A Study of Population Dynamics of Normal and Immune Cells in Presence of Tumor Cells

Dr. Naseem Ahmad,Gurpreet Kaur

Abstract—This paper deals with the population dynamics of normal, tumor and immune cells at cellular level. The competition model at cellular level has been evolved in equations which defines the dynamics of tumor growth or decay. Qualitative analysis of the nonlinear differential equations has been looked upon to see the behaviour of tumor cells with respect to normal and immune cells. The numerical analysis is one of the tools to see the effect of time.

Keywords— Population dynamics, Cellular interactions, Immune system, Tumor dynamics.

1 Introduction:

Cell is the basic unit of our body. Cells become specialized for particular functions. Each cell type has its cell-division process regulated so that it does not interfere with the activities of other cells or the whole organism. When there are mutations in the normal cell it changes into abnormal cells. Some abnormal cells, however, may begin to divide as if they were "new-born" or undifferentiated cells. Sometimes this division occurs in an uncontrolled fashion. A lump is formed due to the uncontrolled division of cells is called tumor. Tumor can be cancerous (malignant) or non-cancerous (benign). A benign tumor is a known as tumor cell mass that does not fragment and spread beyond its original area of growth. Generally benign impact on the body is not harmful and easy-to-treatment. Benign tumor can be harmful by growing large enough to interfere with normal body functions. Malignant tumors are non-encapsulated growths of tumor cells that are harmful; they have no wall or clear-cut border may spread or invade other parts of the body normal tissue.

Cells of these tumors travel by bloodstream or lymphatic vessels like seeds to other tissues, where they land and start similar growth called metastasize. By giving rise to secondary tumors, or metastases, they become hard to eradicate surgically [1]. Tumor is the formed in the body by sequence of processes [2, 3]. The genetic changes at the cellular level control the interaction of the developing tumor population with each other, normal cells and immune cells [4].

- *Dr. Naseem Ahmad, Department of Mathematics Jamia Millia Islamia, Jamia Nagar, New Delhi-110025. E-mail :naseem_mt@yahoo.com*
- *Gurpreet Kaur , Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, Jamia Nagar, New Delhi-110025, India, PH-+919999479868. E-mail: gurpreet11.2008@gmail.com*

Ongoing research efforts aim to provide a clearer picture of the evolution of the tumor and normal cells with the objective of improving cancer treatment protocols. The field of cancer research had begun to grow rapidly by the end of the 19th century and the beginning of the 20th.the research is based on the concept that cancer is a disease of cells is given by Rudolf Virchow [5]. As cancer progress, tumor cells interact with the surrounding environmental components such as normal cells, immune cells or therapeutic agents that have been externally added to the system. We can, however, examine the evolution of tumor, normal and immune cells and complexity of the system through the use of computational and mathematical modelling and simulation.

In 2010,Mark Robertson[6] reported that the immune system prevents the formation of tumor while Gavin [8] said immune cells becomes weak to stop the formation of tumor even though then cells work as barrier to formation in turn the rate of formation becomes slow. Mutant cells compete with each other for needed resources. The immune system often kills tumor cells like a predator hunting prey, and the tumor cells develop defences against the predation.

The immuno-surveillance hypothesis formulated in the 1950s suggested that the immune system is capable of inhibiting the growth of very small tumors and eliminating them before they become clinically evident [13]. The *cellular scale* refers to cell–cell interactions that are key elements at all stages of tumor formation, whether they are among tumor cells and host cells, or among tumor cells themselves. For example, early in tumor development, if the immune system is active and able to recognize tumor cells, it may be able to develop a destruction mechanism and induce cancer cell death; otherwise, the tumor may evade apoptosis or co-opt the host cells, allowing progressive growth. During

invasion and metastasis, alterations in cell–cell adhesion between individual tumor cells are key to driving the process [12].

Tumor dormancy is a state of malignant cells which, although remaining viable for relatively long periods, show no evidence of multiplication during this time; yet retain all their former and vigorous capacity to multiply**.** In this state tumor cells neither destroyed by the host's natural defence mechanisms nor not grow out rapidly to form a clinically overt tumor [16].

Biological system is very complex. Researchers are trying to understand the complex system. They have a view point to apply Mathematics in the tumor growth dynamics. The experiments are set so far to see the tumor growth could not give the very good information because they are not adequate to get good recommendations [9].It has been seen that the Mathematical modeling is helpful in understanding some important features of tumor dynamics [10,11] since last few decades. Italian scientist Leonardo De Vinci (1452-1591) said "No Human Investigation can claim to be Scientific if it does not pass the test of Mathematical proof".

2.0 Model equations

In almost mathematical models or problem formation, both the normal and tumor cells independently increase according to a logistic growth law. In the present model, we consider the interaction between normal, tumor and immune cells to see the possible results. Let N (t) be the concentration of normal or host cell in the physiologic space or organ or tissue of the human anatomy where tumor cells localized at time t, T (t) be the concentration of tumor cell in the given physiologic space at time t and E (t) the concentration of effector cell or immune cells.

$$\frac{dN}{dt} = r_N N(1-\frac{N}{K_N}) - \alpha_{NT} NT \qquad (2.1)$$

$$\frac{dT}{dt} = r_T T(1-\frac{T}{K_T}) - \alpha_{TN} TN - \alpha_{TE} TE \qquad (2.2)$$

$$\frac{dE}{dt} = s - dE + \alpha_{ET} ET \qquad (2.3)$$

where r_N and r_T be the maximum growth rate of normal cells and tumor cells respectively; K_N and K_T denote the normal and tumor cell carrying capacities respectively which could occupy the tissue space and be adequately supported by the environment in the absence of the competing population; α_{NT} is the interaction rate of normal cell with tumor cells and it is the negative effect of tumor on normal tissue such as tumor-induced extracellular matrix breakdown and micro environmental changes[14], α_{TN} is the competition term of tumor cells with normal cells, α_{TE} is the interaction between tumor cells with effector cells (tumor cells are killed by the effector cells) and α_{ET} is the positive feedback The positive feedback may result from release of tumor antigens or from release of cytokines by active lymphocytes[15]. The parameter s is the "normal" (i.e. not increased by the presence of the tumor) rate of flow of mature effector cell into the region of tumor cell site [10] and d is the natural death of effector cell.

We define the following dimensionless variables

$$N^* = \frac{N}{N_0}, \quad T^* = \frac{T}{T_0}, \quad E^* = \frac{E}{E_0}, \qquad t^* = \alpha_{TE} T_0 t$$

Now incorporating these dimensionless variables in the equations (2.1) through (2.3), we get

$$\frac{dN^*}{dt} = r_1 N^*(1-a_1 N^*) - b_1 N^* T^* \qquad (2.4)$$

$$\frac{dT^*}{dt} = r_2 T^*(1-a_2 T^*) - b_2 N^* T^* - c_2 T^* E^* \qquad (2.5)$$

$$\frac{dE^*}{dt} = \alpha - \beta E^* + b_3 E^* T^* \qquad (2.6)$$

where

$$r_1 = \frac{r_N}{\alpha_{TE} T_0}, \; r_2 = \frac{r_T}{\alpha_{TE} T_0}, \; a_1 = \frac{N_0}{K_N}, \; a_2 = \frac{T_0}{K_T}, \; , b_2 = \frac{\alpha_{TN} N_0}{\alpha_{TE} T_0}$$

$$, \; c_2 = \frac{E_0}{T_0}, b_3 = \frac{\alpha_{ET}}{\alpha_{TE}}, \alpha = \frac{s}{\alpha_{TE} T_0 E_0}, \beta = \frac{d}{\alpha_{TE} T_0}$$

The reverent initial conditions are

$N^* = N_0$

$T^* = T_0$ at $t^* = 0$

$E^* = E_0$

For our convenience, we suppress the starts (*), so we write

$$\frac{dN}{dt} = r_1 N(1-a_1 N) - b_1 NT \qquad (2.7)$$

$$\frac{dT}{dt} = r_2 T(1-a_2 T) - b_2 NT - c_2 TE \qquad (2.8)$$

$$\frac{dE}{dt} = \alpha - \beta E + b_3 ET \qquad (2.9)$$

It is the fact that the initial values of N_0, T_0 and E_0 are non negative, but we cannot predict this fact for the solution of equations (2.7) through (2.9). To be sure, we prove the following lemma.

Lemma *(global existence and uniqueness): - If initial values of N_0, T_0 and E_0 are non-negative, then there exit non negative, unique global solution of the equations (2.7) through (2.9).*

Proof: Solving the differential equations (2.7) to (2.9) and applying the respective initial condition. We get

$$N(t) = N_0 \exp\left(\int_0^t \{r_1(1-a_1N(s)) - b_1T(s)\}ds\right) \quad (2.10)$$

$$T(t) = T_0 \exp\left(\int_0^t \{r_2(1-a_2T(s)) - b_2N(s) - c_2E(s)\}ds\right) \quad (2.11)$$

and,

$$E(t) = \alpha \exp\left(-\int(\beta - b_3T(s))ds\right)\int_0^t \exp\left(\int(b_3T(s)-\beta)ds\right)ds \quad (2.12)$$

Here we observe that $N_0 \geq 0$ for equation (2.10), $T_0 \geq 0$ for equation (2.11) and $\alpha \geq 0$, so $\alpha \exp\left(-\int(\beta - b_3T(s))ds\right) \geq 0$ for equation (2.12).Hence the solutions are non negative.

Also, we see that

$$\frac{dN}{dt} \leq r_1 N (1 - a_1 N)$$

so,

$$N(t) \leq \max(N_0, \frac{1}{a_1}) = N_{\max}$$

Using N_{max}, we can estimate the T from equation (2.11) as follows

$$\frac{dT}{dt} \leq r_2 T (1 - a_2 T) - \eta T$$

Thus,

$$T(t) \leq \max(T_0, \frac{1}{a_2}(1 - \frac{\eta}{r_2})) = T_{\max}$$

With the help of T_{max} in equation (2.12), we get the following inequality

$$\frac{dE}{dt} \leq \alpha + \xi E$$

where $\xi = b_3 T_{\max}$

$$\Rightarrow \quad E \leq e^{-\xi t}(E_0 + \int_0^t \alpha e^{\xi s} ds)$$

Hence Lemma proved.

The closed form solution of the nonlinear model given by the equations (2.7) through (2.9) may not be possible; so we try to study their qualitative behaviour applying stability of the steady states. Assuming that parameters occurring in the model are nonnegative, we consider the steady states of given model. We have dN/dt = 0, dT/dt=0 and dE/dt = 0.Thus, we get the following

$$N = 0, \; N = \frac{1}{a_1} - \frac{b_1 T}{a_1 r_1} \quad (2.13)$$

$$T = 0, \quad T = \frac{1}{a_2} - \frac{b_2 N}{a_2 r_2} - \frac{c_2 E}{r_2 a_2} \quad (2.14)$$

,

and

$$E = \frac{\alpha}{\beta - b_3 T} \quad (2.15)$$

Using the equations (2.13) through (2.15), we obtain the six equilibrium points $E_1(0, 0, \frac{\alpha}{\beta})$, $E_2(\frac{1}{a_1}, 0, \frac{\alpha}{\beta})$, $E_3(0, \overset{*}{T}_1, \overset{*}{E}_1)$ and $E_4(0, \overset{*}{T}_2, \overset{*}{E}_2)$,

if $\Delta = \left(\frac{a_2\beta + b_3}{a_2 b_3}\right)^2 - 4\left(\frac{r_2\beta - c_2\alpha}{a_2 r_2 b_3}\right) > 0$.

Where

$$\overset{*}{T}_1 = \frac{a_2\beta + b_3 - a_2 b_3\sqrt{\Delta}}{2a_2 b_3},$$

$$\overset{*}{E}_1 = \frac{2\alpha a_2 b_3}{2\beta a_2 b_3 - b_3(a_2\beta + b_3 - a_2 b_3\sqrt{\Delta})}$$

$$\overset{*}{T}_2 = \frac{a_2\beta + b_3 + a_2 b_3\sqrt{\Delta}}{2a_2 b_3},$$

$$\overset{*}{E}_2 = \frac{2\alpha a_2 b_3}{2\beta a_2 b_3 - b_3(a_2\beta + b_3 + a_2 b_3\sqrt{\Delta})}$$

$E_5(\hat{N}_1, \hat{T}_1, \hat{E}_1)$ and $E_6(\hat{N}_2, \hat{T}_2, \hat{E}_2)$, if $\Delta = B^2 - 4AC > 0$.

where

$$A = b_1 b_2 b_3 - a_1 a_2 r_1 r_2 b_3,$$

$$B = b_2 b_3 r_1 + b_1 b_2 \beta - a_1 a_2 r_1 r_2 \beta + a_1 b_3 r_1 r_2$$

and $C = a_1 c_2 r_1 \alpha - b_2 r_1 \beta$

$$\hat{N}_1 = \frac{1}{a_1} - \frac{b_1}{a_1 r_1}\left(\frac{B+\sqrt{\Delta}}{2A}\right), \hat{T}_1 = \frac{B+\sqrt{\Delta}}{2A}, \hat{E}_1 = \frac{2\alpha A}{2A\beta - b_2(B+\sqrt{\Delta})}$$

$$\hat{N}_2 = \frac{1}{a_1} - \frac{b_1}{a_1 r_1}\left(\frac{B-\sqrt{\Delta}}{2A}\right), \hat{T}_2 = \frac{B-\sqrt{\Delta}}{2A}, \hat{E}_2 = \frac{2\alpha A}{2A\beta - b_2(B-\sqrt{\Delta})}$$

.

The stability criteria of equilibrium states E_1, E_2, E_4 and E_5 are discussed below.

2.1 The existence and local stability of the prospective equilibrium

The Jacobian matrix due to linearization of (2.7), (2.8) and (2.9) about an arbitrary equilibrium E_0 (N, T, E) is given by

$$J_{E_0}=\begin{pmatrix} r_1-2a_1r_1N-b_1T & -b_1N & 0 \\ -b_2N & r_2-2r_2a_2T-b_2N-c_2E & -c_2T \\ 0 & b_3E & b_3T-\beta \end{pmatrix}$$

The Jacobian matrix of the system equations (2.7), (2.8) and (2.9) about the point E_1 $(0, 0, \frac{\alpha}{\beta})$ is given by the expression

$$J_{E_1}=\begin{pmatrix} r_1 & 0 & 0 \\ 0 & r_2-c_2\frac{\alpha}{\beta} & 0 \\ 0 & b_3\frac{\alpha}{\beta} & -\beta \end{pmatrix}$$

The Eigen values are given by $\lambda_1=r_1(>0), \lambda_2=r_2-\frac{c_2\alpha}{\beta}>0$ and $\lambda_3=-\beta(<0)$. As λ_1 and λ_2 are positive, so the equilibrium point E_1 is unstable and it becomes the saddle point.

Remark: The point E_1 $(0, 0, \frac{\alpha}{\beta})$ is not feasible biologically since it has neither normal nor cancer cells only immune cells. It is also highly unstable.

The Jacobian matrix of the system equations (2.7), (2.8) and (2.9) about E_2 $(\frac{1}{a_1}, 0, \frac{\alpha}{\beta})$ is given by the expression

$$J_{E_2}=\begin{pmatrix} -r_1 & \frac{-b_1}{a_1} & 0 \\ 0 & r_2-\frac{b_2}{a_2}-c_2\frac{\alpha}{\beta} & 0 \\ 0 & b_3\frac{\alpha}{\beta} & -\beta \end{pmatrix}$$

The eigen values are given by $\lambda_1=-r_1(<0), \lambda_2=r_2-\frac{b_2}{a_2}-\frac{c_2\alpha}{\beta}$ and $\lambda_3=-\beta(<0)$. The equilibrium point E_2 is stable as long as $\lambda_2<0$ or $r_2<\frac{b_2}{a_2}+\frac{c_2\alpha}{\beta}$.

This relates to per capita growth rate of tumor cells r_2 to the resistance coefficient $\frac{c_2\alpha}{\beta}$ which measures how efficient the immune system competes with the tumor cells.

Now the Jacobian matrix of the system equations (2.7), (2.8) and (2.9) about the rest point $E_4(0, \overset{*}{T}_2, \overset{*}{E}_2)$ is given by the expression

$$J_{E_4}=\begin{pmatrix} -r_1-b_1\overset{*}{T}_2 & 0 & 0 \\ -b_2\overset{*}{T}_2 & r_2-2a_2r_2\overset{*}{T}_2-c_2\overset{*}{E}_2 & -c_2\overset{*}{T}_2 \\ 0 & b_3\overset{*}{E}_2 & b_3\overset{*}{T}_2-\beta \end{pmatrix}$$

The one of the eigen value is and $\lambda_1=r_1-b_1\overset{*}{T}_2$ another two eigen values is given by the matrix A

$$A=\begin{bmatrix} r_2-2a_2r_2\overset{*}{T}_2-c_2\overset{*}{E}_2-\lambda & -c_2\overset{*}{T}_2 \\ b_3\overset{*}{E}_2 & b_3\overset{*}{T}_2-\beta-\lambda \end{bmatrix}$$

The Eigen values of matrix A are real and negative if the trace (A) <0 and det(A)>0(refer Routh Hurwitz criteria).

Thus the state is asymptotically stable only if the $r_1-b_1\overset{*}{T}_2<0$ or hyperbolic saddle if $r_1-b_1\overset{*}{T}_2>0$, trace (A) <0 and det (A)>0.The point repels in N direction.

Remark:-The equilibrium point $E_4(0, \overset{*}{T}_2, \overset{*}{E}_2)$ corresponds that normal cells in the tumor affected tissue or organ of the person are destroyed. The cancer patient demise or the new organ is implanted. Thus E_4 is highly unstable.

The Jacobian matrix for the point $E_5=(\hat{N}_1, \hat{T}_1, \hat{E}_1)$ is given by

$$J_{E_5}=\begin{pmatrix} -r_1-2a_1r_1\hat{N}_1-b_1\hat{T}_1 & -b_1\hat{N}_1 & 0 \\ -b_2\hat{T}_1 & r_2-2a_2r_2\hat{T}_1--b_2\hat{N}_1-c_2\hat{E}_1 & -c_2\hat{T}_1 \\ 0 & b_3\hat{E}_1 & b_3\hat{T}_1-\beta \end{pmatrix}$$ The characteristic equation is

$$\lambda^3+A_1\lambda^2+A_2\lambda=A_3=0$$

where

$$A_1=2a_1r_1\hat{N}_1+b_1\hat{T}_1+2r_2a_2\hat{T}_1+b_2\hat{N}_1+c_2\hat{E}_1+\beta-r_2-r_1$$

$$A_2=(2a_1r_1\hat{N}_1+b_1\hat{T}_{l1}-r_1)(2r_2a_2\hat{T}_1+b_2\hat{N}_1+c_2\hat{E}_1+\beta-r_2)-b_1b_2\hat{N}_1\hat{T}_1+\gamma$$

$$A_3=b_1b_2\hat{N}_1\hat{T}_1^2+(2a_1r_1\hat{N}_1+b_1\hat{T}_1-r_1)\gamma-\beta b_1b_2\hat{N}_1\hat{T}_1 \quad \text{and}$$

$$\gamma=r_2b_3+2r_2a_2\beta\hat{T}_1+b_2\beta\hat{T}_1-(2r_2a_2b_3\hat{T}_1^2+b_2b_3\hat{N}_1\hat{T}_1+r_2\beta+c_2\beta\hat{E}_1)$$

According to Routh-Hurwitz's criteria, the necessary and sufficient conditions for local stability of co-existence points are $A_1>0$, $A_3>0$ and $A_1A_2>A_3$. The eigen values with negative real parts is locally asymptotically stable.

3. Discussion and Results

3.1 Through phase portrait: the diagrams provide qualitative information about the solution paths of non linear systems. Referring the fig-1, we conclude that the

tumor population reduces extremely while the immune population remains constant.

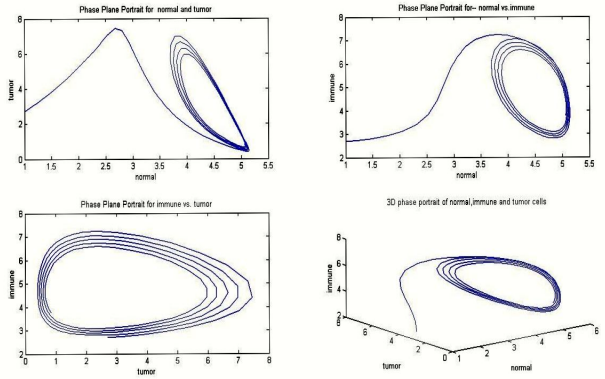

Fig. 1 Phase portraits corresponding (2.7) through (2.9) for the parameter values r1=3.633, r2=4.668, a1=.19, a2=.002, b1=.1817, b2=.3*(10^-5), c2=1, alpha=.051, delta=.567, d=.2, b3=.234

3.2 Through numerical simulation: Referring fig. 2, we see that the tumor cells suddenly spread over and there interfere with the normal and immune cells. As time progresses due to body metabolism, the tendency of tumor cells is to reduce and become constant while normal cells do not interfere. Hence, in the course of time tumor cells remain controlled and normal cells become non-interfering.

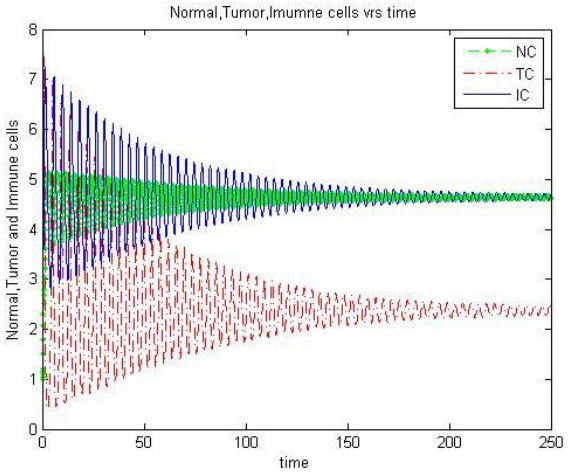

Fig. 2 Dynamical behaviour of the normal, tumor and immune system (2.1) through (2.3) with r1=3.633, r2=4.668, a1=.19, a2=.002, b1=.1817, b2=.3*(10^-5), c2=1, alpha=.051, delta=.567, d=.2, b3=.234, the variation of the populations against the time

Conclusion

Through mathematical model, we presented the population dynamics of three types of cells at a time. Mostly, researches consider the relative study of two types of cells. We managed the study by qualitative analysis and we conclude the following

1. The tumor population reduces extremely while the immune population remains constant.
2. Tumor cells will be in the quiescent state and normal cells become non-interfering of tumor cells.

References

1. Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, Peter Walter, "Molecular Biology of the Cell," NCBI, 2004.
2. R. A. Weinberg, "**U**sing maths to tackle cancer, "Nature, vol. 449, pp. 978-981, 2007.
3. Dariush Sardari, Nicolae Verga, Azim Arbabi, Ahmad Ameri, Soodeh Amirifar, "Physical Modeling of Cancer Tumor Growth: A Preliminary Review," Australian Journal of Basic and Applied Sciences, vol. 3, pp.3531-3536, 2009.
4. R. A. Gatenby, "Models of Tumor Host Interaction as Competing Populations Implications for Tumor Biology and Treatment," J. Theor. Bio., vol.176, pp. 336-344, 1995.
5. Bernard Weinstein, Kathleen Case, "The History of Cancer Research: Introducing an AACR Centennial Series," Cancer Res., vol. 68, no.17 pp. 6861-6862, 2008.
6. Mark Robertson-Tessi, Ardith El-Kareh, Alain Goriely, "A Mathematical Model of Tumor-Immune Interactions," J. Theor. Biol., vol. 294, pp. 56-73, 2010
7. J.C. Arciero, T.L. Jackson, D.E. Kirschner, "A Mathematical Model of Tumor-Immune Evasion and siRNA Treatment," Discrete and Continuous Dynamical Systems–SERIES B, vol. 4,pp. 39-58, 2004.
8. G. P. Dunn, A. T. Bruce, Hiroaki Ikeda, L. J. Old, R. D. Schreiber, "Cancer immunoediting: from immunosurveillance to tumor escape," Nature Publishing Group, vol. 3, pp. 991-998,2002.
9. R. Prehn, "Stimulatory effects of immune reactions upon the growths of untransplanted tumours," Cancer Res., vol. 54, pp. 908-914, 1994.
10. V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor, A.S. Perelson, "Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis," Bull. Math. Biol., vol. 56, pp.295-321, 1994.
11. Magda Galach, "Dynamics of the tumor – immune system competition –the effect of time delay," Int.

J. Appl. Math. Comp. Sci., vol. 13, pp. 395-406, 2003.

12. N. Bellomo, M. Delitala, "From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells," Physics of Life Reviews, vol. 5, pp. 183-206, 2008.
13. Raluca Eftimie, J. L. Bramson, J.D. David, Earn "Interactions between the Immune System and Cancer: A Brief Review of Non-spatial Mathematical Models," Bull Math Bio., vol. 73, pp. 2-32, 2011.
14. R. A. Gatenby, T. L. Vincent, "Application of quantitative models from population biology and evolutionary game theory to tumor therapeutic strategies," Molecular Cancer Therapeutics, vol. 2, pp. 919-927, 2003.
15. C. F. Babbs, "Predicting success or failure of immunotherapy for cancer: insights from a clinically applicable mathematical mode," Am. J. Cancer Res., vol.2, pp.204-213, 2012.
16. E. A. K. Alsabti, "Tumor Dormancy, A Review," J. Cancer Res. Clin. Oncol., vol. 95,pp. 209-220, 1979.