in cancer modeling. He works on tumor-immune system by fuzzy logic, stochastic petri net, agent based models, Markov model and boolean networks.
Email: sd.shafikhani@yahoo.com

Hamid Reza Mirzaie is currently a senior researcher at Dr. Hadjati lab of Department of Medical Immunology, School of Medicine, Tehran University of Medical Sciences, Iran. He completed his PhD at Tehran University of Medical Sciences in 2018 and his undergraduate studies at Isfahan University of Medical Sciences in 2011. He is now actively working on the mechanisms by which the immune system controls cancer and developing rational approaches to improve immune cell immunotherapy.
Email: hamidmirzaei81@gmail.com

Saeid Amanpour is an Associated professor and deputy of research at Cancer Biology Research Center and director of IVF lab at Tehran University of Medical Sciences. He received Ph.D in Veterinary Surgery from Tehran University of Medical Sciences in 1996.

Email: saeidamanpour@yahoo.com

Yasaman Etemadi is an Assistant Professor of Department of Rehabilitation Sciences, Mazandaran University of Medical Sciences. She has received her BSc and MSc in Physical Therapy from Shiraz University of Medical Sciences, Shiraz, Iran in 2007. In 2014, she obtained her Ph.D in Rehabilitation Sciences from University of Social Welfare and Rehabilitation, Tehran, Iran.
Email: etemadiy@gmail.com

Jamshid Hadjati is a Professor in the Department of Medical Immunology, School of Medicine at the Tehran University of Medical Sciences. He completed his PhD at Tehran University of Medical Sciences and his undergraduate studies at University of Urmia. His research interests lie in the area of tumor immunology and immunotherapy, ranging from theory to design to implementation.
Email: hajatij@sina.tums.ac.ir

Amir Homayoun Jafari is currently an associate professor of Biomedical Engineering in Tehran University of Medical Sciences. He has received his PhD degree in Bioelectric Engineering from AmirKabir University of Technology. His works in the field of modeling are basically focused on cancer modeling, immunodeficiency and neuromuscular system. He is also working on nonlinear analysis methods mainly with the aim of applications in BCI and neuroscience. His interests are signal processing as well chaos and game theory used in biological applications. He enjoys strategy games especially chess.
Email: h_jafari@tums.ac.ir