Analysis of Tumor-Immune Response Model by Differential Transformation Method

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Abstract

In this research work, a four-dimensional tumor-immune response model is considered. The considered tumor model is a system of four differential equations consisting of four different cell populations (variables): the tumor cells (TCs), effector cells (ECs), helper tumor cells (HTCs), and Tregs. The interaction among these cell populations is represented by the system of ordinary differential equations (ODEs). The solution of the system is obtained by using the differential transformation method (DTM). DTM is a straightforward method and gives the series solution of the system. Numerical simulation and graphical analysis are also done by choosing four different initial conditions of the system. The solution series of a system for four different cases are obtained and finally compared with each other. The analysis shows that the model behavior is Chaotically dependent on initial conditions.

1. Introduction

Mathematical modeling is one of the most important and accurate tools to understand the complex and heterogenic behavior of real-life problems related to biology. Mathematical modeling is a tool to represent real-life problems into mathematical symbols. These mathematical symbols are used to understand the dynamic behavior of systems with the help of different mathematical methods. Tumor-immune response system is also among these complex biological systems with rich dynamics. So, to understand the dynamic behavior of the tumor-immune response system deeply, we use mathematical modeling. From last two decades, mathematicians and researchers have been continuously working in this field. Researchers have developed new methods and new mathematical models [1-6]. Some important work in this field is mentioned with references as follows [7-13]. In order to describe the mechanisms of the host's immune response against tumor cells (TCs), various types of mathematical models have been proposed [14-19]. The modeling

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of the tumor-immune system described by ordinary differential equations (ODEs) has a long history, which can be traced back to the classic research of Stepanova in 1980 [14]. In 1994, Kuznetsov *et al.* established the famous two-dimensional ODEs model, postulating that tumor growth follows the Logistic growth pattern. They evaluated the parameters of the model by fitting experimental data from mice [17]. In 2003, Stolongo-Costa *et al.* assumed that TCs follows the exponential growth pattern and constructed a two-dimensional ODEs model [15]. In 2004, Galach simplified Kuznetsov's system to account for the effect of immune delay on the tumor-immune system [9]. In 2014, Dong *et al.* constructed a three-dimensional ODEs model focusing on the effects of helper tumor cells (HTCs) on the tumor immune system [20]. In 1998, Kirschner and Panetta generalized Kuznetsov–Taylor model and illustrated the dynamics between TCs, ECs, and IL-2 [21]. In 2006, De Pillis *et al.* constructed the six-dimensional ODEs model to investigate the effects of combined chemotherapy and immunotherapy on tumor control. They briefly analyzed the nature of the model and discussed the optimal treatment using optimal control theory [8]. In 2012, Wilson and Levy established a mathematical model containing Tregs. They studied the absence of treatment, vaccine treatment, anti-TGF treatment, and combination vaccine and anti-TGF treatment, as well as sensitivity analysis of some important parameters [22]. Some important models on tumor growth dynamics and interaction of tumor cells with the immune system can be found [23-26]. Also, in 2018, Radunskaya *et al.* established a mathematical model with blood, spleen, and tumor compartments to study PD-L1 inhibitors in the role of tumor immunotherapy. The model was used to fit parameters with the experimental data. The results showed that increasing the resistance of PD-L1 doses can greatly improve the clearance rate of tumor [1]. On the other hand, the differential transformation method (DTM) is being widely used by researchers for analyzing, obtaining, and comparing the solutions of different mathematical models, especially in the field of bioscience. Mathematicians did some recent research on DTM, and its applications in analyzing and comparing the solutions of tumor-immune interaction models can be seen in [27-29] and references therein.

This research work has considered a four-dimensional tumor model proposed by Yang *et al.* [30]. We applied a new approach called the differential transformation method to analyze the dynamical behavior of solutions of this four-dimensional tumor-immune response model. The tumor-immune response model proposed by Yang *et al.* [30], represented by the system of ODEs can be written as:

$$\frac{dX}{dt} = AX(t)[1 - BX(t)] - CX(t)Y(t)$$
$$\frac{dY}{dt} = DY(t)Z(t) - EY(t)U(t) - FY(t)$$
$$\frac{dZ}{dt} = G + HX(t)Z(t) - IZ(t)$$
$$\frac{dU}{dt} = JY(t) + KZ(t) - LU(t) \tag{1}$$

Where, $X, Y, Z,$ and U are the variables, which represent the populations of tumor cells, effector cells, helper tumor cells, and Tregs, respectively. The parameters with their biological interpretation and numerical values are mentioned in Table 1. The initial values

are always greater than or equal to zero. *i.e.*, $X(0) = X_0 \geq 0$, $Y(0) = Y_0 \geq 0$, $Z(0) = Z_0 \geq 0$ and $U(0) = U_0 \geq 0$.

Table 1. Model parameters with biological meaning and numerical values.

Model parameters	Numerical values	Biological interpretation	Reference
A	1.636	Growth rate of tumor cells	
B	0.002	Maximum Carrying Capacity	
C	1	Loss rate parameter of tumor cells	
D	0.48	Activation rate of effector cells	
E	0.5	Inhibition rate of Treg cells	
F	0.3743	Mortality rate of effector cells	[20]
G	0.38	Birth rate of helper tumor cells	
H	0.12	Stimulation rate of HTCs by TCs	
I	0.055	Average natural lifespan of HTCs	
J	0.15	Activation rate of Tregs by ECs	
K	0.2	Activation rate of Tregs by HTCs	
L	0.25	Per capita decay rate of Tregs	

2. Differential Transformation Method (DTM)

In this section, some important definitions and concepts of differential transformation method are presented with references to articles [31-33].

Definition 2.1: Consider an analytic function $f(t)$, analytic in a domain K. Then $f(t)$ will be continuously differentiated with respect to time t.

$$\frac{d^n f(t)}{dt^n} = \psi(t, n), \text{ for all } t \in K.$$

For $t = t_i$, $\psi(t, n) = \psi(t_i, n)$, where $n \in Z^+$, defined as N-domain.

Therefore, the above equation can be written as

$$F(n) = \psi(t_i, n) = \left[\frac{d^n f(t)}{dt^n}\right]\Bigg|_{t=t_i} \tag{2}$$

Where, $F(n)$ is called as the spectrum of $f(t)$ at $t = t_i$.

Definition 2.2: The analytic function $f(t)$ in Taylor's Series expansion can be written as

$$f(t) = \sum_{n=0}^{\infty} \left[\frac{(t-t_i)^n}{n!}\right] F(n) \tag{3}$$

Eqn. (3) is called the inverse differential transform of $F(n)$. From Eqn. (2) and Eqn. (3), we have

$$f(t) = \sum_{n=0}^{\infty} \left[\frac{(t-t_i)^n}{n!}\right] F(n) = D^{-1} F(n). \tag{4}$$

Where, D denotes the differential transformation of function $f(t)$.

Now, by using the above differential transformation process, a differential equation or the system of differential equations within the domain can be transformed into an algebraic equation or the system of algebraic equations in N-domain and therefore, the function $f(t)$ is obtained by a finite no. of terms of Taylor's series expansion with the addition of remainder $r(t)$. Mathematically, we have

$$f(t) = \sum_{n=0}^{\infty} \left[\frac{(t-t_i)^n}{n!}\right] F(n) + r_{n+1}(t) \qquad (5)$$

Consider $f_1(t)$, $f_2(t)$, as the two analytic uncorrelated functions with time t. Let $F_1(n)$, $F_2(n)$ be the two transformed functions corresponding to the functions $f_1(t)$, $f_2(t)$ respectively. Now, let us present the list of some fundamental operations using the differential transformation method available readily [31-33] and written in Table 2.

Table 2. Fundamental operations of the differential transform method

Given Function	Transformed Function	Given Function	Transformed Function
$f(t) = f_1(t) \pm f_2(t)$	$F(n) = F_1(n) \pm F_2(n)$	$f(t) = (1+t)^k$	$F(n) = \frac{k(k-1)\ldots(k-n+1)}{n!}$
$f(t) = af_1(t)$	$F(n) = aF_1(n)$	$f(t) = \sin(\alpha t + \beta)$	$F(n) = \frac{\alpha^n}{n!}\sin(\frac{\pi n}{2} + \beta)$
$f(t) = \frac{df(t)}{dt}$	$F(n) = (n+1)F(n+1)$	$f(t) = \cos(\alpha t + \beta)$	$F(n) = \frac{\alpha^n}{n!}\cos(\frac{\pi n}{2} + \beta)$
$f(t) = \frac{d^2 f(t)}{dt^2}$	$F(n) = (n+1)(n+2)\,F(n+2)$	$F(n) = D[f(t)]$, $G(n) = D[g(t)]$	$D[af(t) + bg(t)] = aF(n) + bG(n)$
$f(t) = \frac{d^k f(t)}{dt^k}$	$F(n) = (n+1)(n+2)\ldots(n+k)F(n+k)$	$f(t) = x_1(t)x_2(t)$, $x_1(t) = D^{-1}[F(n)]$, $x_2(t) = D^{-1}[G(n)]$	$D[f(t)] = D[x_1(t)x_2(t)] = \sum_{i=0}^{n} G(i)F(n-i)$
$f(t) = f_1(t)f_2(t)$	$F(n) = \sum_{j=0}^{n} f_1(j)f_2(n-j)$	$f(t) = e^{\lambda k}$	$F(n) = \frac{\lambda^n}{n!}$

3. Solution of Tumor-Immune Response Model by DTM

Consider a tumor-immune response model (1), given by

$$\frac{dX}{dt} = AX(t)[1 - BX(t)] - CX(t)Y(t)$$

$$\frac{dY}{dt} = DY(t)Z(t) - EY(t)U(t) - FY(t)$$

$$\frac{dZ}{dt} = G + HX(t)Z(t) - IZ(t)$$

$$\frac{dU}{dt} = JY(t) + KZ(t) - LU(t)$$

Now, by applying the Differential Transformation Method (DTM) on the above system of differential equations, we will obtain the required recurrence relations, given by

$$X(n+1) = \frac{1}{n+1}\left[AX(n) - AB\sum_{i=0}^{n} X(i)X(n-i) - C\sum_{i=0}^{n} X(i)Y(n-i)\right]$$

$$Y(n+1) = \frac{1}{n+1}\left[D\sum_{i=0}^{n} Y(i)Z(n-i) - E\sum_{i=0}^{n} Y(i)U(n-i) - FY(n)\right]$$

$$Z(n+1) = \frac{1}{n+1}\left[G + H\sum_{i=0}^{n} X(i)Z(n-i) - IZ(n)\right]$$

$$U(n+1) = \frac{1}{n+1}\left[JY(n) + KZ(n) - LU(n)\right] \qquad (6)$$

In order to analyze the above solution of our proposed model (1) numerically, we will fix the numerical values of all the parameters involved in the model taken from Table 1. The analysis and comparison of the approximate solutions of model (1) are made by following four different cases.

Case 1: In this case, choose the initial conditions as; $X(0) = 3$, $Y(0) = 3$, $Z(0) = 2$ and $U(0) = 1$. Therefore, the numerical values of $X(n + 1)$, $Y(n + 1)$, $Z(n + 1)$ and $U(n + 1)$ obtained by differential transformation method are presented in Table 3.

Table 3. Numerical values by DTM of model 1 for n = 0, 1, 2, 3, 4, 5, …

| n	$X(n + 1)$	$Y(n + 1)$	$Z(n + 1)$	$U(n + 1)$
0	−4.121	0.757	0.99	0.6
1	1.7155	0.2952	−0.1535	0.0808
2	−0.651	−0.614	0.0851	−0.0022
3	0.6017	0.2875	0.1908	0.0234
4	−0.7708	0.0901	0.0106	0.0151
5	0.4372	0.0485	0.0604	0.0020
⋮	⋮	⋮	⋮	⋮

Therefore, the numerical solution of model (1) using all the numerical values obtained in Table 3 with the help of DTM is given by

$$X(t) = \sum_{n=0}^{\infty} X(n)t^n = 3 - 4.121t + 1.7155t^2 - 0.651t^3 + 0.6017t^4 - 0.7708t^5 + 0.4372t^6 + \cdots$$

$$Y(t) = \sum_{n=0}^{\infty} Y(n)t^n = 3 + 0.757t + 0.2952t^2 - 0.614t^3 + 0.2875t^4 + 0.0901t^5 + 0.0485t^6 + \cdots$$

$$Z(t) = \sum_{n=0}^{\infty} Z(n)t^n = 2 + 0.99t - 0.1535t^2 + 0.0851t^3 + 0.1908t^4 + 0.0106t^5 + 0.0604t^6 + \cdots$$

$$U(t) = \sum_{n=0}^{\infty} U(n)t^n = 1 + 0.6t + 0.0808t^2 - 0.0022t^3 + 0.0234t^4 + 0.0151t^5 + 0.0020t^6 + \cdots \tag{7}$$
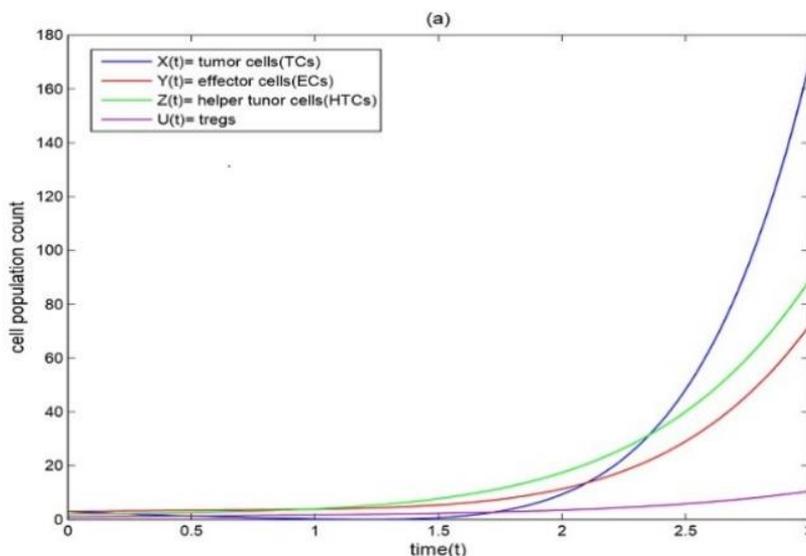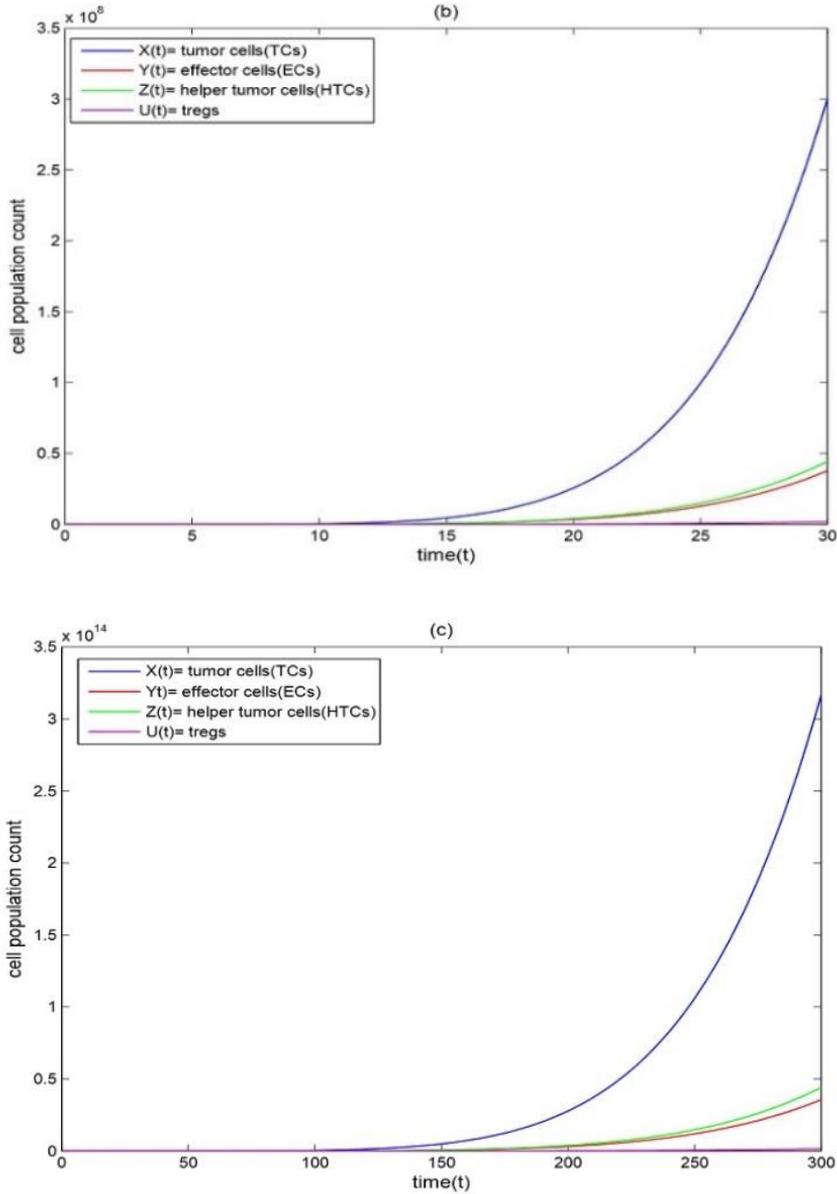
Fig. 1. Graphical analysis of solutions of model 1 for $X(0) = 3$, $Y(0) = 3$, $Z(0) = 2$ and $U(0) = 1$ with three different time intervals $(0, 3), (0, 30)$ and $(0, 300)$ shown respectively in graph (a), (b) and (c).

Case 2: In this case, choose the initial conditions as; $X(0) = 6$, $Y(0) = 5$, $Z(0) = 4$ and $U(0) = 3$. Therefore, the numerical values of $X(n + 1)$, $Y(n + 1)$, $Z(n + 1)$ and $U(n + 1)$ obtained by DTM are presented in Table 4.

Table 4. Numerical values by DTM of model 1 for n = 0, 1, 2, 3, 4, 5, …

n	$X(n+1)$	$Y(n+1)$	$Z(n+1)$	$U(n+1)$
0	−20.1318	0.2285	3.0400	0.800
1	33.8607	2.6532	−3.6716	0.2211
2	−42.6219	−3.0004	2.2618	−0.1305
3	53.4205	1.9999	0.6807	0.0087
4	−68.8462	−1.2362	−1.9006	0.0868
5	83.5559	1.0050	1.9781	−0.00979
⋮	⋮	⋮	⋮	⋮

And the numerical solution of model (1) using all the numerical values obtained in Table 4 with the help of DTM is given by

$$X(t) = \sum_{n=0}^{\infty} X(n)t^n = 6 - 20.1318t + 33.8607t^2 - 42.6219t^3 + 53.4205t^4 - 68.8462t^5 + 83.5559t^6 + \cdots$$

$$Y(t) = \sum_{n=0}^{\infty} Y(n)t^n = 5 + 0.2285\,t + 2.6532t^2 - 3.0004t^3 + 1.9999t^4 - 1.2362t^5 + 1.0050t^6 + \quad \ldots$$

$$Z(t) = \sum_{n=0}^{\infty} Z(n)t^n = 4 + 3.0400t - 3.6716t^2 + 2.2618t^3 + 0.6807t^4 - 1.9006t^5 + 1.9781t^6 + \quad \ldots$$

$$U(t) = \sum_{n=0}^{\infty} U(n)t^n = 3 + 0.80t + 0.2211t^2 - 0.1305t^3 + 0.0087t^4 + 0.0868t^5 - 0.00979t^6 + \quad \ldots \quad (8)$$
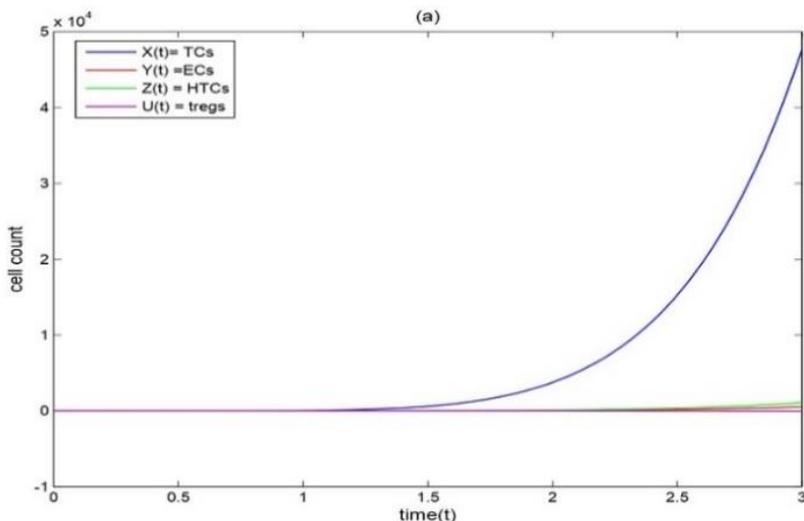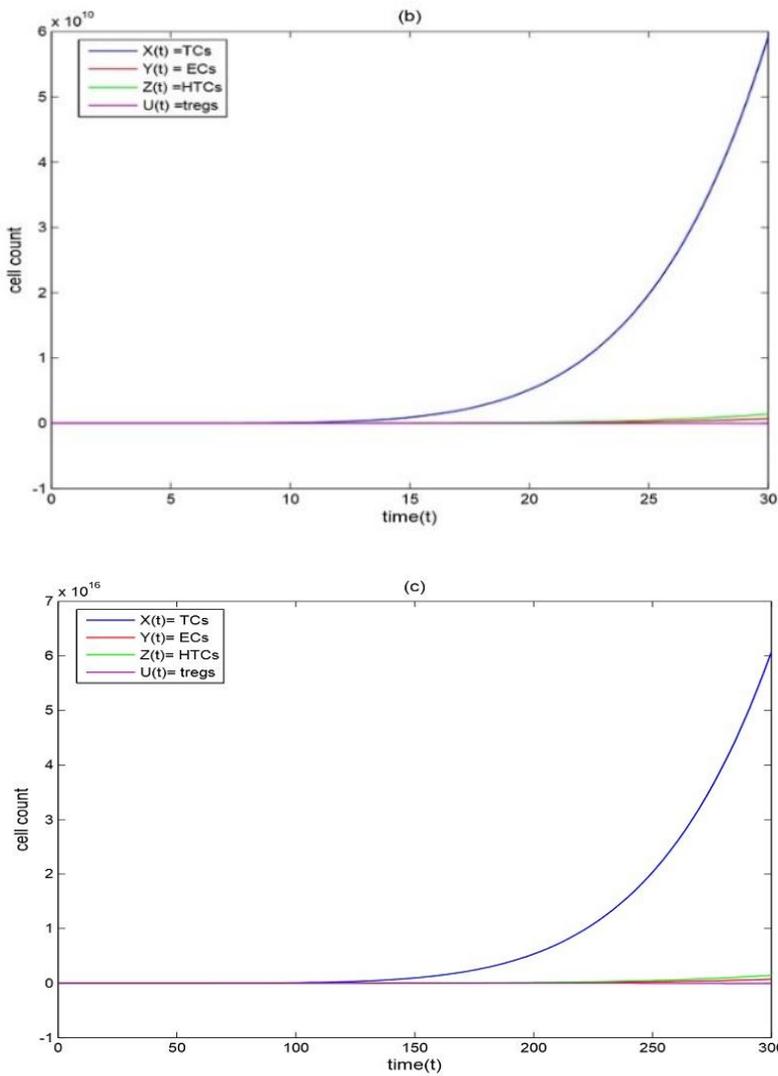
Fig. 2. Graphical analysis of solutions of model 1 for $X(0) = 6, Y(0) = 5, Z(0) = 4$ and $U(0) = 3$ with three different time intervals $(0,3), (0,30)$ and $(0,300)$ shown respectively in graph (a), (b) and (c).

Case 3: In this case, choose the initial conditions as; $X(0) = 60$, $Y(0) = 60$, $Z(0) = 50$ and $U(0) = 40$. Therefore, the numerical values of $X(n+1)$, $Y(n+1)$, $Z(n+1)$ and $U(n+1)$ obtained by DTM are presented in Table 5.

Table 5. Numerical values by DTM of model 1 for n = 0, 1, 2, 3, 4, 5, …

| n	$X(n+1)$	$Y(n+1)$	$Z(n+1)$	$U(n+1)$
0	-3.5136×10^2	2.1754×10^2	3.5763×10^2	9.00
1	9.6697×10^4	5.4092×10^3	-9.363×10^3	50.9536
2	-1.7607×10^6	-7.077×10^4	1.2107×10^5	-3.5132×10^2
3	2.6973×10^7	7.9304×10^6	-4.1094×10^5	3.4214×10^3
4	-4.1844×10^8	-6.4806×10^6	-1.5038×10^7	7.1825×10^3
5	6.6659×10^9	4.4044×10^7	3.4579×10^8	-6.6357×10^5
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$

Similarly, the numerical solution of model (1) using the numerical values written in Table 5 with the help of DTM is given by

$$X(t) = \sum_{n=0}^{\infty} X(n)t^n = 60 - 3.5136 \times 10^2 t + 9.6697 \times 10^4 t^2 - 1.7607 \times 10^6 t^3 + 2.6973 \times 10^7 t^4 - 4.1844 \times 10^8 t^5 + 6.6659 \times 10^9 t^6 + \cdots$$

$$Y(t) = \sum_{n=0}^{\infty} Y(n)t^n = 60 + 2.1754 \times 10^2 t + 5.4092 \times 10^3 t^2 - 7.077 \times 10^4 t^3 + 7.9304 \times 10^6 t^4 - 6.4806 \times 10^6 t^5 + 4.4044 \times 10^7 t^6 + \cdots$$

$$Z(t) = \sum_{n=0}^{\infty} Z(n)t^n = 50 + 3.5763 \times 10^2 t - 9.363 \times 10^3 t^2 + 1.2107 \times 10^5 t^3 - 4.1094 \times 10^5 t^4 - 1.5038 \times 10^7 t^5 + 3.4579 \times 10^8 t^6 + \cdots$$

$$U(t) = \sum_{n=0}^{\infty} U(n)t^n = 40 + 9.00t + 50.9536t^2 - 3.5132 \times 10^2 t^3 + 3.4214 \times 10^3 t^4 + 7.1825 \times 10^3 t^5 - 6.6357 \times 10^5 t^6 + \cdots \tag{9}$$
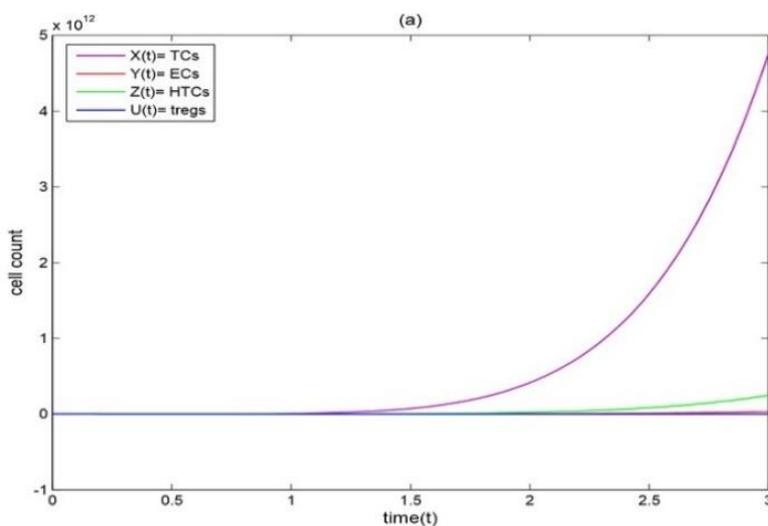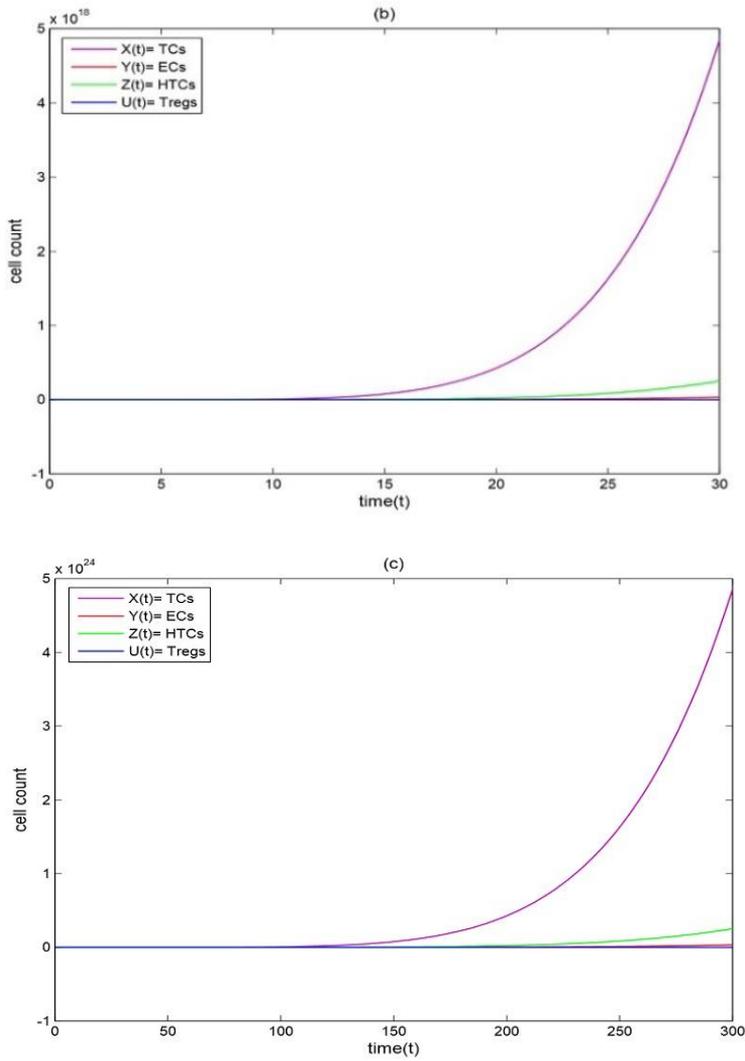
Fig. 3. Graphical analysis of solutions of model 1 for $X(0) = 60, Y(0) = 60, Z(0) = 50$ and $U(0) = 40$ with three different time intervals $(0,3), (0,30)$ and $(0,300)$ shown respectively in graph (a), (b) and (c).

***Case 4:*** In this case, choose the initial conditions as; $X(0) = 0.62$, $Y(0) = 0.60$, $Z(0) = 0.42$ and $U(0) = 0.40$. Therefore, the numerical values of $X(n + 1)$, $Y(n + 1)$, $Z(n + 1)$ and $U(n + 1)$ obtained by DTM are presented in Table 6.

Table 6. Numerical values by DTM of model 1 for n = 0, 1, 2, 3, 4, 5, …

n	$X(n+1)$	$Y(n+1)$	$Z(n+1)$	$U(n+1)$
0	0.6411	−0.2236	0.3881	0.074
1	0.4001	0.0865	0.2099	0.0128
2	0.1668	−0.003	0.1448	0.0173
3	0.0516	0.0074	0.1065	0.006
4	0.0104	0.004	0.0827	0.0042
5	1.9412×10^{-4}	0.0027	0.0673	0.0027
⋮	⋮	⋮	⋮	⋮

Finally, the numerical solution of model (1) using the numerical values written in Table 6 with the help of DTM is given by

$$X(t) = \sum_{n=0}^{\infty} X(n)t^n = 0.62 + 0.6411t + 0.4001t^2 + 0.1668t^3 + 0.0516t^4 + 0.0104t^5 + 1.9412 \times 10^{-4}t^6 + \cdots$$

$$Y(t) = \sum_{n=0}^{\infty} Y(n)t^n = 0.60 - 0.2236\,t + 0.0865t^2 - 0.003t^3 + 0.0074t^4 + 0.004t^5 + 0.0027t^6 + \cdots$$

$$Z(t) = \sum_{n=0}^{\infty} Z(n)t^n = 0.42 + 0.3881t + 0.2099t^2 + 0.1448\,t^3 + 0.1065t^4 + 0.0827t^5 + 0.0673t^6 + \cdots$$

$$U(t) = \sum_{n=0}^{\infty} U(n)t^n = 0.40 + 0.074t + 0.0128t^2 + 0.0173t^3 + 0.006t^4 + 0.0042t^5 + 0.0027t^6 + \cdots \tag{10}$$
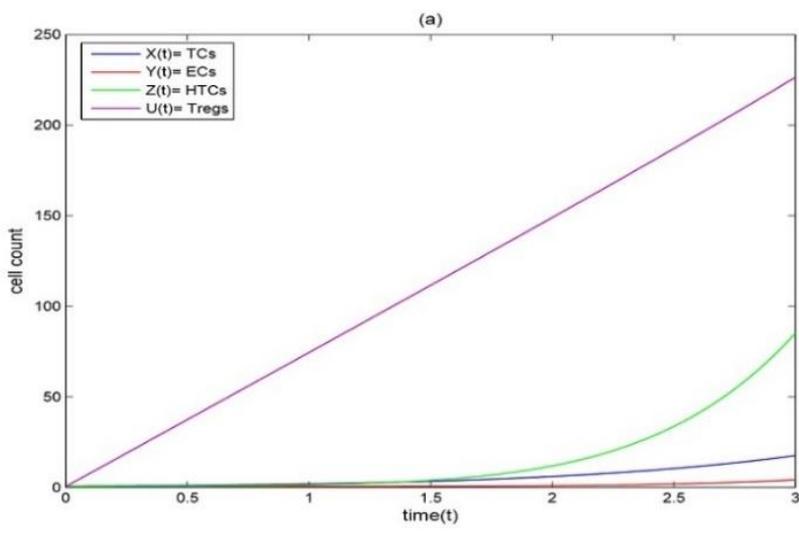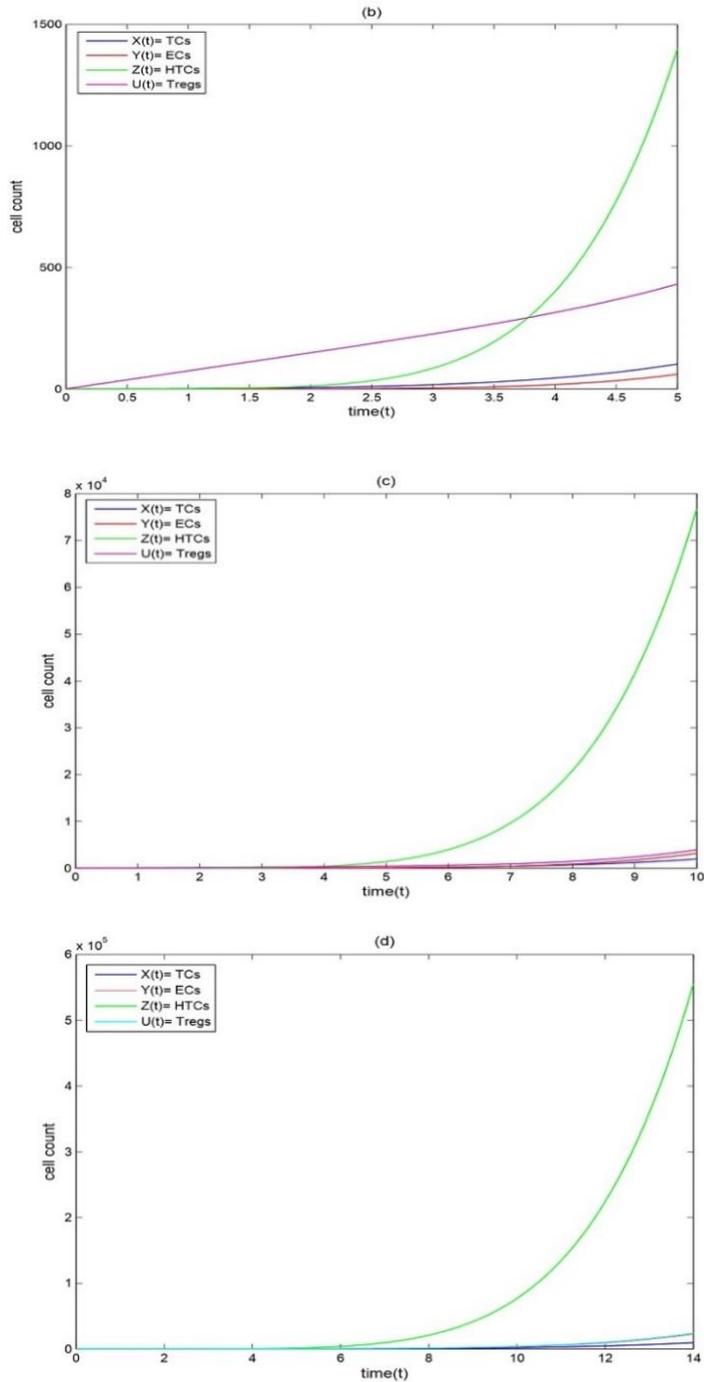
Fig 4. Graphical analysis of solutions of model 1 for $X(0) = 0.62, Y(0) = 0.60, Z(0) = 0.42$ and $U(0) = 0.40$ with three different time intervals $(0,3), (0,5)$ and $(0,10)$ shown respectively in graph (a), (b), (c) and (d).

4. Conclusion

Differential Transformation Method (DTM) is considered one of the most powerful tools for finding the analytical solution of both linear and nonlinear systems of differential equations. In this paper, we applied the same method to analyze the solutions of the tumor-immune response system (1). We have successfully applied DTM to the system of four differential equations. These four differential equations represent the role of regulatory tumor cells in tumor-immune response. We obtained the series solution of model (1) for four different initial conditions. The series solution is obtained and analyzed numerically and graphically by using the suitable values of model parameters. The DTM is better than any other numerical method, as it does not require huge calculations and advanced mathematical software power. DTM is also free from rounding-off error. The series solution, which we have obtained for the considered tumor model (1) by differential transformation method, converges faster than the solutions obtained by any other method.

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