SENSITIVITY ANALYSIS FOR A MATHEMATICAL MODEL OF TUMOR-IMMUNE INTERACTIONS

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A mathematical model, in the form of a system of nonlinear ordinary differential equations, has been utilized to investigate the interaction between immune cells and tumor cells. Immune cells included are natural killer cells, circulating lymphocytes, $CD8^+$ T cells, $CD4^+$ T cells and cytokines. The dual role of the $CD4^+$ T cells in activating $CD8^+$ T cells and in killing the tumor via secretion of cytokines is represented in the model. Sensitivity analysis is performed, for two sets of human data, to identify the most effective body parameters in eliminating tumor cell population. Both numerical sensitivity coefficient method and sensitivity function method are implemented, and the results are compared. While the first method identifies the most effective parameters at a specific instant of time, like many published works, the second method recognizes these parameters over a wide time interval. The required order of the most effective parameters is identified, so this sensitivity analysis answers the question: Which parameter can be changed to get the largest effect on the tumor size? The obtained results provide a valuable tool to identify the parameters that would be increased or decreased prior to starting a treatment.

Keywords: Mathematical Modeling, System of Nonlinear Ordinary Differential Equations, Sensitivity Analysis, Tumor-Immune Interactions.

MSC2010: 92B05, 93A30, 34A34, 90C31.

1. Introduction

Mathematical language is always used to describe the world. No wonder, mathematical modeling can be applied to many systems, physical, chemical, biological, or else to explain them, to examine the effect of their different components, and to predict their behavior. Mathematical models for tumors are not exceptional, many tumor models had been implemented. Many of them focus on the tumor growth due to its internal pressure and nutrient concentration [1, 2, 3]. Other mathematical models focus on the interactions between immune system cells and tumor cells to investigate the interaction dynamics to develop the suitable treatment strategy for each case. Most of these models are in the form of systems of ordinary differential equations [4, 5, 6, 7, 8, 9]. Some other models use delayed differential equations [10, 11, 12, 13] or fractional differential equations [14, 15]. Also, some models depend upon the convolutional neural network [16]. However, most of them had considered the role of some immune cells and neglected the role of the others. In our previous work [17, 18], a mathematical model representing the interaction between immune system cells and tumor cells was developed. The role of a wide range of immune cells had been considered.

To guarantee a good response to the treatment and to avoid tumor recurrence after the treatment, system parameters must be adjusted. Hence, sensitivity analysis is performed to

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mathematical models to investigate the effect of changing different parameters on the output of the model [19, 20]. In many research work, sensitivity analysis had been performed by changing each parameter by a certain small value at a specific instant to obtain a numerical sensitivity coefficient [7, 21, 22, 23, 24, 25, 26, 27]. This numerical sensitivity coefficient for each parameter is a measure of the sensitivity of the output to that parameter. Hence, the most effective parameters are determined in order. However, it is valid at this instant only and extending its validity to the entire time interval is questionable. Additionally, there is no criterion for specifying the value of the perturbation. A powerful alternative is to use the sensitivity function method [23, 25, 26, 28, 29, 30, 31], which is also called "the direct differential method" [20]. In this method, the sensitivity analysis is performed over a time interval and sensitivity coefficient curves are plotted in this interval. Due to the wide range of the sensitivity function, a normalization is implemented for each sensitivity coefficient to obtain a dimensionless value for it [20, 22, 23, 25, 26, 28, 29]. Keeping in mind that changing system parameters, using cancer vaccines for example, can drive the system from an unstable equilibrium state to a stable equilibrium state [8, 17]. Sensitivity analysis establishes the order of the most effective parameters, so it answers the question: Which parameter is best to change to get the largest effect on the tumor size?

In this paper, a proposed model of tumor-immune interaction is considered. The immune system cells counted of are natural killers, circulating lymphocytes, $CD8^+$T cells, $CD4^+$T cells and cytokines. The traditional role of $CD4^+$T cells in activating $CD8^+$T cells is reflected as well as its role in killing the tumor via secretion of cytokines. A sensitivity analysis is performed to the proposed model to identify the most effective parameters on the tumor size. Sensitivity analysis is achieved by calculating the numerical sensitivity coefficients and by the method of normalized sensitivity function. The results of the two methods are compared, discussed, and the conclusions are extracted.

2. Mathematical Model

The following mathematical model is implemented to illustrate the interaction between the tumor and immune cells [17]:

$$\frac{dT}{dt} = aT\left(1 - bT\right) - cNT - DT - \frac{c_1 T}{a_1 + T} I \tag{1}$$

$$\frac{dN}{dt} = eC - fN + \frac{gT^2}{h + T^2} N - pNT \tag{2}$$

$$\frac{dL}{dt} = -mL + \frac{jD^2T^2}{k + D^2T^2} L - qLT + \left(r_1 N + r_2 C\right) T - uNL^2 + \frac{p_i I}{g_i + I} L \tag{3}$$

$$\frac{dY}{dt} = \frac{\beta_1 T}{\alpha_1 + T} I - \mu_1 Y - \delta_2 TY \tag{4}$$

$$\frac{dC}{dt} = \alpha - \beta C \tag{5}$$

$$\frac{dI}{dt} = -\mu_i I + \frac{\beta_2 T}{\alpha_2 + T} Y \tag{6}$$

where, $T(t)$ is the tumor cells population, $N(t)$ is the natural killer cells population, $L(t)$ is the $CD8^+$T cells population, $Y(t)$ is the $CD4^+$T cells population, $C(t)$ is the circulating lymphocytes cell population not including natural killer cells and active $CD8^+$T and $CD4^+$T cells and $I(t)$ is the concentration of the cytokine. D is the fractional kill rate, which is defined as follows:

$$D = d\frac{\left(L/T\right)^l}{s + \left(L/T\right)^l} \tag{7}$$

The definitions and the values of all the parameters included on the model for two patients are included in [17]. Also, a detailed description of each term in the model is included in [17]. Equation (6) shows that $CD4^+T$ cells activates the cytokine which in term activates $CD8^+T$ cells as can be noticed in equation (3) and both cytokine and $CD8^+T$ cells assist in killing tumors as presented in equations (1) and (7).

3. **Sensitivity Analysis**

The numerical sensitivity coefficient is given by:

$$S = \frac{(\Delta y/\Delta\lambda)}{(y/\lambda)} \tag{8}$$

where S is the numerical sensitivity coefficient for the system output y with respect to the parameter λ. The main disadvantage of this method is that it is not accurate in many cases, also, the sensitivity coefficients in this method is calculated at a certain time instant. This time instant not necessarily representing the sensitivity at other time instances.
As an alternative method to calculate the sensitivity coefficients, *the sensitivity function method* is considered. A general form of the system of differential equations is given by:

$$\frac{dy_i(\lambda,t)}{dt} = f_i(y_1, y_2, \ldots, y_n, \lambda, t), \quad y_i(0) = y_{i0}, \quad i = 1, 2, \ldots, n \tag{9}$$

where y_i is the model outputs y_1,y_2,...,y_n. The sensitivity coefficients are the first order derivative of the model outputs with respect to the model parameter λ:

$$S_i = \frac{dy_i}{d\lambda} \tag{10}$$

hence

$$\frac{dS_i}{dt} = \frac{d}{dt}\left(\frac{\partial y_i}{\partial\lambda}\right) \tag{11}$$

consequently

$$\frac{dS_i}{dt} = \frac{\partial}{\partial t}\left(\frac{\partial y_i}{\partial\lambda}\right) + \sum_{r=1}^{n}\frac{\partial}{\partial y_r}\left(\frac{\partial y_i}{\partial t}\right)\frac{\partial y_r}{\partial\lambda}$$

which can be written as

$$\frac{dS_i}{dt} = \frac{\partial}{\partial\lambda}\left(\frac{\partial y_i}{\partial t}\right) + \sum_{r=1}^{n}\frac{\partial}{\partial y_r}\left(\frac{\partial y_i}{\partial t}\right)S_r \tag{12}$$

Since the evaluation is taken at the nominal value of the parameter, then

$$\frac{\partial y_i}{\partial t} = f_i$$

Accordingly, equation (12) can be written as

$$\frac{dS_i}{dt} = \frac{\partial f_i}{\partial\lambda} + \sum_{r=1}^{n}\frac{\partial f_i}{\partial y_r}S_r \tag{13}$$

Equation (13) can be rewritten in the matrix form:

$$\begin{bmatrix} \frac{dS_1}{dt} \\ \frac{dS_2}{dt} \\ \vdots \\ \frac{dS_n}{dt} \end{bmatrix} = \begin{bmatrix} \frac{\partial f_1}{\partial\lambda} \\ \frac{\partial f_2}{\partial\lambda} \\ \vdots \\ \frac{\partial f_n}{\partial\lambda} \end{bmatrix} + \begin{bmatrix} \frac{\partial f_1}{\partial y_1} & \frac{\partial f_1}{\partial y_2} & \cdots & \frac{\partial f_1}{\partial y_n} \\ \frac{\partial f_2}{\partial y_1} & \frac{\partial f_2}{\partial y_2} & \cdots & \frac{\partial f_2}{\partial y_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial y_1} & \frac{\partial f_n}{\partial y_2} & \cdots & \frac{\partial f_n}{\partial y_n} \end{bmatrix} \begin{bmatrix} S_1 \\ S_2 \\ \vdots \\ S_n \end{bmatrix} \tag{14}$$

Equation (14) can be generalized to any number of parameters m as follows:

$$\frac{d\mathbf{S}}{dt} = \mathbf{f}_\lambda + \mathbf{J}\,\mathbf{S} \tag{15}$$

where $\mathbf{S} = \begin{bmatrix} S_{11} & S_{12} & \dots & S_{1m} \\ S_{21} & S_{22} & \dots & S_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ S_{n1} & S_{n2} & \dots & S_{nm} \end{bmatrix}$, $\mathbf{f}_\lambda = \begin{bmatrix} \frac{\partial f_1}{\partial \lambda_1} & \frac{\partial f_1}{\partial \lambda_2} & \dots & \frac{\partial f_1}{\partial \lambda_m} \\ \frac{\partial f_2}{\partial \lambda_1} & \frac{\partial f_2}{\partial \lambda_2} & \dots & \frac{\partial f_2}{\partial \lambda_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial \lambda_1} & \frac{\partial f_n}{\partial \lambda_2} & \dots & \frac{\partial f_n}{\partial \lambda_m} \end{bmatrix}$ and $\mathbf{J} = \begin{bmatrix} \frac{\partial f_1}{\partial y_1} & \frac{\partial f_1}{\partial y_2} & \dots & \frac{\partial f_1}{\partial y_n} \\ \frac{\partial f_2}{\partial y_1} & \frac{\partial f_2}{\partial y_2} & \dots & \frac{\partial f_2}{\partial y_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial y_1} & \frac{\partial f_n}{\partial y_2} & \dots & \frac{\partial f_n}{\partial y_n} \end{bmatrix}$.

Such that:

$$S_{ij} = \frac{\partial y_i}{\partial \lambda_j}, \quad i = 1, 2, \dots, n \quad , j = 1, 2, \dots, m \tag{16}$$

The system of differential equations defined by (15) can be solved using a suitable numerical method with the initial conditions $S_{ij}(0) = 0$. After that, the solution will be normalized to bound the range of the sensitivity functions using the following formula:

$$(S_{ij})_n = \frac{S_{ij}}{y_i/\lambda_j} \tag{17}$$

4. Results and Discussion

The proposed model has 31 parameters, a, a_1, b, c, c_1, d, e, f, g, g_i, h, j, k, l, m, p, p_i, q, r_1, r_2, s, u, α, α_1, α_2, β, β_1, β_2, μ_1, μ_i and δ_2. There are 6 model outputs T, N, L, Y, C and I. Since the tumor cell population T is the main output of the model, the focus of this research work is on the effect of each parameter on T only. Therefore, the initial conditions used for N, L, Y, C and I in all cases are fixed to the following values: $N(0) = 10^3$, $L(0) = 10$, $Y(0) = 10^6$, $C(0) = 6 \times 10^8$, and $I(0) = 0$. Four cases are considered. To calculate the numerical sensitivity coefficients each parameter is increased and decreased by 5% of its nominal value given in [17], and the change in tumor size ΔT is calculated using the system of differential equations (1-6). Equation (8) is used to calculate the numerical sensitivity coefficients which are given in Table 1. The normalized sensitivity functions given in equation (17) are computed and plotted for each case in Figures 1-4. For more clearness, the averages of the normalized sensitivity functions are calculated and presented in Table 2.

In the first case, sensitivity analysis is performed for the data of the first patient included in [17]. The initial conditions used for the tumor cell population is $T(0) = 10^5$. The normalized sensitivity functions are plotted in Figure 1. The obtained sensitivity coefficients, at $t = 7$ days, are shown in Table 1, which shows that the most effective parameters are d, β_2, μ_i and c_1, respectively. This sequence coincides with the sequence obtained from the sensitivity function method shown in Figure 1 at this instant of time. However, as shown in the figure, the order of effective parameters changes with time. So, the sensitivity function method introduces a more general and powerful way to track the sensitivity of the model of each parameter along any time interval. Table 2 shows that the order of the most effective parameters is β_2, μ_i, d and c_1.

In the second case, sensitivity analysis is performed for the data of the first patient included in [17]. Simulation is performed to a larger tumor of initial size $T(0) = 10^7$. The normalized sensitivity functions are plotted in Figure 2. Numerical sensitivity analysis is performed by measuring the change in tumor size ΔT at $t = 20$ days. The sensitivity coefficients are shown in Table 1, which implies that most effective parameters are b, a, l and β_2, respectively. At $t = 20$, the instantaneous values of the normalized sensitivity functions, as shown in Figure 2, shows that the most effective parameters are b, a, l and β_2 also. However, as shown in the figure, the order of the effective parameters is changed with

TABLE 1. **Numerical sensitivity coefficients.**

	First Patient				Second Patient			
	$T(0) = 10^5$		$T(0) = 10^7$		$T(0) = 10^5$		$T(0) = 10^7$	
	Increasing	Decreasing	Increasing	Decreasing	Increasing	Decreasing	Increasing	Decreasing
a	3.03169	2.63292	0.122388	0.185525	-0.185383	-0.214762	0.122234	0.185264
a_1	2.47467	2.30135	9.71 E-7	9.74 E-7	-8.88 E-3	-1.158 E-2	9.71 E-7	9.72 E-7
b	-8.67 E-5	-8.68 E-5	-0.936493	-1.03325	-2.87 E-6	-2.88 E-6	-0.93649	-1.03325
c	-9.13 E-7	-8.80 E-7	-9.44 E-10	3.42 E-10	-2.59 E-6	-2.59 E-6	5.36 E-10	-8.78 E-10
c_1	-2.88022	-3.55867	-1.29 E-4	-1.29 E-4	-1.869 E-2	-2.206 E-2	-1.28 E-4	-1.28 E-4
d	-8.0517	-13.1622	-3.5 E-5	-3.52 E-5	-7.548 E-2	-7.364 E-2	-1.1 E-5	-1.13 E-5
e	2.063 E-4	2.062 E-4	1.01 E-9	-1.81 E-10	-7.26 E-4	-7.25 E-4	1.31 E-8	-8.54 E-10
f	-2.47 E-5	-2.48 E-5	-1.25 E-9	1.57 E-10	3.79 E-4	3.948 E-4	3.43 E-9	-8.95 E-10
g	7.50 E-6	7.48 E-6	-7.00 E-10	-1.37 E-10	-4.61 E-6	-4.61 E-6	2.43 E-10	-2.08 E-9
g_i	2.665 E-3	2.934 E-3	5.86 E-11	1.94 E-9	1.7 E-5	1.89 E-5	5.61 E-10	-1.14 E-9
h	-4.67 E-8	-4.74 E-8	-5.11 E-10	-3.44 E-10	4.38 E-6	4.82 E-6	9.31 E-10	-5.18 E-11
j	-1.084 E-2	-1.085 E-2	-1.22 E-8	-1.08 E-8	-7.44 E-8	-7.44 E-8	1.34 E-9	-1.63 E-9
k	1.775 E-3	1.842 E-3	6.37 E-9	6.76 E-9	7.09 E-8	7.84 E-8	2.65 E-10	-4.91 E-10
l	1.42606	1.44702	3.423 E-4	6.761 E-4	0.166259	0.20166	1.07 E-4	2.07 E-4
m	0.131979	0.130768	2.38 E-7	2.40 E-7	0.116547	0.138489	1.51 E-6	1.53 E-6
p	-1.551 E-4	-1.597 E-4	1.13 E-8	1.11 E-9	2.96 E-5	2.96 E-5	1.99 E-8	6.50 E-10
p_i	-2.899 E-3	-2.9 E-3	-1.57 E-9	-1.45 E-9	-1.82 E-5	-1.82 E-5	2.18 E-9	-1.58 E-9
q	6.586 E-2	6.57 E-2	6.75 E-5	7.87 E-5	3.13 E-5	3.13 E-5	1.77 E-5	2.01 E-5
r_1	-1.111 E-3	-1.111 E-3	-6.21 E-11	5.03 E-11	-7.66 E-4	-7.66 E-4	2.67 E-9	-5.79 E-10
r_2	-0.825142	-0.901681	-7.57 E-5	-7.17 E-5	-0.128672	-0.119826	-2 E-5	-2 E-5
s	0.407421	0.420416	3.36 E-5	3.71 E-5	6.522 E-2	7.334 E-2	1.07 E-5	1.19 E-5
u	1.184 E-3	1.184 E-3	4.41 E-10	1.62 E-9	4.55 E-5	4.55 E-5	-4.25 E-10	-1.46 E-9
α	-0.420455	-0.443736	-6.12 E-5	-5.84 E-5	-0.129504	-0.120775	-1.68 E-5	-1.63 E-5
α_1	6.806 E-2	6.913 E-2	9.40 E-10	3.78 E-9	0.562034	0.56566	3.95 E-9	2.65 E-9
α_2	0.621521	0.630966	1.13 E-8	1.30 E-8	0.42598	0.42864	1.54 E-8	1.15 E-8
β	6.995 E-3	6.992 E-3	3.96 E-6	4.01 E-6	2.908 E-2	2.973 E-2	9.54 E-7	9.61 E-7
β_1	-2.02993	-2.31315	-3.21 E-5	-3.15 E-5	-0.951725	-1.08276	-3.2 E-5	-3.14 E-5
β_2	-4.57593	-6.36571	-1.62 E-4	-1.58 E-4	-0.968519	-1.10739	-1.62 E-4	-1.58 E-4
μ_1	0.59066	0.571686	7.57 E-6	7.61 E-6	1.00448	1.0696	7.55 E-6	7.58 E-6
μ_i	5.82898	4.66424	1.449 E-4	1.632 E-4	1.0467	1.0126	1.44 E-4	1.62 E-4
δ_2	4.023 E-2	4.013 E-2	9.31 E-5	1.008 E-4	7.85 E-4	7.84 E-4	9.2 E-5	1 E-4

TABLE 2. **Averages of the normalized sensitivity functions.**

	First Patient		Second Patient	
	$T(0) = 10^5$	$T(0) = 10^7$	$T(0) = 10^5$	$T(0) = 10^7$
a	1.74721	1.39152	0.590797	1.39023
a_1	2.00595	2.80785 E-5	0.394974	2.80293 E-5
b	-9.96375 E-5	-0.463767	1.66451 E-6	-0.463827
c	-3.38749 E-7	-1.84701 E-9	-2.23775 E-6	-1.57075 E-9
c_1	-2.88325	-3.68397 E-3	-0.363492	-3.67771 E-3
d	-3.66016	-4.85825 E-4	-6.02073 E-2	-1.14819 E-4
e	1.86791 E-4	-1.81157 E-9	-3.83569 E-4	-1.22424 E-9
f	-2.21857 E-5	1.10318 E-11	1.3788 E-4	3.81143 E-12
g	6.69324 E-6	-3.34704 E-12	-1.06694 E-6	-1.15638 E-12
g_i	2.71134 E-3	3.12353 E-8	1.21932 E-5	3.83704 E-9
h	-3.63254 E-8	6.28229 E-19	8.75083 E-7	2.06901 E-19
j	-1.04187 E-2	-2.74481 E-7	-1.22417 E-8	-2.6459 E-9
k	1.79434 E-3	1.44397 E-7	1.22409 E-8	2.52704 E-9
l	1.49524	5.80725 E-3	0.250135	1.31761 E-3
m	0.128329	5.94124 E-6	0.105051	3.56425 E-5
p	-1.40033 E-4	9.87548 E-9	9.90897 E-6	3.97582 E-9
p_i	-2.81429 E-3	-3.16934 E-8	-1.2286 E-5	-3.89307 E-9
q	6.51789 E-2	9.87913 E-4	1.20859 E-5	1.69363 E-4
r_1	-1.12093 E-3	-1.10473 E-8	-3.93083 E-4	-2.48185 E-9
r_2	-0.862093	-1.01527 E-3	-0.105423	-2.07815 E-4
s	0.413894	4.85783 E-4	5.84669 E-2	1.14817 E-4
u	1.13489 E-3	3.68151 E-9	9.49411 E-6	2.31177 E-10
α	-0.428153	-6.96811 E-4	-0.101776	-1.29773 E-4
α_1	4.32472 E-2	6.81436 E-8	0.319447	6.80195 E-8
α_2	0.357265	3.65075 E-7	0.657277	3.64432 E-7
β	6.89561 E-3	1.93237 E-5	1.24961 E-2	3.09539 E-6
β_1	-1.68621	-8.62082 E-4	-1.08484	-8.60548 E-4
β_2	-4.57218	-4.54608 E-3	-1.44835	-4.53826 E-3
μ_1	0.442406	2.07158 E-4	1.19002	2.0679 E-4
μ_i	4.35748	4.29802 E-3	1.43112	4.29064 E-3
δ_2	3.3188 E-2	2.61786 E-3	8.34325 E-3	2.61335 E-3

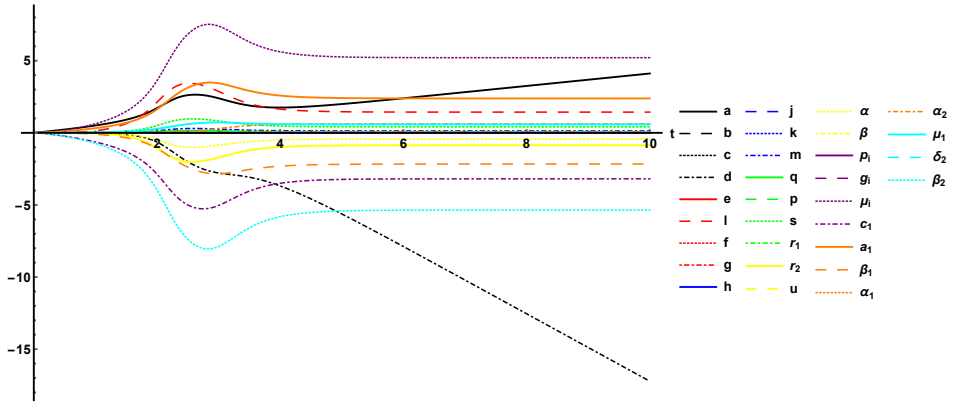


FIGURE 1. Normalized sensitivity functions for first patient's data with $T(0) = 10^5$.

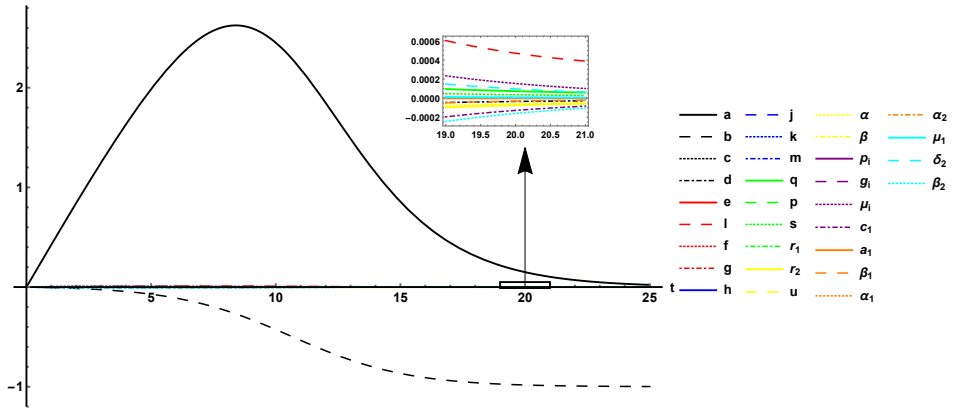


FIGURE 2. Normalized sensitivity functions for first patient's data with $T(0) = 10^7$.

time and parameter a is the most effective parameter most of the time in the considered time interval. This fact is reflected in Table 2 which specifies the order of the most effective parameters to be a, b, l and β_2.

In the third case, sensitivity analysis is performed for the data of the second patient included in [17]. The initial conditions used for the tumor cell population is $T(0) = 10^5$. Numerical sensitivity analysis is performed by measuring the change in tumor size ΔT at $t = 40$ days, and the obtained sensitivity coefficients are shown in Table 1. The most effective parameters are μ_1, β_2, μ_i and β_1, respectively. This sequence coincides with the sequence obtained from the sensitivity function method shown in Figure 3 at this instant of time. Because of the variation of the order of most effective parameters with time as shown in Figure 3, Table 2 specifies the order as β_2, μ_i, μ_1 and β_1.

In the fourth case, sensitivity analysis is performed for the data of the second patient included in [17]. Simulation is performed to a larger tumor of initial size $T(0) = 10^7$. Numerical sensitivity analysis is performed by measuring the change in tumor size ΔT at $t = 20$ days. Sensitivity coefficients are shown in Table 1. The most effective parameters are b, a, β_2 and l, respectively. Same sequence is obtained from the sensitivity function method shown in Figure 4 at this instant of time. However, the order of the effective parameters is changed with time as shown in Figure 4 and parameter a is the most effective parameter

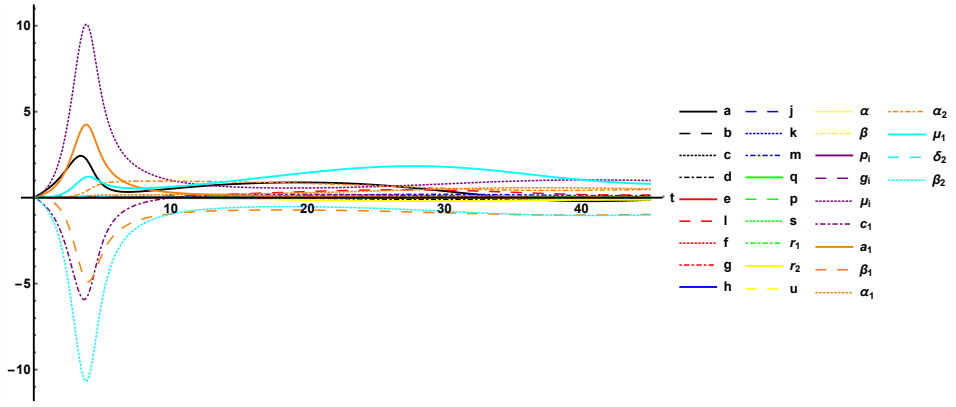


FIGURE 3. Normalized sensitivity functions for second patient's data with $T(0) = 10^5$.

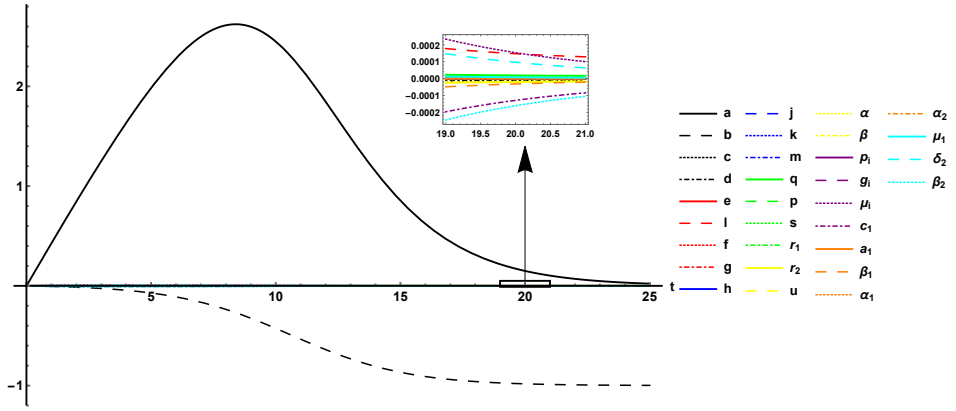


FIGURE 4. Normalized sensitivity functions for second patient's data with $T(0) = 10^7$.

most of the time in the considered time interval. Therefore, Table 2 shows that the order of the most effective parameters is a, b, β_2 and μ_i.

The results obtained in this section prove that the most effective parameters change with the change of the initial tumor size and with the change of the patient's data. The two sensitivity methods used give the same results at any specific instant of time, however, if a wide interval of time is considered, their results do not coincide.

5. **Representative Cases**

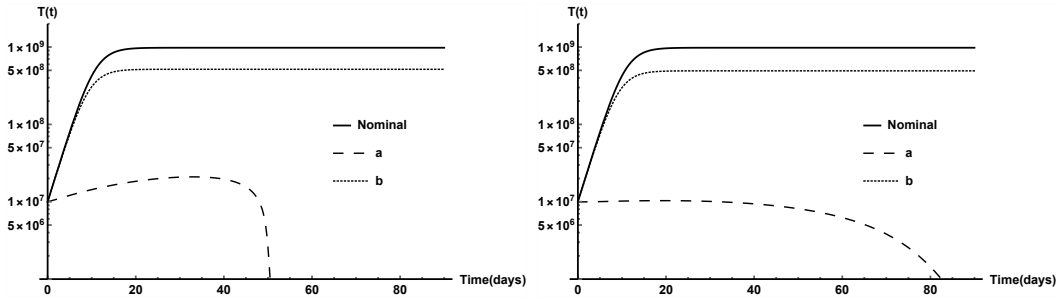
In section 4, it can be noticed that the order for the most effective parameters obtained by the numerical sensitivity coefficient method does not coincide with the order obtained by the sensitivity function method. In this section we would like to specify the more reliable method. Therefore, the second and the fourth cases in section 4 are revisited.

First, the simulation is performed for the second case three times. In the first run, the values of all parameters are the nominal values. In the second run, the values of all parameters are the nominal values except the value of a which decreases by 90% of its nominal value. In the third run, the values of all parameters are the nominal values except the value of b which increases by 90% of its nominal value. Results shown in Figure 5a

illustrate that changing a are much more effective that changing b. This outcome agrees with the prediction of the sensitivity function method.

Second, the simulation is performed for the fourth case three times. In the first run, the values of all parameters are the nominal values. In the second run, the values of all parameters are the nominal values except the value of a which decreases by 99% of its nominal value. In the third run, the values of all parameters are the nominal values except the value of b which increases by 99% of its nominal value. Results shown in Figure 5b illustrate that changing a are much more effective that changing b. This outcome agrees with the prediction of the sensitivity function method.

Hence, it can be concluded that the sensitivity function method is more reliable than the numerical sensitivity coefficient method. Results of the last method could be incorrect in some cases.



(A) (B)

FIGURE 5. Verification of Results: (A) Results of first patient's data for 3 cases: with nominal values of all parameters, decreasing a by 90% and increasing b by 90%. (B) Results of second patient's data for 3 cases: with nominal values of all parameters, decreasing a by 99% and increasing b by 99%.

6. **Conclusions**

In this paper, sensitivity analysis has been performed for a mathematical model representing the tumor-immune interactions to identify the most effective parameters on tumor size. Sensitivity coefficient curves for all parameters are plotted over a time interval and a normalized coefficient has been computed for each parameter to specify the order of the most effective parameters. Results have proved that both the list and the order of the most effective parameters change with the change of initial tumor size and patient's data. If this analysis would be performed prior to the treatment, these parameters can be specified and adjusted, using cancer vaccines for example, to get the largest effect on the tumor size from the subsequent treatment.

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