Modeling Tumor Growth

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This paper describes the mathematical model of tumor growth, taking into account treatment with one or multiple injections of siRNA. The model consists of a system of differential equations describing the growth of tumor cells, effector cells, TGF-β, and the effect of siRNA treatment.
Introduction

Much progress has been made in the discovery of new information about tumors and the success in finding treatments to reduce and clear them. There are three main ways that malignant tumors can be treated. These treatments include traditional chemotherapy, radiation therapy and immunotherapy. The main goal of the treatment is to suppress the appropriate immune response to assist the body in combating the tumor, rather than affecting it directly. In order to do this, siRNA will be injected into the body to slow production of TGF-β, a growth factor that aids in the production of tumor cells and masks the tumor from immune detection. Tumors are derived from one or more normal cells that have undergone malignant transformations. The efforts of reducing or clearing tumor cells depends on the strength of the immune responses that impact success or failure of the immune system’s attack on tumor cells. Also, there have been previous investigations of tumor-immunity dynamics. Previous efforts of mathematical models have helped to keep intact our understanding of tumor-immune dynamics.

Methodology

Common practice is to use the cytokines and IL-2 (Interleukin 2) to help the immune system fight the tumor. The cytokines represent the pro and anti-inflammatory molecules that participate in the immune system. They are low weight molecular protein mediators involved in cell growth, inflammation, immunity, differentiation and repair. The IL-2’s are produced by T-helper cells when stimulated by an infection. The main interleukin that is used is the IL-2, because of its activity toward lymphocytes. Previous studies have shown that there is no situation in which a tumor could be cleared by the body unless indefinite treatment with both types of therapy is simultaneously considered. This is because there is a disadvantage to using the IL-2 treatment. The disadvantage is that IL-2 alone clears the tumor but at the expense of over-
stimulating the immune system. Because of this, we look at the possibility of using the cytokines as a form of treatment.

TGF-β, Transforming Growth Factor-beta, is another important factor in tumor growth. Tumors can evade immune surveillance by secreting an immune-suppressive factor such as TGF-β. TGF-β plays a crucial role in normal wound healing, inflammation and growth stimulatory angiogenesis in other words, blood vessel formation. It is present in both healthy and tumor cells. In healthy cells, TGF-β regulates the cell cycle and stops production of new cells at a certain point. In tumor cells, the path of TGF-β is mutated and the cell cycle is no longer regulated so tumor cells keep producing. It also turns effector cells, which fight off mutated cells, into regulatory cells, which do not fight off mutated cells. Therefore TGF-β causes tumor cells to keep producing without being fought off. This process is shown in the flow chart below.

Previous experiments have shown that small tumors produce little or no TGF-β. Most large tumors do secrete TGF-β, and rely heavily on its growth stimulatory effects.
Mathematical Model without siRNA treatment

The basic model that illustrates how tumor cell population changes over time (without the
effects of siRNA which we’ll discuss later) is given as follows:

\[
\begin{align*}
\frac{dE}{dt} &= \frac{cT}{1 + \gamma S} - \mu_1 E + \left( \frac{EI}{g_1 + I} \right) \left( p_1 - \frac{q_1 S}{q_2 + S} \right), \\
\frac{dT}{dt} &= rT \left( 1 - \frac{T}{K} \right) - \frac{aET}{g_2 + T} + \frac{p_2 ST}{g_3 + S}, \\
\frac{dI}{dt} &= \frac{(g_4 + T)(1 + \alpha S)}{p_3 ET} - \mu_2 I, \\
\frac{dS}{dt} &= \frac{p_4 r^2}{\tau^2 + T^2} - \mu_3 S.
\end{align*}
\]

With initial conditions

\[E(0) = E_0, \quad T(0) = T_0, \quad I(0) = I_0, \quad S(0) = S_0.\]

The parameters are each explained in the appendix.

The first equation is the rate of production of effector cells. The first term represents the
attraction of effector cells due to the presence of the tumor cells. The second term is the normal
loss due to cell death. The third term asserts that proliferation of the effector cells is dependent
upon the presence of IL-2 and is decreased when TGF-β is present.

Equation 2 is the rate of production of the tumor cells. The first term represents the
logistic growth of the tumor. The second term represents a reduction in the tumor population due
to immune clearance. The third term represents tumor growth due to the presence of TGF-β.

The third equation represents production of IL-2 production. The first term represents
basic production of IL-2 with each parameter defined in the appendix. The second term
represents normal cell death.

The last equation represents TGF-β. The first term represents the switch that the tumor
cells undergo in which they start producing TGF-β in order to grow. The second term represents
the decay of TGF-β.

Due to the stiffness of this system of differential equations, it is only necessary when running numerical simulations. After dropping the over-bar notation for convenience, the new model is as follows:

\[
\begin{align*}
\frac{dw}{dt} &= \frac{cx}{1 + \gamma z} - \mu_1 w + \left(\frac{wy}{1 + y}\right)\left(p_1 - \frac{q_1 z}{q_2 + z}\right) \\
\frac{dx}{dt} &= rx\left(1 - \frac{x}{K}\right) - \frac{aw x}{1 + x} + \frac{p_2 x z}{1 + z} \\
\frac{dy}{dt} &= \frac{p_3 w x}{(g_4 + x)(1 + \alpha z)} - y \\
\frac{dz}{dt} &= \frac{p_4 x^2}{\tau_c^2 + x^2} - z
\end{align*}
\]

With initial conditions

\[w(0) = w_0 \quad x(0) = x_0 \quad y(0) = y_0 \quad z(0) = z_0\]

Using the aforementioned models, in order to understand the effects of TGF-β production we must first look at the behavior of passive tumors where TGF-β is not present (S(t) = 0). The equations above show that stability of the tumor cell growth rate varies greatly as the antigenicity parameter c (ability for the immune system to detect a tumor) increases past certain thresholds. For \(0 < c < 8.55 \times 10^{-6}\) an asymptotically stable node results where the tumor mass has grown to its carrying capacity undetected by the body’s immune system. For the range \(8.55 \times 10^{-6} < c < 0.0032\) a stable limit cycle results. The tumor mass oscillates from very high to very low values. As c increases, the amplitude and period of these oscillations decrease. Finally for the range \(0.0032 \leq c\), a stable spiral is produced. This indicates that the tumor mass will experience damped oscillations until becoming small and dormant. These results are graphically represented below in Figures 2-4 with additional descriptions.
Now we consider the case of the aggressive tumor where TGF-β is produced \((S(t) \neq 0)\). Tumors producing TGF-β will experience an increase in growth rate as well as a greater ability to avoid detection from the immune system. The behavior of the tumor cells for varying \(c\) is similar to that of the passive tumor, but in the aggressive case the parameter \(p_4\) (the maximum value of TGF-β production) affects tumor growth. For \(0 < c < 8.55e-6\) we once again have an asymptotically stable node representing a large tumor mass that has reached its carrying capacity for all values of \(p_4\) (Figure 2 below).

![Figure 2 – small c, several values of p_4 (Dimensionless Units)](image-url)
For the range $8.55 \times 10^{-6} < c < 0.0032$ and a small value $p_4$, the behavior of the tumor is very similar to the passive case with oscillations between very high and very low values of $T$. When $p_4$ increases, the amplitude of the oscillations increase until eventually uncontrolled tumor growth results. In this case a large tumor mass is produced, a vastly different result from that of the passive tumor. These cases are shown below. Time is relative because the system has been nondimensionalized.

Lastly we consider the final range for $c$. Here we look at $c = 0.0035$, the lowest value for the immune system to control tumor growth initially. We see that for small enough $p_4$ the tumor experiences damped oscillations as time increases until it reaches a dormant state. But
when \( p_4 \) increases to greater than 2.84 the spiral becomes a stable node and a large uncontrolled tumor mass results. Too much TGF-\( \beta \) is being produced for the body to detect on its own.

**Mathematical Model with siRNA treatment**

There is a way to help immune suppression from TGF-\( \beta \) if the body doesn’t have a strong enough immune system (c value). To combat immune suppression by tumor cells, we can consider a novel treatment known as siRNA (small interfering Ribonucleic Acid). Now with the
option of using siRNA treatment, it involves initial delivery of dsRNA, double stranded RNA, into tumor cells.

The numerical results of adding siRNA to our system is modeled below. Individual parameters are listed in the appendix.

\[
\begin{align*}
\frac{dE}{dt} &= \frac{cT}{1 + \gamma S} - \mu_1 E + \left(\frac{EI}{g_1 + I}\right)\left(p_1 - \frac{q_1 S}{q_2 + S}\right) \\
\frac{dT}{dt} &= rT\left(1 - \frac{T}{K}\right) - \frac{aET}{g_2 + T} + \frac{p_2 ST}{g_3 + S} \\
\frac{dl}{dt} &= \frac{p_3 ET}{(g_4 + T)(1 + \alpha S)} - \mu_2 l \\
\frac{dS}{dt} &= \frac{p_4 T^2}{\tau_c^2 + T^2} - \mu_3 S \\
\frac{dA}{dt} &= D_i(t) - \mu_4 A \quad i = 1 \text{ or } 2 \\
D_1(t) &= D_0 = \text{constant} \\
D_2(t) &= D_0 \sum_{i=1}^{n} e^{-\left(t_i - \tau\right)^2/\sigma^2}
\end{align*}
\]

With initial conditions
\[
E(0) = E_0 \quad T(0) = T_0 \quad I(0) = I_0 \quad S(0) = S_0
\]

The first three equations are the same. The fourth equation represents the rate of production of TGF-β. The first term assumes that the production of extracellular TGF-β is inhibited as a result of the siRNA. The second term is normal decay. The last equation is for siRNA being injected into the body. The first term represents the dose of free siRNA as a function of time. It can either be a continuous infusion or one or more injections per day for 11 days. The second term is the decay of the free siRNA.

Just like the previous model, this new model is stiff. Therefore, just as we did before, we must non-dimensionalize the system to get the following (See Appendix A 3 for scaling):
\[
\begin{align*}
\frac{dw}{dt} &= \frac{cx}{1 + \gamma z} - \mu_1 w + \left(\frac{wy}{1 + y} \right) \left( p_1 - \frac{q_1 z}{q_2 + z} \right) \\
\frac{dx}{dt} &= rx \left( 1 - \frac{x}{K} \right) - \frac{axw}{1 + x} + \frac{p_2xz}{1 + z} \\
\frac{dy}{dt} &= \frac{(g_4 + x)(1 + az)}{p_3wx} - y \\
\frac{dz}{dt} &= \frac{p_4x^2}{\tau_c^2 + x^2} - z \\
\frac{dv}{dt} &= D_i(t) - \mu_4 v
\end{align*}
\]

With initial conditions
\[w(0) = w_0 \quad x(0) = x_0 \quad y(0) = y_0 \quad z(0) = z_0\]

Using this new model we will consider the case where \( c = 0.002, p_4 = 0.5, \) and \( \gamma = 10. \)

The first case will be for a continuous infusion of siRNA. Instead of the uncontrolled tumor growth that would result without treatment, we instead see that the tumor mass will experience oscillations with a fairly low amplitude. As the value of \( a \) (strength of the immune response to the tumor) increases from 0.1 to 0.11 and then to 0.12, the amplitude of the oscillations decreases. This shows that administration of a constant dose of siRNA serves to greatly suppress tumor growth. Note that for \( a \geq 0.13 \) the results would be identical to those without siRNA treatment, indicating that the immune system would be capable of controlling the tumor growth unaided. A visual representation is below. Figure 1 is for \( a = 0.1 \) and figure 2 is for \( a = 0.12 \)

![Tumor Cell Density vs. Time (a=0.1)](image-url)
Next we consider $D_2(t)$ where siRNA is administered periodically through one or more rounds of siRNA injected once a day for 11 days. In the figure below we see that a single round of siRNA injections (left column) administered at time $t = 1000$ with $a = 0.1$ (top row) results in an initial small peak followed by a small tumor mass until $t$ reaches a certain point where the siRNA is no longer having any affect.

At this point the tumor once again becomes uncontrolled. As $a$ increases to 0.11 and 0.12
(2nd and 3rd rows) the initial peak becomes smaller but the behavior afterwards remains practically identical. When we increase the dosage of siRNA to two rounds (right column), we get much more favorable results. siRNA is now administered at $t = 1000$ and $t = 5500$. The plot shows that for two rounds of siRNA treatment the point at which tumor growth becomes uncontrolled is delayed greatly. It is clear from these results that proper siRNA treatment will control tumor oscillations through proper periodic injections. Again, this model is dimensionalized so time has no units.

**Our Results**

In order to improve the model we decided to experiment with a number of different possibilities for varying continuous doses of siRNA treatment. Several ideas were tested in MATLAB in order to find a more ideal treatment. Ultimately the most favorable results were produced when we doubled the dosage of siRNA administered continuously for every other 1000 time steps. For $a' = 0.1$ and $a' = 0.11$ the tumor experienced small oscillations but eventually grew to its carrying capacity. For $a' = 0.12$ the tumor growth stabilized, experiencing small oscillations until the end of the time period. These results are shown in the figures below.
**Model Limitations**

Although our results were favorable we see that they were not necessarily an improvement over the previous scenario where two rounds of siRNA were administered periodically. The problem here is that there is practically a limitless number of possibilities for altering the siRNA dosage. Trying to analyze the most favorable scenario is really a matter of trial and error.
A second limitation is that the model is highly dependent on initial conditions. The reference paper did not provide the specific values for these initial conditions, and thus it was very difficult to replicate scenarios where multiple siRNA injections were administered periodically. Experimental data is necessary here in order to realistically alter the model.

**Conclusion**

Many models of tumor growth have been presented in the past, but in our reference paper the authors create a new model with the addition of TGF-β. This addition resulted in uncontrolled tumor growth in cases where the tumor would have otherwise experienced damped oscillations. The authors then went on to include the addition of siRNA treatment in the model in order to suppress TGF-β production. With a continuous injection of siRNA the tumor experienced small oscillations and never resulted in uncontrolled growth. The authors then considered periodic injections of siRNA. In these cases the tumor remained small and dormant until the treatment wore off. When two rounds of periodic injections were considered, the tumor remained dormant for a much longer time period, and with a high enough immune response experienced only small oscillations without becoming uncontrolled, similar to the continuous case. When we doubled the continuous dosage and administered alternating continuous doses, the results were comparable to the two-round scenario. Whichever treatment would be preferable depends on which is more realistic. Experimental data would be necessary to determine which method has the least detrimental effects on the body.

In the end, the case with the most ideal results is having either continuous infusions of siRNA or 2 doses per day as long as you have a strong immune system. Increased values of c and a (the body’s ability to detect and stand against the tumor) can keep the tumor cells regulated but with those alone, the tumor almost always results in an uncontrollable tumor mass.
Acknowledgements

This information was obtained from the article, "A Mathematical Model of Tumor-Immune Evasion and SiRNA Treatment" written by J.C. Arciero, T.L. Jackson, and D.E. Kirschner.

APPENDIX A

Parameters for the model of tumor growth without siRNA treatment are as follows:

E: Effector cells;  T: Tumor cells;  I: IL-2;  S: TGF-β

c: Antigenicity of tumor
γ: Inhability parameter
p1: Maximum rate of effector cell proliferation in the absence of TGF-β
g1, q2, g3, g4: Half-Saturation constants
q1: Maximum rate of anti-proliferative effect of TGF-β
µ1, µ2, µ3: Decay constants
r: Intrinsic growth rate constant
K: Carrying capacity
a: Strength of immune response to tumor cells
p2: Maximum rate of increased proliferation
p3: Maximal rate constant in accordance with IL-2 production
α: Measure of inhibition caused by TGF-β
p4: Maximum rate of TGF-β production
τc: Critical tumor cell at which TGF-β production switch occurs

New parameters for the tumor growth model with siRNA treatment:

A: Total free and bound strands of SiRNA
f: Proportion of A that is bound
ki: Inhibitor constant
µ4: Decay constant

D1: Continuous infusion dose
D2: Multiple injection dose of SiRNA
ti : Specific time of injection
n: Number of injections
ε: 10
Non-dimensional scaling:

\[ w = \frac{E}{g_2}, \quad x = \frac{T}{g_2}, \quad y = \frac{I}{g_1}, \quad z = \frac{S}{g_3}, \quad \bar{t} = \frac{\mu_2 t}{}, \]
\[ \bar{\mu}_i = \frac{\mu_i}{\mu_2}, \quad \bar{c} = \frac{c}{\mu_2}, \quad \bar{\gamma} = \frac{\gamma g_3}{}, \quad \bar{p}_1 = \frac{p_1}{\mu_2}, \quad \bar{p}_2 = \frac{p_2}{\mu_2}, \]
\[ \bar{p}_3 = \frac{p_3 g_2}{\mu_2 g_1}, \quad \bar{q}_1 = \frac{q_1}{\mu_2}, \quad \bar{q}_2 = \frac{q_2}{g_3}, \quad \bar{r} = \frac{r}{\mu_2}, \quad \bar{K} = \frac{K}{g_2}, \]
\[ \bar{\alpha} = \frac{\alpha}{\mu_2}, \quad \bar{g}_4 = \frac{g_4}{g_2}, \quad \bar{\alpha} = \frac{\alpha g_3}{}, \quad \bar{p}_4 = \frac{p_4}{\mu_2 g_3}, \quad \bar{\tau}_c = \frac{\tau_c}{g_2}. \]

(3) Non-dimensional scaling

\[ \bar{k}_i = \frac{k_i}{fA_0}, \quad A_0 = \frac{k_i}{f}, \quad \bar{D} = \frac{Df}{\mu_2 k_i}, \quad \bar{\mu}_4 = \frac{\mu_4(1 - f)}{\mu_2}. \]