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].

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 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 since last few decades. Italian scientist Leonardo De Vinci (1452-1519) 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.

\[
\frac{dN}{dt} = r_N N \left(1 - \frac{N}{K_N}\right) - \alpha_{NT} NT
\]  
(2.1)

\[
\frac{dT}{dt} = r_T T \left(1 - \frac{T}{K_T}\right) - \alpha_{TN} TN - \alpha_{TE} TE
\]  
(2.2)

\[
\frac{dE}{dt} = s - dE + \alpha_{ET} ET
\]  
(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; \( \alpha_{NT} \) 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]; \( \alpha_{TN} \) is the competition term of tumor cells with normal cells, \( \alpha_{TE} \) is the interaction between tumor cells with effector cells (tumor cells are killed by the effector cells) and \( \alpha_{ET} \) 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 [11] and \( d \) is the natural death of effector cell.

We define the following dimensionless variables

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

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

\[
\frac{dN}{dt} = r_t N (1 - a N^*) - b_T N T^*
\]  
(2.4)

\[
\frac{dT}{dt} = r_T T (1 - a T^*) - b_N N^* T^* - c_T E^*
\]  
(2.5)

\[
\frac{dE}{dt} = \alpha - \beta E^* + b_E E T^*
\]  
(2.6)

where

\[
r_t = \frac{r_t}{\alpha_{TE} T_0}, \quad r_T = \frac{r_T}{\alpha_{TE} T_0}, \quad a = \frac{N_0}{K_N}, \quad b_T = \frac{b_T}{T_0}, \quad c_T = \frac{c_T}{E_0}, \quad d = \frac{d}{\alpha_{TE} T_0}
\]

The reverent initial conditions are

\[
N^* = N_0, \quad T^* = T_0, \quad E^* = E_0 \quad \text{at} \quad t^* = 0
\]

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

\[
\frac{dN}{dt} = r_t N (1 - a N) - b_T N T
\]  
(2.7)

\[
\frac{dT}{dt} = r_T T (1 - a T) - b_N N T - c_T E
\]  
(2.8)

\[
\frac{dE}{dt} = \alpha - \beta E + b_E E T
\]  
(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
$$N(t)=N_0 \exp \left( \int_{0}^{t} \left[ r_1 (1-a_1 N(s)) - b_1 T(s) \right] ds \right)$$
(2.10)
$$T(t)=T_0 \exp \left( \int_{0}^{t} \left[ r_2 (1-a_2 N(s)) - b_2 N(s) - c_2 E(s) \right] ds \right)$$
(2.11)
and,
$$E(t) = \alpha \exp \left( \int_{0}^{t} \left( \beta - b_3 T(s) \right) ds \right) \exp \left[ \int_{0}^{t} \left( b_3 T(s) - \beta \right) ds \right]$$
(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
$$\alpha \exp \left( \int_{0}^{t} \left( \beta - b_3 T(s) \right) ds \right) \geq 0 \text{ for equation (2.12). Hence the solutions are non-negative.}$$

Also, we see that
$$\frac{dN}{dt} \leq r_1 N \left( 1 - a_1 N \right)$$
so,
$$N(t) \leq \max \left( N_0, \frac{1}{a_1} \right) = N_{\text{max}}$$

Using $N_{\text{max}}$, we can estimate the $T$ from equation (2.11) as follows
$$\frac{dT}{dt} \leq r_2 T \left( 1 - a_2 T \right) - \eta T$$
Thus,
$$T(t) \leq \max \left( T_0, \frac{1}{a_2} \left( 1 - \frac{\eta}{r_2} \right) \right) = T_{\text{max}}$$

With the help of $T_{\text{max}}$ in equation (2.12), we get the following inequality
$$\frac{dE}{dt} \leq \alpha + \xi E$$
where
$$\xi = b_3 T_{\text{max}}$$
$$\Rightarrow \quad E \leq e^{-\xi t} \left( E_0 + \int_{0}^{t} \alpha e^{\xi s} ds \right)$$

Hence closed form 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 behavior 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

$$N = 0, N = \frac{1 - b_1 T}{a_1 r_1}$$
(2.13)
$$T = 0, T = \frac{1 - b_2 N}{a_2 r_2} - \frac{c_2 E}{r_2 a_2}$$
(2.14)
and
$$E = \frac{\alpha}{\beta - b_3 T}$$
(2.15)

Using the equations (2.13) through (2.15), we obtain the six equilibrium points $E_1 (0, 0, \frac{\alpha}{\beta})$, $E_2 (0, 0, \frac{\alpha}{\beta})$, $E_3 (0, T_1, E_1)$ and $E_4 (0, T_2, E_2)$.

If $\Delta = \left( \frac{a_2 b_3 - a_1 b_3}{a_2 b_3} \right)^2 - 4 \left( \frac{r_3 - c_2 a_1}{a_2 r_2 b_3} \right) > 0$.

Where
$$T_1 = \frac{a_2 b_3 - a_1 b_3 \sqrt{\Delta}}{2a_2 b_3}$$
$$E_1 = \frac{2aa_2 b_3}{2a_2 b_3 - b_3 \left( a_2 b_3 + a_2 b_3 \sqrt{\Delta} \right)}$$
$$T_2 = \frac{a_2 b_3 - a_1 b_3 \sqrt{\Delta}}{2a_2 b_3}$$
$$E_2 = \frac{2aa_2 b_3}{2a_2 b_3 - b_3 \left( a_2 b_3 + a_2 b_3 \sqrt{\Delta} \right)}$$

$E_5 (N_1, T_1, E_1)$ and $E_6 (N_2, T_2, E_2)$, if $\Delta = B^2 - 4AC \geq 0$.

where
$$A = b_2 b_3 r_1 - a_1 a_2 r_2 b_3$$
$$B = b_2 b_3 r_1 + b_2 b_3 - a_1 a_2 r_2 r_1 a_3 b_3$$
$$C = a_1 a_2 r_2 a_3 - b_2 b_3$$

and
$$N_1 = \frac{1}{a_1} - \frac{b_1}{a_1 r_1} \left( \frac{B + \sqrt{\Delta}}{2A} \right), T_1 = \frac{B + \sqrt{\Delta}}{2A}, E_1 = \frac{2AA}{2AB - b_2 \left( B - \sqrt{\Delta} \right)}$$
$$N_2 = \frac{1}{a_1} - \frac{b_1}{a_1 r_1} \left( \frac{B - \sqrt{\Delta}}{2A} \right), T_2 = \frac{B - \sqrt{\Delta}}{2A}, E_2 = \frac{2AA}{2AB - b_2 \left( B - \sqrt{\Delta} \right)}$$

The stability criteria of equilibrium states $E_1, E_2, E_3$ 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
The Jacobian matrix of the system equations (2.7), (2.8) and (2.9) about the point $E_i(0, 0, \frac{\alpha}{\beta})$ is given by the expression

$$J_{E_i} = \begin{pmatrix} r_i - 2a_i r_i N - b_i T & -b_i N & 0 \\ -b_i N & r_i - 2a_i r_i T - b_i N - c_i E & -c_i T \\ 0 & b_i E & b_i T - \beta \end{pmatrix}$$

The one of the eigen value is and $\lambda_1 = r_i - b_i T_2$ another two eigen values is given by the matrix $A$

$$A = \begin{pmatrix} r_i - 2a_i r_i T & -b_i T & \lambda - c_i T_2 \\ b_i E & b_i T - \beta & 0 \end{pmatrix}$$

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 $r_i - b_i T_2 < 0$ or hyperbolic saddle if $r_i - b_i T_2 > 0$, trace $(A) < 0$ and $\det(A) > 0$. The point repels in N direction.

Remark: The equilibrium point $E_i(0, T_2, E_2)$ 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 $E_i$ is highly unstable.

The Jacobian matrix for the point $E_i = (N_1, T_1, E_1)$ is given by

$$J_{E_i} = \begin{pmatrix} -r_1 & -b_1 N & 0 \\ -b_1 N & b_2 T - c_2 E - c_2 T & 0 \\ 0 & b_1 E & b_1 T - \beta \end{pmatrix}$$

The eigen values are given by $\lambda_1 = -r_1(> 0)$, $\lambda_2 = r_2 - b_2 E$ and $\lambda_3 = -\beta(< 0)$. The equilibrium point $E_2$ is stable as long as $\lambda_2 < 0$ or $r_2 < \frac{b_2 E}{a_2} + \frac{c_2 \alpha}{\beta}$. 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 $E_i(0, T_2, E_2)$ is given by the expression

$$J_{E_i} = \begin{pmatrix} -r_i - b_i T_2 & 0 & -b_i T \\ -b_i T_2 & r_i - 2a_i r_i T_2 - b_i T_2 - c_i E & -c_i T_2 \\ 0 & b_i E_2 & b_i T_2 - \beta \end{pmatrix}$$

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

where

$$A_1 = 2a_i r_i T_1 N_1 + b_i T_1 - r_1 N_1 + c_2 E_1 + \beta - r_i$$

$$A_2 = (2a_i r_i T_1 T_2 - r_1 N_1) (2a_i r_i T_2 + b_i T_2 + c_2 E_2 + \beta - r_2) - b_i b_2 N_1 T_1 + \gamma$$

$$A_3 = b_i b_2 N_1 T_1 + (2a_i r_i T_1 T_2 - r_1 N_1) \gamma - \beta b_i b_2 T_1$$

According to Routh-Hurwitz’s criteria, the necessary and sufficient conditions for local stability of co-existence points are $A_1 > 0$, $A_2 > 0$ and $A_1 A_2 > A_3$. 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 $r_1=3.633$, $r_2=4.668$, $a_1=19$, $a_2=0.002$, $b_1=1.1817$, $b_2=3\times10^{-5}$, $c_2=1$, $\alpha=.051$, $\delta=.567$, $d=2$, $b_3=.234$.

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 $r_1=3.633$, $r_2=4.668$, $a_1=.19$, $a_2=.002$, $b_1=.1817$, $b_2=3\times10^{-5}$, $c_2=1$, $\alpha=.051$, $\delta=.567$, $d=2$, $b_3=.234$, 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


