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Research Article

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Mathematical Modelling of Cell-Mediated Immune Response to Tumor Growth with Finite Difference Analysis

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Abstract

Immunotherapy is a newly emerging approach to cancer treatment that seeks to stimulate a body's immune defenses, especially T cells, to combat and potentially eliminate tumors. This paper reflects some research outcome tumor growth model solved by using Finite Difference Method. Using accumulated data we take a look at possible models for the growth of cancer cells, incorporating the positive effect of the immune system. Relevant tumor–immune interactions depend on stochasticity, since the dynamics involve a small and decreasing number of cells, and spatiotemporal heterogeneity, since the dynamics occur in a localized tumor environment. Mathematical modelling is been very powerful tool to developed the tumor cell interaction and plays vital role in treatment is well. We have used the finite difference method which is a numerical method very important technique for solving a wide variety of differential equations which discretize the model equation.

Keywords: Modelling Tumor Treatment, Finite Difference Method, Immunotherapy

1. Introduction

Recent progress in cancer immunology and advances in immunotherapy suggest that the immune system plays a fundamental role in combatting tumors, and hence can be used as a vehicle to prevent or cure cancer. Although theoretical and experimental studies of tumor-immune dynamics date back to the early 1890s, fundamental questions concerning complex interactions between the immune system and the growing tumor remain. For example, contemporary research programs are driven by questions concerning how components of the immune system synergize to limit cancer development, how tumors escape immune recognition and control, and why some immunotherapies inhibit growth of certain tumors while stimulating the growth of others. Indeed, the multidimensional nature of these complex interactions requires cross disciplinary approaches to capture more realistic dynamics of the essential biology.

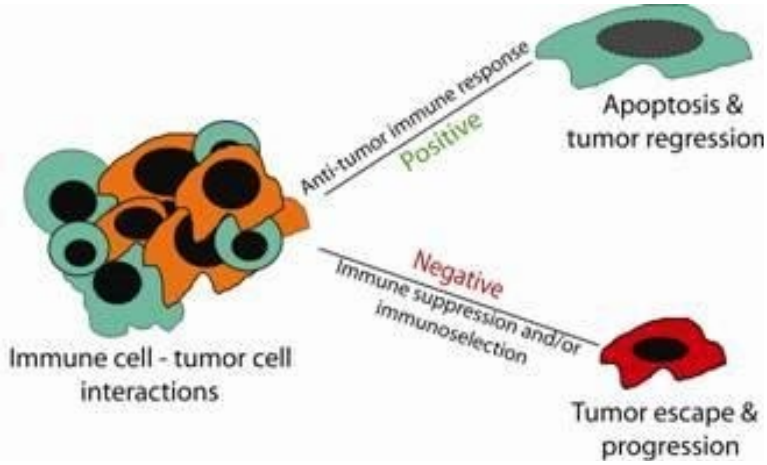


Figure1: Tumor-Immune Dynamic

A variety of mathematical models have applied a range of modeling approaches to study tumor– immune interactions. Tumor–immune models have been formulated using ordinary differential equations (ODE), delay differential equations (DDE), partial differential equations (PDE), impulsive differential equations, and fractional differential equations. Other papers develop agent based models (ABM), cellular automata (CA), and hybrid formulations.

One such approach combines cancer immunology with mathematics to model the interactions. In particular, mathematical modeling has been used to understand immune surveillance of developing tumors, the role of the immune system's response in maintaining tumor dormancy, and the potential impact of enhancing anti-tumor immune responses through cancer vaccination. Other novel uses of mathematical modeling involve optimizing preventative vaccination strategies against tumor cells and studying the feasibility of virotherapy, which involves infecting patients with viruses engineered to favor the infection of tumor cells, rendering the cancer a target of the patient's immune response. Understanding these intricate interactions between cancer and the immune system offers scientists and clinicians powerful insights into stimulating and modulating immune responses to prevent or treat cancer and advance the development of cancer immune therapies.

This volume brings together a range of topics on mathematical models of tumor-immune system dynamics by applied mathematicians and scientists. The mathematical methods we used to study the dynamics of the tumor-immune system in this paper is Finite Difference method.

Numerical methods for approximating solutions to the model are constructed which incorporate the underlying Poisson geometry of the continuous system. These methods preserve the periodicity of solutions, and the error in the first integrals remains bounded. Simulations are used to show that these methods produce more accurate results than standard numerical methods.

1.1. Model Formulation

The model equations that we have generated are commonly used to describe the dynamics of the interaction between two groups. Rosenzweig and McArthur would later extend the model to include three groups interaction [9].

To make the model more realistic, we modify it so that the tumor cell demonstrates logistic growth rather than exponential growth. We also add in terms that allow both populations to disperse from their initial location. Through numerical analysis via Matlab, we simulate the outcome of such modifications. The model is a pair of differential equations that describe a simple case of Tumor cell-immune cell (or parasite-host) dynamics.

The assumptions of the model in its most basic form are as follows:
1. The tumor cell always finds enough food to sustain itself and grow exponentially when the immune cell is absent.
2. The supply of the immune cell population depends entirely on the size of the tumor cell population.
3. The immune cell have an unlimited killing capacity.
4. The rate of change of the cell populations are proportional to their respective sizes.
5. No external changes that favor one of the populations occur. Genetic adaptation is inconsequential.

Given the above-mentioned assumptions, the set of differential equations representing the model is given by

$$\frac{\partial C}{\partial t} = \alpha C - \beta CU$$
$$\frac{\partial U}{\partial t} = \gamma CU - \mu U \qquad (1)$$

Where $C(t)$ is the number of prey at time t, $C(t)$ is the immune cell at time t ,α is the natural growth rate of tumor cell in the absence of immune cell, β is the rate of tumor cell loss due to tumor-immune interaction, γ is the growth of immune cell due to tumor-immune interaction, and μ is the rate of predator loss due to natural death or immigration. α,β,γ and μ are positive constants. The system has two equilibrium points, (C,U) (0,0) (extinction) and (C,U) = (μ / γ, β / α) (coexistence) [7].

The basic model is unrealistic for a few reasons. First, it can be shown that coexistence equilibrium point is not stable. Instead, the tumor and immune cell populations cycle repeatedly without ever settling, and while this cyclic behavior has been observed in nature, it is not common. One key improvement on the models is the incorporation of a diffusion effect. Takeuchi analyzed the diffusion effect on the stability of this systems, and Hastings derived conditions for global stability of the systems with diffusion [5,10]. Next, it does not consider any competition among tumor or immune cell, and thus, prey population may grow infinitely without any resource limits. Exponential growth of a population cannot continue indefinitely.

The goal of this paper is to come up with a more realistic version of the tumor-immune interaction model and to provide a tool that allows researchers to explore dynamics of spatiotemporal dynamics of tumor-immune models with diffusion. We consider a modified system with logistic growth of the tumor cell. We also allow both immune cell and tumor cell to disperse by diffusion. Then, solutions of the model will be estimated using a finite forward difference scheme under varying initial population distributions and dispersion rates.

The modified model is

$$\frac{\partial C}{\partial t} = D_1 \frac{\partial^2 C}{\partial x^2} + \alpha C\left(1 - \frac{C}{k}\right) - \beta CU$$
$$\frac{\partial U}{\partial t} = D_2 \frac{\partial^2 U}{\partial x^2} + \gamma CU - \mu U \qquad (2)$$

Where k > 0 is the tumor carrying capacity and D1 &D2are the diffusion constants. We non- dimensionalize the system by using,

$$c = \frac{C}{k},\ u = \frac{\beta U}{\alpha},\ \ t = \alpha t,\ \ x = \left(\frac{x}{D_2}\right)^{1/2},\ \ D = \frac{D_1}{D_2},$$

$$a = \frac{\gamma k}{\alpha},\ \ b = \frac{\mu}{\gamma k}$$

Considering only the one-dimensional problem, and dropping the asterisks for notational simplicity:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} + c(1-c-u)$$

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + au(c-b)$$

$$0 < x < L, \mathrm{t} > 0$$

It is easy to check that *(c,u) = (b,*1-*b)* is a non-trivial solution to the model. Also, note as $c = \frac{c}{k}$,$0 < c < 1$.
If we assume that the net flux at the boundaries is zero, then the zero flux *k* boundary conditions are imposhed,

1.2. Numerical Methods used for Analysis

To approximate the solutions of the system, we use a finite-difference method. The domain of the model is partitioned in time using a mesh t_0, t_1, t_2,.....t_N and in space using a mesh x_0, x_1, x_2,.....x_J . We use a uniform partition for both, so the difference between two consecutive time points will be *Δt* and between two consecutive space points will be *Δx* . The point c_n^j will be the approximation of *c* at location *j* and at time *n*. The same is true for u_n^j. Of the three common methods for approximating solutions using a finite difference, we have chosen the forward difference method. This method was chosen because it is an explicit method of determining solutions. Estimated values of $c_n^{j+1}$and u_n^{j+1}can be computed as a function of their respective values at time step *n.* To estimate the derivative term $\frac{\partial c}{\partial x}$, we use

$$\frac{\partial c}{\partial t} = \frac{c_j^{n+1} - c_j^n}{\Delta t}$$

and to estimate the dispersion term $\frac{\partial^2}{\partial x}$, we use

$$\frac{c_j^{n+1} - c_j^n}{\Delta t} = c_j^n\left(1 - c_j^n + u_j^n\right) + D\frac{c_{j+1}^n - 2c_j^n + c_{j-1}^n}{\Delta x^2}$$

$$\frac{u_j^{n+1} - u_j^n}{\Delta t} = au_j^n\left(c_j^n - b\right) + \frac{u_{j+1}^n - 2u_j^n + u_{j-1}^n}{\Delta x^2}$$

The second equation may be rewritten in a similar manner. Solving for $c_j^{n\square 1}$and $u_j^{n\square 1}$respectively, the scheme for the finite forward-difference method is

$$c_j^{n+1} = \Delta t\, u_j^n\left(1 - c_j^n + u_j^n\right) + D\left(\frac{\Delta t}{\Delta x^2}\right)\left(c_{j+1}^n - 2c_j^n + c_{j-1}^n\right) + c_j^n$$

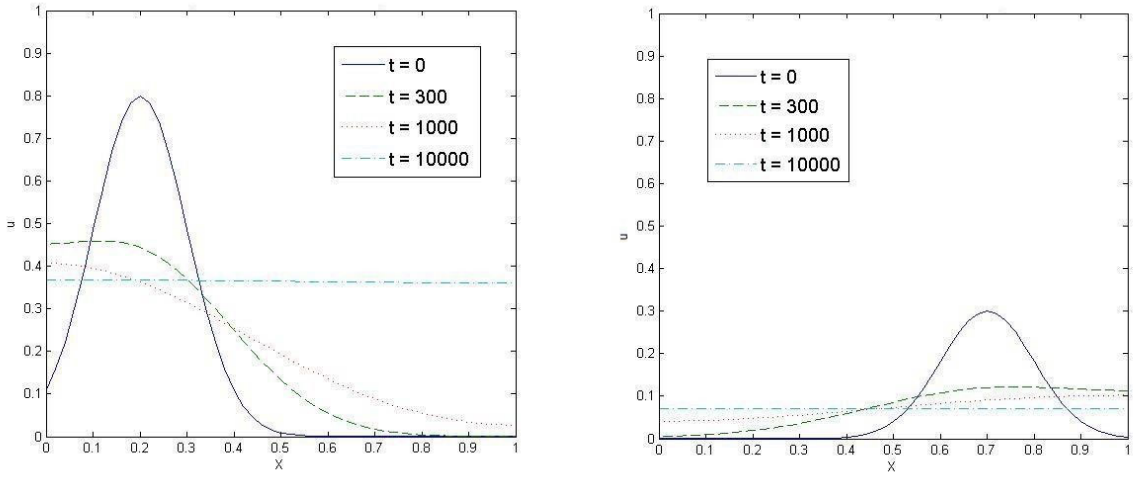
$$u_j^{n+1} = a\,\Delta t\, u_j^n\left(c_j^n - b\right) + \left(\frac{\Delta t}{\Delta x^2}\right)\left(u_{j+1}^n - 2u_j^n + u_{j-1}^n\right) + u_j^n$$

For $2 \le j \le N_x - 2$. For the mesh points next to the boundary, we use

$$c_1^n = c_2^n, c_{N_x-1}^n = c_{N_x-2}^n, u_1^n = u_2^n, v_{N_x-1}^n = v_{N_x-2}^n.$$

2. Result

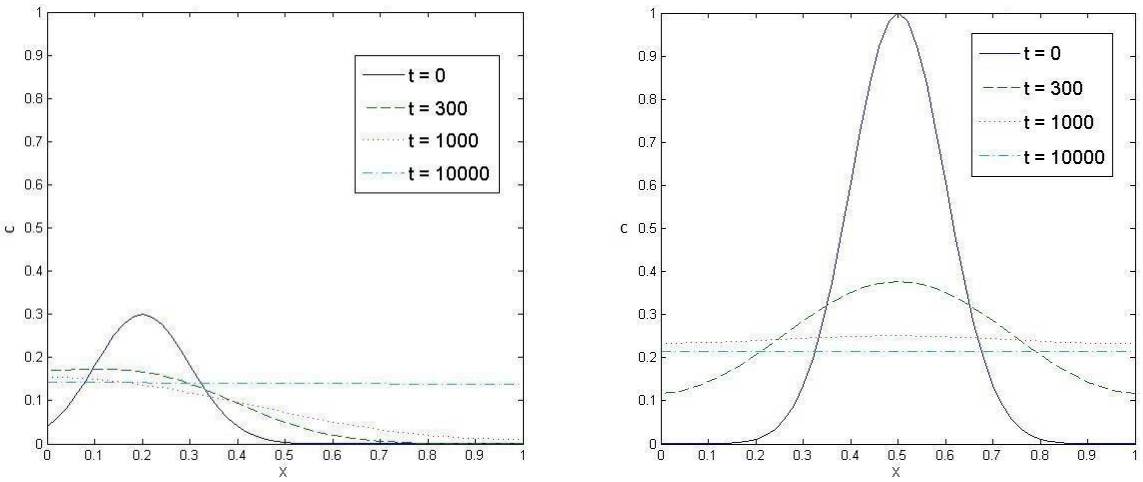
Using Matlab (see Appendix for code), we have tested the model under varying parameter values and initial conditions. We assume both populations have a normal distribution on the interval [1]. In Figure 1, the Tumor cell population has a large population most concentrated at x = 0.2 and that the Immune cell have a smaller population most concentrated at x=0.7 . Thus, $c^0(x)$ = 0.8exp $(-50(x-0.2)^2)$ and $u^0(x)$ = 0.3exp$(-50(x-0.7)^2)$. The graphs show the initial distribution along with the distribution at t=300, t=1000, t =1000 time steps. Other parameter values are a = 0.1, b =1 and D = 0.5.



(2a) (2b)

Figure 2: Numerical approximations of the model equation with a larger population of Tumor-cells and a smaller population of Immune-cells [2]. Figure 2a shows the distribution of the population of the Tumor-cells at various time steps, and Figure 2b shows the distribution of population of the Immune-cells at various time steps.

Next, we assumed a lower population of tumor cell and a higher concentration of Immune cell for increase the speed of treatment. I also shifted the concentration of Immune cell toward the center of the interval, so that $c^0(x) = 0.3\exp(-50(x-0.2)^2)$ and $u^0(x) = \exp(-50(x-0.5)^2)$ (See Figure 2). Other parameter values are a =0.7, b=0.3 and D = 0.5.



(3a) (3b)

Figure 3: Numerical approximations of the model equation with a reduced population of Tumor-cells and a higher population of Immune -cells [2]. Figure 3a shows the distribution of the population of the Tumor-cells at various time steps, and Figure 3b shows the distribution of population of the Immune-cells at various time steps.

The results shown here are consistent with varying values of a , b , and D. The presence of a dispersal term in the model has a stabilizing effect, and this result has been proven in several variations of the model equations [10]. Increasing D causes the populations to achieve a uniform distribution more quickly. After the populations are (nearly) uniform, the two populations will then begin to converge to the stable solution, which considered as a equilibrium point of two cells.

3. Conclusion

Mathematical models of tumor–immune interactions provide an analytical framework in which to address specific questions regarding tumor–immune dynamics and tumor treatment options. The beginning of a tumor's life cycle can be modeled rather accurately with many different types of growth functions. We have mentioned that the number of tumor cells not only grows, but cells can also be killed by effector cells. We accounted for immune cells in our model. Once we attained a suitable model, we used finite difference analysis to determine the number of effector cells our body would need to produce in order to make sure that that tumor cells would always go into remission. Though the non-trivial solution to the system is potentially unrealistic, it can be easily modified to more closely mimic what happens in nature. Specifically, one such modification is the addition of a diffusion term which causes the solution to be stable. The model itself can be numerically solved using finite difference methods. The Matlab code provided in the appendix can be easily modified to reflect other changes in the model as it suits the user.

By seeing where our two cells intersect, we can find equilibrium points. These are points in which our immune-cells growth and tumor growth are in steady states [3]. We care about these points because we hope that we can stop tumor growth from occurring. It is important to have our effector cells in a steady state because sometimes the number of tumor cells is dependent on the number of effector cells. To make sure we have no cancer growth, we cannot have any effector cell growth or decay either. This results can be play an important role in modeling tumor-immune dynamics.

References

1. Olinick, M. (2014). *Mathematical modeling in the social and life sciences*. John Wiley & Sons.
2. Wu, J. T., Byrne, H. M., Kirn, D. H., & Wein, L. M. (2001). Modeling and analysis of a virus that replicates selectively in tumor cells. *Bulletin of mathematical biology, 63*(4), 731–768.
3. DePillis, L., Gallegos, A., & Radunskaya, A. (2013). A model of dendritic cell therapy for melanoma. *Frontiers in oncology, 3,* 56.
4. Nicholas, James. (2011). Cancer Research UK, *The Cancer Cell.*
5. Democheli, R., Tereziani, M., Valagussa, P., Moliterni, A., Zambetti, M., & Bonadonna, G. (1994). Local recurrences following mastectomy: support for the concept of tumor dormancy. *JNCI: Journal of the National Cancer Institute, 86*(1), 45-48.
6. Lotka, A. J. (1925). *Elements of physical biology.* Williams & Wilkins.
7. Nasritdinov, G., & Dalimov, R. (2010). Limit cycle, trophic function and the dynamics of intersectoral interaction. *Current Research Journal of Economic Theory, 2*(2), 32-40.
8. Rosenzweig, M. L., & MacArthur, R. H. (1963). Graphical representation and stability conditions of predator-prey interactions. *The American Naturalist, 97*(895), 209-223.
9. Takeuchi, Y. (1986). Global stability in generalized Lotka-Volterra diffusion systems. *Journal of mathematical analysis and applications, 116*(1), 209-221.
10. M. M. Panchal and T. R. Singh. (2019). Finite Difference Schemes to Nonlinear Parabolic System of Cancer Invasion and Interaction of Cancer Cell with Surrounding Tissues. *Int. Journal Of Advanced technology in Engineering and sciences, 7* (2), 01-11.
11. M. M. Panchal and T. R. Singh. (2019). Numerical solution of the mathematical modelling of tumor growth during the process of angiogenesis. *Int. Journal of Recent Scientific Research. 2* (4c), 3801038014.

Appendix

Matlab code used to numerically solve the Lotka-Volterra model with diffusion by using a forward finite difference scheme

```
% Forward Method
clear;
L = 1; %total length of spatial interval
T = 1; %total length of time interval
% Parameters needed to solve the equation within the explicit method  maxk = 10000; % Number of time steps  dt = T/maxk;
nx = 50; % Number of space steps  dx = L/nx;  a = .7;  b = .3;  nu=dt/(dx*dx);
k=50; %parameter in population normal distributions
D =.5; % diffusion constant
% Initial distributions  for j = 1:nx+1  x(j) =(j-1)*dx;
%u(j,1) =.8; %sin(pi*x(j)); %other initial distributions  u(j,1)=0.8*exp(-k.*((x(j)-0.2)).^2);
%v(j,1) =.4;
%v(j,1)=.25+.5.*sin(pi*x(j));  v(j,1)=0.3*exp(-k.*((x(j)-0.7)).^2);  end
% Implementation of the forward method  for n=1:maxk % Time Loop  j = 1; %left-hand boundary
u(j,n+1) = D*nu.*(u(j,n)+u(j+1,n)-2.*u(j,n))+ dt*(u(j,n)).*(1-u(j,n)v(j,n))+u(j,n);
v(j,n+1) = nu.*(v(j,n)+v(j+1,n)-2.*v(j,n)) + dt*a.*(v(j,n)).*(u(j,n)-b) + v(j,n);
for j=2:nx; % Space Loop
u(j,n+1) = D*nu.*(u(j-1,n)+u(j+1,n)-2.*u(j,n))+ dt*(u(j,n)).*(1-u(j,n)v(j,n))+u(j,n);
v(j,n+1) = nu.*(v(j-1,n)+v(j+1,n)-2.*v(j,n)) + dt*a.*(v(j,n)).*(u(j,n)-b) + v(j,n);  end
%right-hand boundary  j = nx+1;
u(j,n+1) = D*nu.*(u(j-1,n)+u(j,n)-2.*u(j,n))+ dt*(u(j,n)).*(1-u(j,n)v(j,n))+u(j,n);
v(j,n+1) = nu.*(v(j-1,n)+v(j,n)-2.*v(j,n)) + dt*a.*(v(j,n)).*(u(j,n)-b) + v(j,n);  end
% Graphical representation of the temperature at different selected times  figure(1)
plot(x,u(:,1),'-',x,u(:,300),'--',x,u(:,1000),':',x,u(:,10000),'-.')  axis([0 1 0 1]) %specifies limits of axes (0, 1) x (0, 1)  title('Prey distributions
at various time steps')  xlabel('X')  ylabel('u')  figure(2)
plot(x,v(:,1),'-',x,v(:,300),'--',x,v(:,1000),':',x,v(:,10000),'-.')  axis([0 1 0 1])
title('Predator distribution at various time steps')  xlabel('X')  ylabel('v')
```