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Mathematical Model Solid Tumor at the Stage of Angiogenesis with Immune Response

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Abstract:

Multiple scale approaches to modeling biological phenomena are going rapidly. We present here, a mathematical model of solid tumor at the stage of angiogenesis with immune response. A system of ordinary differential equations is used to describe the dynamic process of interaction between the immune system and the tumor. Analytical and numerical techniques (MATLAB) are used to describe the tumor's response to immune response and the effect of parameter variation. We conclude biological effect the solid tumor at the stage of angiogenesis with immune response.

Keywords: Mathematical Modeling, Tumor growth, Angiogenesis, Differential equations, immune response.

Introduction:

Cancer is a generic term for a large class of diseases that can affect any part of the body and its synonyms are malignant tumors and neoplasms. A normal feature of cancer is the fast production of abnormal cells growing beyond their usual boundaries and often invading adjoining parts of the body, spreading to other organs. Some modern trends in treatment of cancer are based on the ability of certain forms of tumors to stimulate immune response. The goal of immunotherapy is to enhance the anti-tumor resistance of an organism and improve the immune system condition.

During its solid stage a tumor is small enough to take in nutrients and to expel waste by diffusion. However diffusion is not sufficient to support any continued growth of the tumor. This is because the tumor consumes nutrients at a rate proportional to its volume whereas the supply of nutrients is delivered at a rate proportional to its surface area. The avascular tumor can sometimes become dormant and there is an indefinite period for which growth stops (Folkman, 1985). The tumor can overcome this deficiency by acquiring a blood supply and it does so by inducing neighboring blood vessels to grow towards the tumor (angiogenesis). The tumor releases angiogenic factors, which diffuse into the surrounding tissue. The first reaction to this stimulus is that the endothelial cells (EC) in the neighboring vessels and nearest to the chemical source start to alter their structure.

Angiogenesis is decisive to tumor growth, but it is not unique to that process: formation of a functional vascular circuitry occurs during embryogenesis and later in growing tissues. Vascularization occurs by two distinct processes: vasculogenesis, which occurs only during early embryogenesis and produces a largely-unstructured capillary bed, and angiogenesis, which refines this basic circuitry and produces the complex system of large and small vessels that permeate a tissue. Under normal physiological conditions angiogenesis is regulated by a balance between angiogenesis-promoting factors such as TAFs and factors that inhibit this process. In normal tissue, angiogenesis is largely absent, except in the ovary, throughout the menstrual cycle, during wound healing, and during placenta formation. However, it does occur under a variety of pathological conditions, such as diabetic retinopathy, arthritis, and chronic inflammation.

A number of previous mathematical models have also coupled tumor growth with immune system dynamics. Most of these tumor-immune system models are fully deterministic, and while some models consider spatial tumor–immune

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interactions, these often focus on very simple spatial domains.

H. M. yang (2012) concludes that the dynamical trajectories depend on the initial conditions supplied to the system, and also on interacting parameters. The cumulative effect of mutation is essential to originate a cancer cell. M Kohandel et.al. (2007) have developed a simple mathematical model, based on preclinical studies, that incorporates tumor cells and the vascular network, as well as their interplay in order to study the optimal combination of anti-angiogenic therapy and radiotherapy. The model utilizes a reaction–diffusion equation to study the spatial and temporal arrangement of cells in a growing tumor.

Understanding the dynamics of cancerous tumor growth may help develop better prognoses for patients and more effective treatment plans. In this work we represent biological effect the solid tumor at the stage of angiogenesis with immune response through graph.

Mathematical Model:

Our mathematical model is a system of ordinary differential equations which are designed for the concentration of Normal cells(C), concentration of epithelial cells (E), concentration of cancer cells (T), concentration of pre-angiogenesis cells (P), and concentration of angiogenesis cells (A), concentration of immune cells (I). Here we assume that the problem is time dependent, therefore all the dependent variables are function of t only.

Concentration of Normal cells

$$\frac{dC}{dt} = \alpha_1 C\left(1-\frac{C}{R_1}\right) - \beta_1 CT - \mu_1 C$$

(1)

If *C (t)* is the concentration of Normal cells, α_1 is the intrinsic growth of normal cells, μ_1 is the mortality rate of normal cells, β_1 is rate of inhibition of normal cells by cancer cells and R_1 is carrying capacity of normal cells.

Concentration of epithelial cells

$$\frac{dE}{dt} = \alpha_2 E\left(1-\frac{E}{R_2}\right) - \gamma ET - \mu_2 E$$

(2)

If *E (t)* is the concentration of epithelial cells, α_2 is the intrinsic growth of epithelial cells, μ_2 is the mortality rate of epithelial cells, γ epithelial sprouting rate and R_2 is carrying capacity of epithelial cells.

Concentration of cancer cells

$$\frac{dT}{dt} = \alpha_3 AT\left(1-\frac{T}{R_3}\right) - \beta_2 CT - \mu_3 T - aTI$$

(3)

If *T (t)* is the concentration of *cancer* cells, α_3 is the intrinsic growth of *cancer* cells, μ_3 is the mortality rate of *cancer* cells, a killing rate of cancer cells due to immune response, β_2 is rate of inhibition of *cancer* cells and R_3 is carrying capacity of *cancer* cells.

Concentration of pre-angiogenesis cells

$$\frac{dP}{dt} = \gamma ET - \delta P - \mu_4 P$$

(4)

If *P(t)* is the concentration of pre-angiogenesis cells, μ_4 is the mortality rate of pre-angiogenesis cells, γ epithelial sprouting rate and δ transfer rate from pre-angiogenesis to angiogenesis cells.

Concentration of angiogenesis cells

$$\frac{dA}{dt} = \delta P + \varepsilon TA\left(1-\frac{A}{R_4}\right) - \mu_5 A$$

(5)

If *A(t)* is the concentration of pre-angiogenesis cells, μ_5 is the mortality rate of pre-angiogenesis cells, ε is the intrinsic growth of cancer cells, δ transfer rate from pre-angiogenesis to angiogenesis cells and R_4 is carrying capacity of cancer cells.

Concentration of immune cells

$$\frac{dI}{dt} = bTI - gI^2$$

(6)

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If $I(t)$ is the concentration of immune cells, b is the unsaturated rate of immune response and g is the clearance rate of immune response.

Let us simplify the model which can be written as following

$$\frac{dC}{dt} = \alpha_1 C\left(1-\frac{C}{R_1}\right) - \beta_1 CT - \mu_1 C$$

$$\frac{dE}{dt} = \alpha_2 E\left(1-\frac{E}{R_2}\right) - \gamma ET - \mu_2 E$$

$$\frac{dT}{dt} = \alpha_3 AT\left(1-\frac{T}{R_3}\right) - \beta_2 CT - \mu_3 T - aTI$$

(A)

$$\frac{dP}{dt} = \gamma ET - \delta P - \mu_4 P$$

$$\frac{dA}{dt} = \delta P + \varepsilon TA\left(1-\frac{A}{R_4}\right) - \mu_5 A$$

$$\frac{dI}{dt} = bTI - gI$$

Numerical Solution:

We are considering the matrix method for solving the simultaneous differential equations of the form:

$$\frac{dC}{dt} = \alpha_1 C\left(1-\frac{C}{R_1}\right) - \beta_1 CT - \mu_1 C$$

$$\frac{dE}{dt} = \alpha_2 E\left(1-\frac{E}{R_2}\right) - \gamma ET - \mu_2 E$$

$$\frac{dT}{dt} = \alpha_3 AT\left(1-\frac{T}{R_3}\right) - \beta_2 CT - \mu_3 T - aTI$$

(B)

$$\frac{dP}{dt} = \gamma ET - \delta P - \mu_4 P$$

$$\frac{dA}{dt} = \delta P + \varepsilon TA\left(1-\frac{A}{R_4}\right) - \mu_5 A$$

$$\frac{dI}{dt} = bTI - gI$$

Table1: Values of Parameter *C(0)=9, E(0)=10, P(0)=0.07, A(0)=0.71, T(0)=0.7992, I(0)=1.152*

Parameters	***Fixed Values***	***Alternatives Values*****	***Units***
α_1	*0.1*		*/day*
α_2	*0.1*		*/day*
α_3	*0.2*	*5.0*	*$[A]^{-1}\times$per day*
ε	*0.01**	*0.1*	*$[T]^{-1}\times$per day*
μ_1	*0.01*		*/day*
μ_2	*0.05*		*/day*
μ_3	*0.05*	*0.005*	*/day*
μ_4	*0.01*		*/day*
μ_5	*0.01*		*/day*
R_1	*10*		*[C]*
R_2	*20*		*[E]*
R_3	*5*	*0.1*	*[T]*
R_4	*1*	*0.2*	*[A]*
δ	*0.1*		*/day*
γ	*0.01**	*0.02*	*$[T]^{-1}\times$per day*
β_1	*0.01**		*$[T]^{-1}\times$per day*
β_1	*0.01**		*$[C]^{-1}\times$per day*
a	*0.3672*		*cm^3/ng.day*
b	*0.001152*		*cm^3/cells.day*
g	*0.38*		*l/ng.day*

The characteristic equation is

$$\begin{bmatrix} \alpha_1\left(1-\frac{\tilde{C}}{R_1}\right)-\mu_1 & 0 & -\beta_1\tilde{C} & 0 & 0 & 0 \\ 0 & \alpha_2\left(1-\frac{\tilde{E}}{R_2}\right)-\mu_2 & -\gamma\tilde{E} & 0 & 0 & 0 \\ 0 & 0 & \alpha_3\tilde{A}\left(1-\frac{\tilde{T}}{R_3}\right)-\beta_1\tilde{C}-\mu_3 & 0 & 0 & -a\tilde{T} \\ 0 & -\gamma\tilde{T} & 0 & -\delta-\mu_4 & 0 & 0 \\ 0 & 0 & 0 & \delta & \varepsilon\tilde{T}\left(1-\frac{\tilde{A}}{R_4}\right)-\mu_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & b\tilde{T}-g \end{bmatrix} = 0$$

After putting the values of parameters the characteristic equation is as follows:

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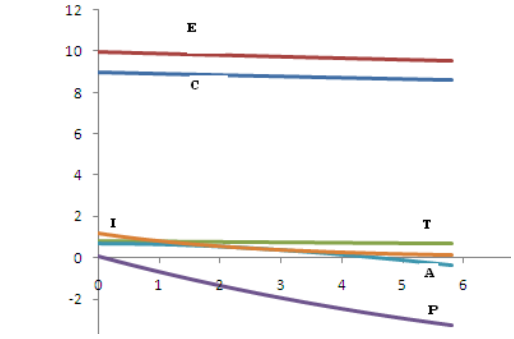
$$\begin{bmatrix} 0 & 0 & -0.09 & 0 & 0 & 0 \\ 0 & 0 & -0.1 & 0 & 0 & 0 \\ 0 & 0 & -0.0207 & 0 & 0 & -0.0293 \\ 0 & -0.07992 & 0 & -0.11 & 0 & 0 \\ 0 & 0 & 0 & 0.1 & -0.00768 & 0 \\ 0 & 0 & 0 & 0 & 0 & -0.378 \end{bmatrix} = 0$$

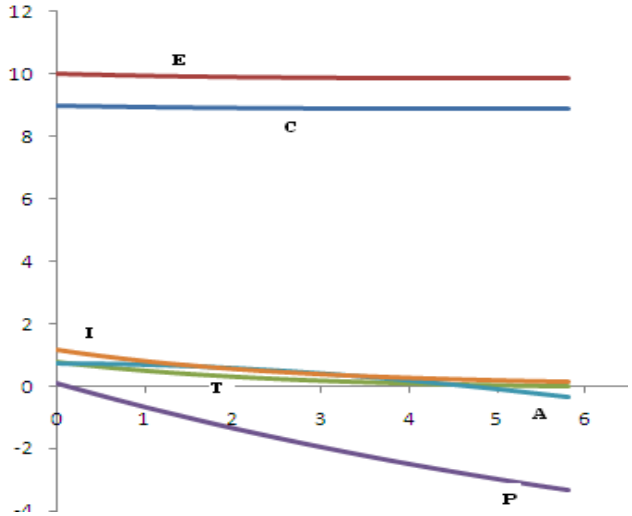
Finally, it may be shown that, according to the types of solution to the auxiliary equation, the solution of the differential equation will take one of the following three forms, in which A, B C D, E and F are arbitrary constants:

$$\begin{bmatrix} C \\ E \\ T \\ P \\ A \\ I \end{bmatrix} = A \begin{bmatrix} 1.00 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} e^{0t} + B \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1.00 \\ 0 \end{bmatrix} e^{-0.0077t} + C$$

$$\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0.715 \\ -0.699 \\ 0 \end{bmatrix} e^{-0.11t} + D \begin{bmatrix} 0 \\ 0.104 \\ 0 \\ -0.076 \\ -0.991 \\ 0 \end{bmatrix} e^{0t} + E \begin{bmatrix} 0.127 \\ 0.141 \\ 0.029 \\ -0.126 \\ 0.973 \\ 0 \end{bmatrix} e^{-0.0207t} +$$

$$F \begin{bmatrix} 0.019 \\ 0.022 \\ 0.082 \\ 0.006 \\ -0.002 \\ 0.996 \end{bmatrix} e^{-0.3780t}$$





In above figures we illustrate the dynamics of system taking into account the values of parameters given in Table 1. Figure 1(a) represents the behavior of all parameters when immune response of a patient is not working and Figure 1(b) represents the behavior of all parameters when immune response of a patient is working. It is clear through figure 1(b) that concentration of cancers cell is less in 6 hrs analysis.

Conclusion:

Currently the hardest challenges in modeling tumor growth and treatment are estimating parameters in models that are mathematically simple and are applicable. Our approach in this work to develop the simplest model that can show the effect of immune response to solid tumor at the stage of angiogenesis. We observed that behavior of solid tumor at the stage of angiogenesis with immune response. Further

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considerations, such as the role of blood and mathematical models, will also from the focus of future studies.

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Appendix:

Tabular representation of all parameters when immune response of patient is not working.

Without immune Response						
t	C	E	T	P	A	I
0	9	10	0.7992	0.07	0.71	1.152
0.0044	8.9997	9.9997	0.7991	0.0665	0.71	1.1501
0.0087	8.9994	9.9993	0.7991	0.063	0.71	1.1482
0.0131	8.9991	9.999	0.799	0.0595	0.71	1.1463
0.0174	8.9987	9.9986	0.7989	0.0559	0.71	1.1444
0.0392	8.9972	9.9969	0.7986	0.0384	0.71	1.135
0.061	8.9956	9.9951	0.7982	0.0209	0.7099	1.1257
0.0828	8.994	9.9934	0.7978	0.0035	0.7099	1.1165
0.1046	8.9925	9.9916	0.7975	-0.0139	0.7097	1.1073
0.2136	8.9847	9.983	0.7957	-0.1002	0.7085	1.0626
0.3226	8.9769	9.9743	0.7939	-0.1853	0.7064	1.0198
0.4316	8.9691	9.9657	0.7921	-0.2694	0.7033	0.9786
0.5406	8.9613	9.957	0.7903	-0.3524	0.6993	0.9391
0.7906	8.9436	9.9373	0.7862	-0.5389	0.6868	0.8544
1.0406	8.926	9.9177	0.7822	-0.7199	0.6698	0.7774
1.2906	8.9084	9.8982	0.7781	-0.8955	0.6483	0.7073
1.5406	8.8909	9.8788	0.7741	-1.0661	0.6226	0.6435
1.7906	8.8736	9.8595	0.7701	-1.2316	0.5927	0.5855
2.0406	8.8563	9.8403	0.7661	-1.3923	0.5587	0.5327
2.2906	8.8391	9.8212	0.7622	-1.5482	0.5209	0.4846
2.5406	8.822	9.8022	0.7583	-1.6995	0.4794	0.4409

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2.7906	8.805	9.7833	0.7543	-1.8464	0.4342	0.4012
3.0406	8.788	9.7645	0.7504	-1.9889	0.3854	0.365
3.2906	8.7712	9.7458	0.7466	-2.1271	0.3333	0.3321
3.5406	8.7544	9.7272	0.7427	-2.2612	0.2778	0.3022
3.7906	8.7378	9.7086	0.7389	-2.3914	0.2192	0.2749
4.0406	8.7212	9.6902	0.7351	-2.5176	0.1575	0.2501
4.2906	8.7047	9.6719	0.7313	-2.6401	0.0927	0.2276
4.5406	8.6883	9.6537	0.7275	-2.7588	0.0251	0.207
4.7906	8.672	9.6355	0.7238	-2.874	-0.0453	0.1884
5.0406	8.6557	9.6175	0.72	-2.9857	-0.1184	0.1714
5.2906	8.6396	9.5995	0.7163	-3.0941	-0.1941	0.1559
5.5406	8.6235	9.5816	0.7126	-3.1991	-0.2723	0.1419
5.7906	8.6075	9.5639	0.7089	-3.3009	-0.353	0.1291

Tabular representation of all parameters when immune response of patient is working.

With immune system						
t	C	E	T	P	A	I
0	9	10	0.7992	0.07	0.71	1.152
0.0044	8.9997	9.9997	0.7977	0.0665	0.71	1.1501
0.0087	8.9994	9.9993	0.7961	0.063	0.71	1.1482
0.0131	8.9991	9.999	0.7946	0.0595	0.71	1.1463
0.0174	8.9988	9.9986	0.793	0.0559	0.71	1.1444
0.0392	8.9972	9.9969	0.7854	0.0384	0.71	1.135
0.061	8.9957	9.9952	0.7778	0.0209	0.7099	1.1257
0.0828	8.9942	9.9935	0.7703	0.0035	0.7099	1.1165
0.1046	8.9926	9.9918	0.7629	-0.0139	0.7097	1.1073
0.2136	8.9853	9.9837	0.7266	-0.1002	0.7085	1.0626
0.3226	8.9784	9.976	0.6917	-0.1854	0.7064	1.0198
0.4316	8.9718	9.9686	0.6583	-0.2695	0.7033	0.9786
0.5406	8.9655	9.9616	0.6262	-0.3525	0.6993	0.9391
0.7906	8.9522	9.9469	0.5575	-0.5391	0.6868	0.8544
1.0406	8.9403	9.9337	0.4951	-0.7203	0.6698	0.7774
1.2906	8.9298	9.922	0.4383	-0.8964	0.6483	0.7073
1.5406	8.9206	9.9117	0.3868	-1.0674	0.6225	0.6435
1.7906	8.9124	9.9027	0.3399	-1.2337	0.5926	0.5855
2.0406	8.9052	9.8947	0.2974	-1.3952	0.5586	0.5327
2.2906	8.899	9.8878	0.2587	-1.5523	0.5207	0.4846
2.5406	8.8936	9.8817	0.2236	-1.7049	0.479	0.4409

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2.7906	8.8889	9.8766	0.1917	-1.8533	0.4336	0.4012
3.0406	8.8849	9.8721	0.1627	-1.9976	0.3847	0.365
3.2906	8.8816	9.8684	0.1364	-2.1379	0.3323	0.3321
3.5406	8.8788	9.8653	0.1126	-2.2743	0.2766	0.3022
3.7906	8.8765	9.8628	0.0909	-2.407	0.2176	0.2749
4.0406	8.8747	9.8607	0.0713	-2.536	0.1554	0.2501
4.2906	8.8733	9.8592	0.0535	-2.6615	0.0902	0.2276
4.5406	8.8722	9.858	0.0374	-2.7835	0.022	0.207
4.7906	8.8716	9.8573	0.0227	-2.9022	-0.049	0.1884
5.0406	8.8712	9.8569	0.0095	-3.0177	-0.1229	0.1714
5.2906	8.8711	9.8568	-0.0025	-3.1301	-0.1994	0.1559
5.5406	8.8713	9.857	-0.0134	-3.2394	-0.2786	0.1419
5.7906	8.8717	9.8575	-0.0232	-3.3457	-0.3603	0.1291