IMMUNE SYSTEM RESPONSE TO TUMOR GROWTH

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Introduction

In wealthy countries, around one out of five people dies from cancer. Cancer, also known as malignancy, is an abnormal growth of cells. More than hundreds of types of cancer exist, including breast cancer, skin cancer, and colon cancer. This disease allows cells to kill their host and then themselves. According to the principles of natural selection, which are based on survival, this should not be happening. So why does it? Well, natural selection acts in two ways here. One, cells undergo high rates of reproduction and as a result high rates of genetic variation. In other words, the more cells reproduce, the more mutations tend to occur, resulting in more genetic variation. Therefore, natural selection acts on the cells that show more selective advantages, which are caused by mutations. Two, natural selection provides all animals with defense mechanisms to fight off cancer. These defense mechanisms are known as oncogene proteins and tumor suppressor proteins. However, this is not as effective as one might expect since the heritability of cancer is insignificant compared to other factors (i.e. mutations and old age) contributing to the development of cancer. Therefore, the selective advantages of not having it are microscopic. Cell proliferation are controlled by biological concepts such as birth and death and foreign cells are controlled by the immune system. The development of cancerous tumors requires multiple stages, which is known as tumor progression. As cells undergo modifications, the defense mechanisms become weaker, and this results in more genetic variation. These modifications do not happen instantly. In fact, mutations happen slowly and successively. For example, after the Hiroshima and Nagasaki bomb went off, which caused mutation in genes due to the bombs’ radiation, only around 10 years later did the population start to develop cancer. In most cases, tumors don’t grow faster than regular cells. However, they multiply more times than regular cells would. In other words, regular cells usually need growth factors that attach to the cells to allow themselves to duplicate whereas tumorous cells may either produce their own growth factors or mutate in a way so that they do not require
special proteins to reproduce. The last stage required for a population of cells to be clinically considered as cancerous is a process known as metastasis. This stage allows cells to escape from the defense mechanisms that allow controlled cell migration. As a result, destructive tumors can spread throughout the body causing death.

In this project, we will consider mathematical models for the immune system response to the growth of tumors. This will lead us to determine mathematically the strength of the immune system, which can either destroy the tumor or let it grow indefinitely. To do so, the following assumptions are made:

1. The tumor cells have undergone some type of mutation, which have led them to become cancerous.
2. The tumor is spherically symmetric.
3. The immune system is able to recognize these tumor cells as foreign cells.
4. The immune system is acting in a cytotoxic response (T cells that can induce apoptosis in other cells) in order to destroy the population of tumor cells.
Mathematical models

1. Law of mass action

To derive the equation of the concentration of tumor cells as a result of the immune system response, the law of mass action must be used. Here, we will determine where the law of mass action comes from in order to use it in the following sections.

The law of mass action states that the rate of a chemical reaction is proportional to the product of the masses of the reacting substances. If we take the following equation:

$$A + B \rightarrow C \quad (1)$$

When some chemical A reacts with another chemical B to produce a third chemical C, then the rate of the reaction can be written as

$$k_{AB} \quad (2)$$

Here, A and B are the concentrations of the chemicals and k is the rate constant. By taking the derivative of the product, the reactants and equating it to the reaction rate (2), we get

$$\frac{dC}{dt} = -\frac{dA}{dt} = -\frac{dB}{dt} = k_{AB} \quad (3)$$

Due to thermodynamics principle, the reaction can also be done backwards ($C \rightarrow A + B$), so we can write
As a result, we get

\[
\frac{dC}{dt} = -\frac{dA}{dt} = -\frac{dB}{dt} = k_+ AB - k_- C
\]  

(5)

2. The Michaelis-Menten equation

Leonor Michaelis and Maud Menten mathematically represented the relationship between the rate of a reaction and the concentration of its substrates. Their equation will be used in further sections to derive the equation of the concentration of tumor cells as a result of the immune system response.

They considered the mechanisms of enzyme activity, which is the production of an enzyme-substrate complex before the production of a product and enzyme.

\[
E + S \xrightleftharpoons[k_2]{k_1} ES \xrightleftharpoons[k_2']{k_1'} E + P
\]  

(6)

Here, \( k_1 \) and \( k_2 \) are rate constants. The reaction’s rate law must be

\[
\frac{d[P]}{dt} = k_2 [ES] - k_{-2} [E][P]
\]  

(7)
The concentration of the products is negligible in the beginning since there are not initially any products formed. Thus, the reaction rate can be expressed as

$$\frac{d[P]}{dt} = k_2[ES] \quad (8)$$

When solving for the rate at which ES, the enzyme-substrate complex, is formed, and by making the steady-state approximation, assuming the variation in the concentration of the enzyme-substrate complex is almost zero, we determine analytically that the rate of formation of [ES] equals the rate of its disappearance.

$$\frac{d[ES]}{dt} = k_1[E][S] = k_1([E]_0 - [ES])[S] = -\frac{d[ES]}{dt} = k_{-1}[E][S] + k_2[ES] \quad (9)$$

The simplification of the previous equation leads to

$$k_1([E]_0 - [ES])[S] = k_{-1}[E][S] + k_2[ES] \quad (10)$$

We solve for the concentration of the enzyme-substrate complex which yields to

$$[ES] = \frac{[E]_0[S]}{k_{-1}k_2 + [S]} = \frac{[E]_0[S]}{K_m + [S]} \quad (11)$$

Here, $K_m$ represents the Michaelis constant, a combination of multiple reaction constants.
Michaelis and Menten found that the concentration of the enzyme-substrate complex is proportional to the velocity of the reaction and the initial concentration of the substrates is proportional to the maximum velocity of the reaction. This results in the formula below.

\[ V = \frac{V_{\text{max}}[S]}{K_m + [S]} \]  \hspace{1cm} (12)

Here, \( V \) is the reaction velocity, \( V_{\text{max}} \) is the maximum reaction velocity, \([S]\) is the concentration of the substrate, and \( K_m \) is the Michaelis constant. Furthermore, they took into consideration that when the enzyme is kept constant and the substrate concentration is increased, the rate of the reaction will also increase until it attains a maximum and begins to plateau. Once the plateau is reached, no matter how much the concentration increases by, the reaction will remain at a steady rate. This is because all of the enzyme has been converted to an enzyme-substrate complex in order to facilitate catalysis, meaning the enzyme is at its maximum performance.

3. Immune system response

To describe how a tumor grows in the absence of any response from the immune system, the differential equation used combines logistic growth and diffusion of the cells and is written as:

\[ \frac{aX}{\partial \tau} = rX(1 - \frac{X}{k}) + D \nabla^2 X \]  \hspace{1cm} (13)

Where \( X(r,t) \) is the concentration of the tumor cells (cells per unit volume), \( r \) is the position and \( t \) is the time.
Tumor cells and effector cells (activated T cells) form a complex during the process of lysis. This complex is formed when the activated T cell becomes a naïve (inactivated) T cell attached to a tumor cell. Lysis is the formation of an effector cell (re-activated T Cell) and a product of lysis (dead tumor cell) as a result of the tumor-effector cell complex.

![Visual representation of the tumor cell and activated T cell complex before inactivation.](image)

**Fig. 2. Visual representation of the tumor cell and activated T cell complex before inactivation.**

This process is represented below (14).

\[
E + X \xrightarrow{k_1} C \xrightarrow{k_2} E + P
\]  

Here, \(E(r,t)\) is the concentration of the effector cells that represents the cytotoxic response, \(C\) is the complex of the effector cell and tumor cell and \(P\), considered as waste, is the product which forms from lysis and will later on be removed from the body.
Fig. 1. Visual representation of the tumor cell and an activated T cell reaction producing a dead tumor cell and a reactivated T cell. Complex not displayed.

As previously explained, the law of mass action is used here to derive both the effector cell (E) equation as well as the complex (C) equation:

\[
\frac{dE}{dt} = -k_1 EX + k_2 C, \quad \frac{dC}{dt} = k_1 EX - k_2 C
\]  

(15)

Since lysis occurs faster than other chemical reactions in the body, we can make the quasi-steady-state assumption, which allows us to reduce the number of rate constants:

\[
k_1 EX - k_2 C = 0
\]  

(16)

By adding both equations in (3), we get:

\[
\frac{d}{dt} (E + C) = 0
\]  

(17)
In this case, we consider \( E + C = E_0 \) which is the combination of effector cells and complex of effector cells. The quasi-steady-state assumption gives us:

\[
E = \frac{k_2 E_0}{k_2 + k_1 X}
\]  

(18)

The rate at which \( X \) can be eliminated by the immune system response can be written as the following equation:

\[
-k_1 E X = -\frac{k_2 k_1 E_0 X}{k_2 + k_1 X}
\]  

(19)

A Michaelis-Menten equation (as previously explained) can be used and the equation for the concentration of tumor cells with the cytotoxic response is given by:

\[
\frac{\partial X}{\partial \tau} = r X \left( 1 - \frac{X}{K} \right) - \frac{k_2 k_1 E_0 X}{k_2 + k_1 X} + D \nabla^2 X
\]  

(20)
The following shows the Python code for the function of concentration of tumor cells versus its position (seen in equation (20)).

```python
import numpy
import matplotlib.pyplot as plt
import matplotlib.animation as animation

temp = 0

t = 100
nx = 51
T = 100
nt = 1001 #the number of timesteps we want to calculate
dt = T / (nt - 1)
K = 10**5
k1 = 2.9*10**(-4)
x2 = 0.028
r = 0.0226
X = numpy.zeros((nx, nx))

#IC's
def iniCond(x):
    return 1/(1+x**2)

for k in range(nx):
    X[0][k] = iniCond(k)
Xtemp = numpy.zeros((nx, nx))

prev = X.copy()
bigK = X.copy()
smallKs = X.copy()
gradients = X.copy()

for i in range(nt-1):
    c = -1 # 1st, 2nd order
    d = -1 # 2nd, 2nd order
    e = -1 # 2nd, 2nd order
    for j in range(nx):
        Xtemp = X.copy()
        if j == 0:
            c = 0
            d = 1
            e = 2
        elif j == nx - 1:
            c = -2
            d = -1
            e = 0
        else:
            c = 0
            d = 0
            e = 1

        # equation for t
        prev[i][j] = Xtemp[i][j]
        bigK[i][j] = r*Xtemp[i][j]-Xtemp[i][j]/K
        smallKs[i][j] = -(k2+k1)*X[i][j]/(k2+k1)*temp[i][j]
        gradients[i][j] = temp[i][j]/((-2*Xtemp[i][j]+d)*temp[i][j]+e)/((dr+e))
        X[i][j] = prev[i][j] + dt*(bigK[i][j] + smallKs[i][j] + gradients[i][j])
        #X[i][j] = Xtemp[i][j] + dt*(-2*Xtemp[i][j]+d)*X[i][j]/(k2+k1)*temp[i][j]+(k2+k1)*temp[i][j]+Xtemp[i][j]

check = 5
print(X[check])
# print("Previous value")
# print(prev[check])
```
Fig. 3.

The initial conditions set up at the beginning of the code were determined according to a research paper¹.

To code partial derivatives, second order finite difference equation approximation was used. A stencil of 3 sampled points was used to determine the first step as a forward difference, the intermediary steps as a central difference, and the last step as a backward difference.

Since there are no possible negative values for position, we must first use the forward difference approximation in order to plot the first point based on the next two. The more precise, central
difference approximation was used to compute derivatives at all points other than the first and the last (since we cannot use the points before the first or after the last as reference). Finally, the backwards approximation method was used in order to compute derivatives at the last point based on the 2 previous points.

The graph demonstrates that the concentration of tumor cells that are further from the center is affected more by the immune system response than tumor cells with larger radii. We can assume that this is because smaller tumor cells are easier to target by the immune system than larger ones.

The following figure shows the Python code for the animation of concentration of tumor cells versus its position.

```
import matplotlib

# First: set up the figure, the axis, and the plot element we want to animate
fig = plt.figure()
ax = plt.axes(xlim=(0, 40), ylim=(0, 1))
ax.grid()
line, = ax.plot([], [], lw=2)
plt.title('Concentration of Tumor Cells as a Function of its Position')
plt.xlabel('Position of Tumor Cells')
plt.ylabel('Concentration of the Tumor (Cells/Unit Volume)')

# initialization function: plot the background of each frame
def init():
    line.set_data([], [])
    return line,

# initialization function: plot the background of each frame
def animate(i):
    x = numpy.linspace(0, 8, nx)
y = y[1]
#x = numpy.linspace(0, 100, 100)
#y = x**2
line.set_data(x, y)
ax.plot(x, y)
return line,

# call the animator.  blit=True means only re-draw the parts that have changed.
ani = animation.FuncAnimation(fig, animate, init_func=init, frames=nt, blit=True)

writer = animation.writers['ffmpeg']
#writer = Writer(fps=24, metadata=dict(artist='Me'), bitrate=1800)
ani.save('animation1.mp4', writer=writer, dpi=200)

plt.show()
```

Fig. 4
Fig. 5. Concentration of Tumor Cell vs Position of Tumor Cell at initial, minimal and final concentrations of the tumor cell.

Below is the link to the coded animation which has been separated in Fig. 5.

https://drive.google.com/file/d/1uvn3CfNldOAO27Q12Fp_NZiKK1V-zEK/view?usp=sharing

The initial graph represents the initial condition of the tumor cells before the immune system has started to attack the cancerous tumors. The minimal graph demonstrates the lowest concentration of tumor cells after the immune system has started to respond to the tumor cells. Finally, the final graph demonstrates the increase of the concentration of tumor cells after the immune system can longer fight off the cancerous tumors.
Conclusion

As indicated by the animation and previous graphs, the concentration of tumor cells that are further from the center have a larger effect by immune system response. The change in concentration, displayed by the animation, decreases over time. This is why tumor cells that are further from the center are affected by the immune system response at a faster rate. At a certain point (when the y value is approximately 0.35), the immune system can no longer destroy the tumor cells, which cause the tumor cells to grow back (as seen in the animation). Since the immune system response is not strong enough to completely destroy the tumor cells, further methods such as chemotherapy have to be used in order to remove all tumor cells.

Access to our Jupyter File:

https://drive.google.com/file/d/1YZcLQ972wwAa3okCPsQmBgRdcn3RPqu1/view?usp=sharing
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Bibliography


