Abstract

Using Eric Werner’s theory of linear cancer networks and the work of Shelby Wilson and Doron Levy, we develop a mathematical model to study the growth and responsiveness of passive and aggressive tumors to various immunotherapy treatments. In our aggressive tumor case, we show that remission is only achieved after combination treatment with TGF-β inhibitors and a peptide vaccine. Our model predicts that because stem cell population is not completely eliminated, the cancer reoccurs by day 300. Additionally, we show that combination treatment has limited effectiveness on low antigenicity aggressive tumors and that vaccine treatment is not effective for either low or high antigenicity passive tumors.

1 Introduction

Cancer is a leading cause of death in the world today. Although an enormous amount of resources have been spent in search of a cure, much is still unknown about the dynamics of how cancer cells are created and destroyed (Kirschner & Panetta, 1998; Werner, 2011).

The general consensus is that cancer is caused by mutated cells, which are unable to die and thus grow uncontrollably and that cancer requires many mutations to transform normal cells into cancer cells (Werner, 2011). Eric Werner attempts to present a unified theory of cancer based on developmental control networks (Werner, 2011). A developmental control network is a system of instructions that changes the state of a cell and its offspring (Werner, 2011). These instructions contain information that when interpreted by the cell, results in the development of a multicellular organism. Werner argues that the general theories of cancer do not explain how cancer is controlled, or how cancer cells develop and differentiate. Werner proposes that pathological developmental control networks cause cancer and in order to fully understand cancer we must understand the networks that govern it (Werner, 2011). Although Werner classifies cancer networks into various types such as linear, exponential, and stochastic, our research only focuses on linear cancer networks (Werner, 2011).

1.1 Linear Cancer Networks

In linear cancers the developmental control network of the parent cell A causes it to divide into one daughter cell of type A and another cell of type B (Werner, 2011). This network results in a tumor that consists only of cells of types A and B. The growth rate of the tumor depends on the rate of cell division of the A cells. Only cells of type A are cancerous. Although all of the tumor cells inherited the cancer network from the parent A cell, in cells of type B the cancer network that generated them is inactive (Werner, 2011). Examples of linear cancers are basal cell carcinoma and grade 1 glioma of the brain (Werner, 2011).

1.2 Treatment Of Linear Cancers

Since linear cancers only have a few cancerous cells that are proliferating (the A cells), the main goal of treatment should be to remove these active cancer cells (Werner, 2011). Although B cells are considered to be passive they still contain the cancer network that they inherited from the A stem cells. Thus, there is a chance that these networks could be activated, giving rise to new cancerous cells. As a result treatments such as radiation therapy could be potentially harmful because of the danger of activating passive cancer cells (Werner, 2011). This could explain the growing body of medical evidence that suggests a link between radiation therapy and the development of second cancers (Ng et al., 2002; Tsang et al., 1993).

1.2.1 Treatment of Linear Cancers With Immunotherapy

Immunotherapy is a form of treatment that aims to improve the ability of the immune system to fight cancer cells (Stewart & Smyth, 2011). One of the major advantages of immunotherapy over traditional cancer treatments such as radiation and chemotherapy is that the immune system is much more discriminatory in its actions, targeting only cancer cells and leaving the majority of the healthy tissues of the body unharmed (Joshi et al., 2009). This substantially lessens the risk of activation of the passive cancerous networks of the B cells, making immunotherapy a potentially ideal candidate for the treatment of linear cancers. Paul Ehrlich, an immunologist in the early 20th century was the first person to conceive of the idea that the immune system is capable of scanning for and eradicating the tumors that arise in our bodies before they become clinically manifested (Malmberg, 2004). Although, this idea was controversial at first experimental evidence has shown that when cancer cells proliferate to a detectable number within the human
body, the body’s immune system is activated into a “search and destroy” mode (Nani & Freedman, 2000). This spontaneous immune response is possible only if the cancer cells have unique surface markers called tumor specific antigens. Tumor cells that possess these antigens are known as immunogenic cancers (Nani & Freedman, 2000). The recognition of cancerous cells by the immune system is called immune surveillance and cancer progression occurs when this process fails (Stewart & Smyth, 2011).

1.2.2 TGF-β: An Agent of Both Tumor Suppression and Progression

Transforming growth factor-β (TGF-β) is a protein that acts as a strong inhibitor of cell growth and an inducer of programmed cell death or apoptosis (Akhurst & Derynck, 2001). TGF-β is present in both normal and tumor cells. It plays a beneficial role in wound healing, inflammation, and new blood vessel formation (Arciero, Jackson, & Kirschner, 2004). At early stages of tumorigenesis, for example, when the tumor is still benign, TGF-β acts directly on cancer cells to suppress tumor growth (Akhurst & Derynck, 2001). However, as time elapses genetic changes allow, TGF-β to stimulate tumor progression by its activities on both the cancerous and non-malignant structural cell types of the tumor. Experimental evidence has shown that small tumors produce little or no TGF-β while large tumors produce large amounts of TGF-β and rely heavily on its angiogenesis promoting and immuno-suppressive effects. The discovery of TGF-β’s immuno-suppressive effects has led scientists to implement new forms of treatment aimed to inhibit TGF-β production. Unfortunately, several studies such as Terabe et al. demonstrate that TGF-β inhibition alone is not enough to eliminate tumors (Terabe et al., 2009; Wilson & Levy, 2012). In a study, Terabe et al. examined whether the inhibition of TGF-β can enhance immune responses caused by a peptide vaccine. Their goal was to ascertain under which conditions this enhanced tumor response slows down or stops tumor growth in mice. They found that treatment with only anti-TGF-β had no impact on tumor growth but anti-TGF-β did greatly enhance the effects of the peptide vaccine (Terabe et al., 2009; Wilson & Levy, 2012). Shelby Wilson and Doron Levy developed a mathematical model in order to quantitatively study the results of Terabe et al. (Wilson & Levy, 2012). We modified their model in order to study the effects of combination treatment on a linear cancer network.

2 The Wilson-Levy Model

\[
\frac{dT}{dt} = a_0(1 - c_0 T) - \delta \frac{ET}{1 + c_1 G} - \delta_0 TV \quad (1)
\]
\[
\frac{dG}{dt} = a_1 \frac{T^2}{c_2 + T^2} - dG \quad (2)
\]
\[
\frac{dE}{dt} = \frac{fET}{1 + sTG} - rE - \delta_1 E - \delta_1 E \quad (3)
\]
\[
\frac{dR}{dt} = rE - \delta_1 R \quad (4)
\]
\[
\frac{dV}{dt} = g(t) - \delta_1 V \quad (5)
\]

Equation (1) describes the growth rate of the tumor \((T)\) measured in mm². The tumor is assumed to grow logistically with a growth rate of \(a_0\) and a carrying capacity of \(\frac{1}{c_0}\). The second term of (1) represents the rate at which the effector cells \((E)\) are able to destroy tumor cells. The co-efficient \(f\) represents the tumor’s antigenicity and it measures the degree that the tumor is able to stimulate an immune response. The term \((1 + c_1 G)\) represents the negative effect that TGF-β \((G)\) production has on the effector cells’ ability to attack the tumor cells. The last term represents the action of the vaccine on the tumor cells (Wilson & Levy, 2012).

Equation (2) represents the rate of change in the concentration of TGF-β measured in ng/ml. The switch in the amount of TGF-β production between small and large tumors is modeled by the first term in (2). The coefficient \(c_2\) represents the tumor cell population at which the switch occurs and \(a_0\) is the maximum rate of TGF-β production (Arciero et al., 2004; Wilson & Levy, 2012).

Equation (3) represents the rate of change of the number of effector cells in the system. The first term represents the rate at which effector cells are recruited to attack the tumor. The term \((1 + sTB)\) represents the negative effect of both TGF-β production and tumor growth on the effector cells’ ability to proliferate (Wilson & Levy, 2012). The co-efficient \(r\) represents the fraction of effector cells that differentiate into regulatory T-cells. The final term in (3) represents the death rate of effector cells (Wilson & Levy, 2012).

Equation (4) represents the number of Tregs in the system (Wilson & Levy, 2012). This model assumes that only CD8+ cells become Tregs. The term \(r\) is the rate that Tregs differentiate or are recruited by effector T cells. \(\delta\) represents the death rate of Tregs (Wilson & Levy, 2012).

Equation (5) represents the rate of change of the vaccine which is modeled as an addition of 5000 activated T-cells, \(g(t)\) is a constant multiple of a Dirac Delta function centered at \(t = 3\).

3 The Modified Model

We modified Wilson and Levy’s equations by modeling the rate of change of the A and B cells separately in order to better understand how these two populations behave. To highlight the role that TGF-β plays in tumor growth and immuno-suppression we followed the example of (Arciero et
al., 2004) and chose to consider two scenarios of tumor development namely:

- Passive tumors that do not produce TGF-\(\beta\)
- Aggressive tumors that produce TGF-\(\beta\).

### 3.1 Passive Tumor Model

\[
\frac{dA}{dt} = kA(1 - \frac{A}{M_1}) - hEA - hAV \tag{6}
\]

\[
\frac{dB}{dt} = kA\frac{A}{M_1}(1 - \frac{B}{M_2}) - hEB - hBV - d_1B \tag{7}
\]

\[
\frac{dE}{dt} = fEB - rE - d_3E \tag{8}
\]

\[
\frac{dV}{dt} = g(t) - d_3V \tag{9}
\]

Equation (8) describes the growth rate of the \(A\) cells of the tumor which are assumed to follow logistic growth with a growth rate of \(k\) and a carrying capacity of \(M_1\). The term \(hEA\) represents the rate that effector cells attack the \(A\) stem cells.

Equation (9) represents the growth rate of the \(B\) cells. The fraction of \(A\) cells that differentiate into \(B\) cells is represented by \(\frac{A}{M_1}\). We assume that the \(B\) cells are non-dividing. The term \(M_2\) represents the carrying capacity of \(B\) cells. The term \(d_1B\) represents the natural death rate of \(B\) cells which we assume to be very low. The term \(hEB\) represents the rate that effector cells attack the \(B\) cells. We assume that the effector cells are able to attack the \(A\) and \(B\) cells at the same rate. Equation (11) models the vaccine and it is identical to equation (5), where \(d_3\) represents the death rate of the vaccine. The terms \(AV\) and \(BV\) represent the detrimental effect that the vaccine has on both the \(A\) and \(B\) cells. We assume that the vaccine is equally effective against \(A\) and \(B\) cells.

### 3.2 Aggressive Tumor Model

\[
\frac{dA}{dt} = kA(1 - \frac{A}{M_1}) - h\frac{EA}{1+c_1G} - hAV \tag{10}
\]

\[
\frac{dB}{dt} = kA\frac{A}{M_1}(1 - \frac{B}{M_2}) - h\frac{EB}{1+c_1G} - hBV - d_1B \tag{11}
\]

\[
\frac{dG}{dt} = a\frac{A^2}{c_2 + A^2} - d_2G \tag{12}
\]

\[
\frac{dE}{dt} = \frac{fEB}{1 + sBG} - rE - d_3E \tag{13}
\]

\[
\frac{dV}{dt} = g(t) - d_3V \tag{14}
\]

Equations (12), (13) and (16) are nearly identical to those of the passive tumor model. Equation (14) represents the rate at which TGF-\(\beta\) is produced by the tumor. We assume that TGF-\(\beta\) is only produced by \(A\) cells. There is a growing body of medical evidence that shows the link between TGF-\(\beta\) production and cancer stem cells (Dreesen & Brivanlou, 2007; Tang et al., 2008; Mishra, Shetty, Tang, Stuart, & Byers, 2005). \(h\) represents the rate that the effector cells are able to destroy both the \(A\) and \(B\) cells.

### 4 Simulations

In order to better understand the behavior of our models we performed numerical simulations using Mathematica 9’s NDSolve command. The code that we used will be made available upon request. All of our simulations are measured in days. We simulated the growth of four types of tumors namely:

- Low Antigenicity Passive Tumors
- High Antigenicity Passive Tumors
- Low Antigenicity Aggressive Tumors
- High Antigenicity Aggressive Tumors
4.1 Simulation of Passive Tumor Model

The following are the parameters that we used:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f$</td>
<td>$5 \times 10^{-6} \leq f \leq 0.05$</td>
<td>(Arciero et al., 2004)</td>
</tr>
<tr>
<td>$k$</td>
<td>0.18</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$r$</td>
<td>0.01</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$h$</td>
<td>$10^{-5}$</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$d_3$</td>
<td>$10^{-5}$</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$M_1$</td>
<td>40</td>
<td>estimated</td>
</tr>
<tr>
<td>$M_2$</td>
<td>369</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$a$</td>
<td>0.3</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$d_1$</td>
<td>$10^{-9}$</td>
<td>estimated</td>
</tr>
</tbody>
</table>

4.1.1 Simulations of Low Antigenicity Passive Tumors

Throughout the paper, for low antigenicity tumors we use a value of $5 \times 10^{-6}$. From the graph, we can see that both the $A$ and $B$ cells grow to reach their carrying capacities while the effector cells eventually die off.

4.1.2 Simulations of High Antigenicity Passive Tumors

We used the same parameters as in the previous case, however we changed the value of $f$ from $5 \times 10^{-6}$ to 0.05. The choice of this value will be addressed further in the discussion. Because of the high antigenicity, the effector cells are able to reduce both the $A$ and $B$ cells to very minute levels fairly quickly. Eventually, the oscillations in the effector cells dampen out. There is biological evidence to support these short term oscillations in cancers such as Chronic Myeloid Leukemia (Kirschner & Panetta, 1998).
4.2 Simulations of Aggressive Tumors

We used the following parameters in our analysis of aggressive tumors:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f$</td>
<td>$5 \times 10^{-6} \leq f \leq 0.62$</td>
<td>(Arciero et al., 2004) (Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$k$</td>
<td>0.1946</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$r$</td>
<td>0.01</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$h$</td>
<td>$10^{-5}$</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$d_3$</td>
<td>$10^{-5}$</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$M_1$</td>
<td>40</td>
<td>estimated</td>
</tr>
<tr>
<td>$M_2$</td>
<td>369</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$d_2$</td>
<td>$7 \times 10^{-4}$</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$c_2$</td>
<td>300</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$c_1$</td>
<td>100</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$a$</td>
<td>0.3</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
<tr>
<td>$d_1$</td>
<td>$10^{-9}$</td>
<td>estimated</td>
</tr>
<tr>
<td>$s$</td>
<td>300</td>
<td>(Wilson &amp; Levy, 2012)</td>
</tr>
</tbody>
</table>

4.2.1 Simulation of Low Antigenicity Aggressive Tumors

From the graph, we can see that both the $A$ and $B$ cells eventually reach carrying capacity. The amount of TGF-$\beta$ produced by the $A$ cells steadily increases while the effector cells eventually die off.

5 Treatment

Following the example of (Wilson & Levy, 2012) we divide treatment into three cases in order to test their relative effectiveness on both the $A$ and $B$ cells, namely:

- TGF-$\beta$ inhibition
- Vaccine treatment
- Combination Treatment

5.1 Treatment of Passive Tumors

Since passive tumors do not produce TGF-$\beta$ we consider only vaccine treatment, which is modeled by the introduction of 5000 effector cells on day 3 of simulation.

5.1.1 Vaccine Treatment for Low Antigenicity Passive Tumors

Although, the vaccine is able to reduce the number of $B$ cells it does not eliminate them. The vaccine is also unable to keep the $A$ cells from reaching their carrying capacity resulting in continual cancerous growth.
5.1.2 Vaccine Treatment for High Antigenicity Passive Tumors

Figure 6: As in the no treatment case, both the A and B cells are reduced to nearly zero.

This case is very similar to the no treatment case, with the tumor being reduced to near zero with oscillations eventually damping out.

5.2 Treatment of Aggressive Tumors

5.2.1 TGF-β inhibition for Low Antigenicity Aggressive Tumors

As in (Wilson & Levy, 2012), TGF-β inhibition is modeled as an increase of $c_2$ from 300 to 7000. For low antigenicity aggressive tumors, TGF-β inhibition has a nearly negligible effect on the final tumor size. Although, the rate of TGF-β production is greatly slowed down, both the A and B cells eventually reach their carrying capacities and the effector cells die off.

Figure 7: TGF-β inhibition for Low Antigenicity Aggressive Tumors

5.2.2 TGF-β Inhibition for High Antigenicity Aggressive Tumors

Although, the production of TGF-β is slowed down, the A and B cells still grow to reach their carrying capacities.

Figure 8: TGF-β inhibition for High Antigenicity Aggressive Tumors

5.2.3 Vaccine Treatment of Low Antigenicity Aggressive Tumors

As in the previous case, the vaccine reduces the size of the tumor but is unable to eradicate it completely.

Figure 9: Vaccine Treatment of Low Antigenicity Aggressive Tumors

5.2.4 Vaccine Treatment of High Antigenicity Aggressive Tumors

Even though the vaccine, slows down tumor growth, and prevents the A cells from reaching their carrying capacity for the first hundred days, it fails to eradicate the tumor.

Figure 10: Vaccine Treatment of High Antigenicity Aggressive Tumors

5.2.5 Combination Treatment for Low Antigenicity Aggressive Tumors

As in (Wilson & Levy, 2012), combination treatment is modeled by both the increase in $c_2$ from 300 to 7000 and the administration of the vaccine. Although, the size of the tumor is greatly reduced (The A and B cell populations make up 20 and 60 mm² respectively) the tumor is still present after 100 days.
5.2.6 Combination Treatment for High Antigenicity Aggressive Tumors

Although, the tumor size is reduced to nearly zero, by approximately day 30, the tumor eventually starts growing again by approximately the 300th day.

5.2.7 Summary of Simulations

<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>No Treatment</th>
<th>Anti-TGF-β</th>
<th>Vaccine</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Antigenicity</td>
<td>Grow to carrying capacity</td>
<td>Not applicable</td>
<td>Final A size: 75% of carrying capacity Final B size: 17% of carrying capacity</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Passive Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Antigenicity</td>
<td>Effectors cells reduce to minute levels fairly quickly but oscillate for a long time before eventually damping out</td>
<td>Not applicable</td>
<td>No noticeable effect</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Aggressive Tumor</td>
<td>Grow to carrying capacity</td>
<td>TGF-β production greatly slowed down but A and B cells still grow to carrying capacity</td>
<td>Final A size: 75% of carrying capacity Final B size: 19% of carrying capacity</td>
<td>Final A size: 75% of carrying capacity Final B size: 19% of carrying capacity</td>
</tr>
<tr>
<td>Low Antigenicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive Tumor</td>
<td>Initial spike in effector cells but both A and B cells still grow to carrying capacity</td>
<td>Large spike in effector cells but both A and B cells still grow to capacity</td>
<td>A size and B cells reduced to nearly zero shortly after vaccine treatment but cancer recurs on approximately day 300</td>
<td></td>
</tr>
</tbody>
</table>

6 Stability Analysis

6.1 Dimensionless Models

For ease of analysis, we followed the example of (Kirschner & Panetta, 1998; Arciero et al., 2004) and non-dimensionalized our mathematical models using the following scaling.

\[
x = \frac{A}{M_1} \quad y = \frac{B}{M_2} \quad z = c_1 G \quad w = \frac{fE}{r}
\]

\[
\tau = kt \quad \eta_1 = \frac{hr}{kf} \quad \eta_2 = \frac{hG}{kd_3} \quad \mu = \frac{M_1}{M_2}
\]

\[
\delta_1 = \frac{d_1}{k} \quad \delta_2 = \frac{d_2}{k} \quad \delta_3 = \frac{d_3}{k} \quad \gamma = \frac{M_2 f}{k}
\]

\[
\beta = \frac{c_2}{M_1^2} \quad \alpha = \frac{ac_1}{k} \quad \sigma = \frac{M_2 \gamma}{c_1} \quad \rho = \frac{r}{k}
\]

\[
v = \frac{d_3 V}{90}
\]

6.1.1 For passive tumors

\[
\frac{dx}{dt} = x(1 - x) - \eta_1 wx - \eta_2 xv \tag{15}
\]

\[
\frac{dy}{dt} = \mu x^2 (1 - y) - \eta_1 wy - \eta_2 yv - \delta_1 y \tag{16}
\]

\[
\frac{dw}{dt} = \gamma wy - \rho w - \delta_3 w \tag{17}
\]

\[
\frac{dv}{dt} = \delta_3 (\tau - 3k) - \delta_3 v \tag{18}
\]

(17) represents the rate of change of the A cells, (18) represents the rate of change of the B cells, (19) represents the rate of change of the effector cells, and (20) represents the rate of change of the vaccine.

6.1.2 For Aggressive Tumors

\[
\frac{dx}{dt} = x(1 - x) - \eta_1 xw \tag{19}
\]

\[
\frac{dy}{dt} = \mu x^2 (1 - y) - \eta_1 wy - \eta_2 yv - \delta_1 y \tag{20}
\]

\[
\frac{dz}{dt} = \alpha x^2 + \beta - \delta_2 z \tag{21}
\]

\[
\frac{dw}{dt} = \gamma \frac{wy}{1 + z} - \rho w - \delta_3 w \tag{22}
\]

\[
\frac{dv}{dt} = \delta_3 (\tau - 3k) - \delta_3 v \tag{23}
\]

(22) represents the rate of change of the A cells, (23) represents the rate of change of the B cells, (24) represents the rate of change of TGF-beta production, (25) represents the rate of change of effector cells and (26) represents the rate of change of the vaccine.

6.2 Stability of Passive Tumors

Mathematica was able to generate five equilibrium points. One of them was negative, therefore its stability was not biologically meaningful, and two produced eigenvalues too complex to analyze. The two equilibria that we were able to analyze were the origin and

\[
x = 1 \quad y = \frac{\mu}{\delta_1 + \mu} \quad w = 0
\]
The origin is unstable while the second equilibrium point is stable iff

$$\delta_3 > \frac{\gamma \mu}{\delta_1 + \mu} - \rho$$  \hspace{1cm} (24)$$

This inequality was derived from the eigenvalues of the second equilibrium point. Biologically, it means that the effector cells are dying off too quickly to fight off the tumor, resulting in them eventually dying off while the tumor reaches its carrying capacity. This confirms our observations in figure (1) and figure (2) because,

$$\frac{\gamma \mu}{\delta_1 + \mu} - \rho = -0.04$$

which is less than $\delta_3$ ($5.55 \times 10^{-5}$) for the low antigenicity passive tumor case, while

$$\frac{\gamma \mu}{\delta_1 + \mu} - \rho = 102.44$$

which is greater than $\delta_3$ for the high antigenicity passive tumor case.

### 6.3 Stability of Aggressive Tumor Model

In order to calculate the stability of the aggressive tumor model, we started by calculating the Jacobian matrix with $v = 0$ and used Mathematica 9 to find the equilibrium points. Although Mathematica 9 was able to find seven equilibrium points, do to the highly nonlinear nature of this model, we were able to analyze only two. They were the origin and

$$x = 1 \quad y = \frac{\mu}{\delta_1 + \mu} \quad z = \frac{\alpha}{(1 + \beta)\delta_2} \quad w = 0$$

The equilibrium point at the origin is unstable while the 2nd equilibrium point is stable iff

$$\delta_3 > \frac{(1 + \beta)\gamma \mu \delta_2}{\alpha \mu \sigma + (1 + \beta)(\delta_1 + \mu)\delta_2} - \rho$$  \hspace{1cm} (25)$$

Like in the previous case, this inequality was derived from the eigenvalues of the second equilibrium point. Biologically, it means that as $\alpha$ increases, the amount of TGF-$\beta$ increases, until it eventually produces enough to suppress the immune system, allowing it to grow to its carrying capacity, while the effector cells eventually die off. This matches our earlier observations in figure (3) and figure (4) for both the low and high antigenicity aggressive tumor cases because

$$\frac{(1 + \beta)\gamma \mu \delta_2}{\alpha \mu \sigma + (1 + \beta)(\delta_1 + \mu)\delta_2} - \rho = -0.05$$

which is less than $\delta_3$ ($5.14 \times 10^{-5}$)

### 7 Sensitivity Analysis

We performed a sensitivity analysis for combination treatment of high antigenicity aggressive tumors. This was done by varying each parameter by a range of percentages, starting from -25% to 25% centered around a baseline for 365 simulated days. The model was found to be most sensitive to $f$, the tumor’s antigenicity, $c_2$, the steepness co-efficient of TGF-$\beta$ production, $c_3$, the rate at which TGF-$\beta$ production and tumor growth inhibit the effector cells, $a$, the maximum rate of TGF-$\beta$ production and $h$, the effector cell tumor death rate.

![Figure 13: Sensitivity Analysis for High Antigenicity Aggressive Tumors Baseline Values: $f=.62$, $c_1=100$, $c_2=7000$, $s=300$, $a=.3$, $d_2=7\times10^{-4}$, $r=0.01$, $h=10^{-4}$.](image)

### 8 Discussion

Qualitatively, the behavior of our model for high antigenicity aggressive tumors agrees with the results of the Wilson-Levy model, with remission only being achieved after combination treatment. However, our model is able to show how each of the various treatments affect the A and B cell populations specifically. Figures (14) and (15) show the changes in A and B cell populations after 300 days respectively.
relative effectiveness of anti-TGF-β, vaccine, and combination treatment against the A and B cell populations respectively. Although, in both cases, anti-TGF-β slowed down tumor growth, the A cells were able to reach their carrying capacity by day 50 while the B cells reached their carrying capacity by day 250. Similarly, in the vaccine treatment case, the vaccine was able to reduce the B cell population from its carrying capacity of 369 to 60 (a reduction of 84%), while it was only able to reduce the A cell population from its carrying capacity of 40 to 35 (a reduction of 13%). Although remission was achieved in our simulations of combination treatment, from figure (14) we can see that the A cell population is not completely destroyed and as a result, the cancer reoccurs by day 300. Our results agree with studies that show that unless immunotherapy is specifically directed toward cancer stem cells, the cancer can still reoccur, even if there is a significant reduction in tumor size after treatment (Palmer et al., 2001).

Conversely, in our simulation of low antigenicity aggressive tumors we showed that although combination treatment succeeded in reducing the size of the tumor, it was unable to eliminate either the A or B cell populations. Furthermore, in our simulations of treatment of both low and high antigenicity passive tumors, we found that the vaccine had little effect. In our no treatment simulations, the behavior of our aggressive tumor model, agreed qualitatively with the behavior of the Wilson-Levy model for both high and low antigenicity tumors.

Our passive tumor model produced more interesting results. In the no treatment case, qualitatively our model agreed with the results of Kirschner and Panetta for values of f between \(5 \times 10^{-6}\) and 0.04 (Kirschner & Panetta, 1998). Extremely low antigenicity tumors were able to effectively escape immunsurveillance and grow to carrying capacity, and as the antigenicity of the tumors increased, the effector cell population began to oscillate, reducing the size of the tumor to nearly zero, before the oscillations eventually dampened out. In contrast, values of \(f \geq 0.05\) caused the effector cells to oscillate without reaching a stable equilibrium for certain initial conditions. In the future, more research will be done to investigate the cause and possible biological implications of this behavior. Other future work will be done to find more biologically realistic parameters to more accurately model the interactions between the effector, vaccine and stem cell populations.

References


