MATHEMATICS MODEL OF COMPACT TUMOR TO ANALYZE THE EFFECT ANTIANGIOGENIC THERAPY

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ABSTRACT

Based on their growth, tumors are classified into benign(compact) tumors and malignant (invasive) tumors. One of the treatments used for tumors is antiangiogenic therapy because this therapy has low toxicity. This study examines the effect of antiangiogenic therapy on compact tumors. The number of tumor cells changes over time are influenced by proliferation, death, and migration tumor cell. Antiangiogenic therapy can inhibit the process of angiogenesis which affect the dynamics of glucose flow. A lack of glucose flow will cause a decrease in tumor cell proliferation process which will decrease tumor growth rate. The finding suggests that maintaining glucose levels at or below a critical threshold (\( g_{cr} \)) is effective therapy.

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1. INTRODUCTION

Mathematical modeling can capture real problems phenomena and take certain assumptions that will be expressed in mathematics equations. In many areas, mathematical models have been widely used in various phenomena, such as in biology, physics, medicine, and others. Oncology, a subset of medical biology, is dedicated to the study and management of cancer. It covers the entire spectrum of cancer care, including prevention, detection, and therapeutic interventions. Various specialties exist within oncology, adapted to different treatment modalities. For instance, radiation oncology concentrates on employing radiation therapy for cancer treatment, while surgical oncology specializes in surgically addressing tumors[1].

Tumors caused by the damage of genetic structure that can make cell growth uncontrolled. On the other hand, gene damage is caused by genetic disorders that is carcinogens (substances that can cause cancer). Tumors can occur in various parts of the human body, from the head to the feet. If the tumor grows on the surface of the body, it will be easily discovered and treated, whereas if the tumor grows inside the body, it will be difficult to know because symptoms rarely arise, even if symptoms arise, generally it has reached an advanced stage so it is difficult to treat [2]. Tumor is a lump that grows on the tissues of the human body abnormally [2]. Tumors can be benign (compact) or malignant (invasive). Benign tumors do not spread, while malignant tumors can spread and attack surrounding body tissues [3]. Malignant tumors are also known as cancer. The ability of cancer cells to grow in human body tissues abnormally under possible conditions is one of the properties of cancer cells. The growth of cancer cells is limited by nutrients. Other properties of cancer cells apart from growing in human body tissues unrestrictedly are tissue invasion and metastasis. Tissue invasion is the process which cancer cells damage surrounding tissues and it will increase unhindered. Metastasis is the spread of cancer cells to other body tissues[4].

Angiogenesis is formation of new blood vessels from existing ones. This process is crucial and regulated by factors like Vascular Endothelial Growth Factor (VEGF). Initially observed during embryonic development in vasculogenesis, angiogenesis is now recognized to occur in adulthood, including during the ovarian cycle, tissue repair, and organ growth. An imbalance in pro and antiangiogenic signals distinguishes normal from abnormal angiogenesis. Research interest in angiogenesis has surged, aiming to understand and control blood vessel growth in various diseases. This special collection compiles original studies and reviews exploring the intricate mechanisms of angiogenesis across different aspects of cell biology[5]. Angiogenesis, the formation of fresh blood vessels from preexisting ones, facilitates tumor cell proliferation. It serves to nourish cancer cells by providing a conduit for nutrients, particularly in nascent cancerous tissues where vascular supply is crucial for sustenance and growth. Consequently, angiogenesis naturally occurs in cancerous tissue, fostering the development of new blood vessels to sustain tumor viability. These newly formed blood vessels not only provide nutrition to the tumor but also function as channels for the spread of cancer cells to the surrounding tissues[6].

Antiangiogenic therapy is one of the medical ways to treat tumors. Tumor treatment with antiangiogenic therapy has the concept of not directly attacking cancer cells, but targeting the blood vessels that needed by tumor cells to grow and develop, through this method, the tumor cannot grow, and rather would shrink if the blood supply is stopped. Antiangiogenics are a class of therapies that use drugs to stop tumors from forming new blood vessels[7]. Without new blood vessels supplying nutrients and oxygen, tumor cells cannot grow. Bevacizumab is first antiangiogenic drug that was approved for medical treatment. Tumor treatment with this antiangiogenic concept is mostly applied only to patients with diseases in primary tumors only or can be said to be in early stages conditions.

Mathematical models for tumor cell have been developed by many researchers. Mathematical modeling is also used to understand and predict the interaction between tumor cells and the immune system. This review provides an overview of recent models that examine the relationship between tumors and the immune system, particularly in spatial aspects. Over the past decade, research has integrated various types of immune cells, including macrophages, cytotoxic T lymphocytes, natural killer cells, dendritic cells, regulatory T cells, and CD4+ T helper cells, to evaluate their impact on tumor development. Although mathematical models provide valuable insights, the integration of specific patient data into these models remains a key goal for improved clinical applications in the future[8]. Mathematical and computational methods are increasingly employed to assist in comprehending and predicting tumor growth and response to treatment. The benefits of mathematical modeling in proliferation include the ability to simulate and predict tumor progression spatially and temporally across a wide range of experimental settings. The essence of proliferation modelling is the integration of accessible and validated biological data with experimental
findings[9]. Quantitative models help explain the complex biological mechanisms of cancer cell plasticity. This review covers models of plasticity, tumor progression, and metastasis using three common mathematical modeling techniques: discrete, continuum, and hybrid, each with their respective advantages and disadvantages. A recurring theme is that cell escape from the tumor microenvironment is driven by a combination of local physiological stress, external stressors, and interactions with the extracellular matrix. The discussion also involves the value of mathematical modeling in understanding cancer in general[10].

One of them is discussing the development of mathematical models on solid cancer growth that induces angiogenesis in the absence of cancer control mechanisms. The result of the study are that cancer is difficult to induce in human body tissues, thus showing that the reparative or regenerative mechanism of cancer cells is numerically efficient and functional[11]. On the continuous model, tumor growth in normal tissue is parabolic, which includes the free movement of tumor cells as parameters. This model usually ignores convective motion, which arise due to the increase in tumor cells. This process can provide an increase the volume of the tumor. The calculations can be done through hyperbolic equations and produce tumors with compact growth type. And such a mechanism is very important for benign tumors. As for tumors with invasive growth types, their development will increase rapidly[12].

2. RESEARCH METHODS

2.1 Block Diagram of Tumor Growth Phenomenon

The block diagram of the tumor growth phenomenon as follows:

![Diagram of Tumor Growth](image)

Figure 1. Diagram of the Tumor Growth

$n$ : tumor cell  
$m$ : necrotic tissue  
$g$ : glucose  
$c$ : capillary  
VEGF : Vascular Endothelial Growth Factor  
AAT : Antiangiogenic therapy.

Green arrows indicate enabling connections and black arrows indicate inhibiting connections.

Tumor cells demonstrate both proliferation and migration, requiring a high concentration of glucose to sustain their activities[13]. Proliferation plays a crucial role in the development and progression of cancer, which is characterized by changes in the expression and/or activity of proteins related to the cell cycle[14]. Proliferation demands more glucose compared to migration, and a decrease in glucose concentration halts proliferation. Tumor cells migrate towards regions with elevated glucose levels; those that reach such areas proliferate, while those unable to face glucose deprivation and undergo cell death. Vascular Endothelial Growth Factor (VEGF) protein are pivotal in tumor cell angiogenesis and blood vessel development,
promoting permeability, proliferation, migration, and new blood vessel formation. Angiogenesis responds to angiogenic stimuli, fostering new blood vessel growth, which serves as nutrient channels for tumor cells, notably for glucose. Antiangiogenic therapy (AAT) aims at the VEGF protein, disrupting the supply of oxygen and nutrients to tumor cells, thereby impeding their growth and resulting in cell death. Furthermore, tumor cells undergo capillary degradation or reduction, facilitated by factors such as the EphB4 enzyme, which thickens capillary walls and limits nutrient infiltration into tissues during growth[15].

2.2 Mathematical Model of Tumor Growth

The mathematical model of tumor growth has four variables that are coordinate functions of space and time \((x, t)\), tumor cell density \(n(x, t)\), necrotic tissue \(m(x, t)\), glucose concentration \(g(x, t)\), and capillary surface area \(c(x, t)\). The mathematical model of tumor growth can be expressed as follows[12]:

\[
\begin{align*}
\frac{\partial n}{\partial t} &= Bn \cdot [1 - \sigma(g)] - Mn \cdot \sigma(g) + D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial (In)}{\partial x} \\
\frac{\partial m}{\partial t} &= Mn \cdot \sigma(g) - \frac{\partial (Im)}{\partial x} \\
\frac{\partial g}{\partial t} &= Pc \cdot [1 - g] - Qn \cdot [1 - \sigma(g)] + D_g \frac{\partial^2 g}{\partial x^2} \\
\frac{\partial c}{\partial t} &= -R \cdot [n + m] c
\end{align*}
\]

\[\sigma(g) = \frac{1}{2} [1 - \tan h ((\epsilon (g - g_{cr})))] ; \]
\[\forall I = Bn \cdot [1 - \sigma(g)] + D_n \frac{\partial^2 n}{\partial x^2} ; \]

The number of changes of tumor cells over time will be influenced by the processes of proliferation, death, migration and convective. Proliferation in tumor cells will occur if the level of glucose concentration is sufficient, the glucose concentration is a nutrient for the tumor cells. If the glucose concentration level decreases, the proliferation rate will slow down that caused tumor cells will death. The process of proliferation and tumor cells death are governed by a sigmoid function \(\sigma(g)\). The sigmoid function is the glucose level for proliferation. Sigmoid function value is zero to one, when it is zero, there will be proliferation in tumor cells, while when it is one, there is no proliferation.

Tumor cells possess the ability to migrate within tissues via diffusion, a process where they move in response to concentration gradients. In normal cells or tissues containing tumor cells, convective motion drives the movement of tumor cells, exerting pressure on them. Tumor cells are inclined to migrate towards capillaries or conduits with varying glucose concentrations, experiencing displacement upon entry into these vessels. Changes in glucose concentration are influenced by inflow into the capillary, consumption by tumor cells, and diffusion throughout the tissue over time. The diffusion process regulates the flow of glucose concentration across capillary walls, while glucose consumption by tumor cells follows a sigmoid function, \(\sigma(g)\). Diffusion entails the movement of molecules from regions of high to low concentration; hence, when glucose concentration is high, tumor cells do not experience diffusion.

When the concentration of glucose is high, tumor cells will divide, otherwise the tumor cells will migrate. Capillary changes over time will be influenced by the process of degradation / decline or death of tumor cells, the decline process is mechanical and chemical so it is difficult to explain phenomenologically.

The basic parameters used are as follows:
Table 1. Parameter Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Model Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Proliferation rate of tumor cells</td>
<td>0.01</td>
</tr>
<tr>
<td>Q</td>
<td>Glucose Consumption Rate of Tumor Cells</td>
<td>12</td>
</tr>
<tr>
<td>Dn</td>
<td>Diffusion Coefficient of Glucose</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td>Angiogenesis Parameter</td>
<td>4</td>
</tr>
<tr>
<td>g_cr</td>
<td>Critical glucose level</td>
<td>0.1</td>
</tr>
<tr>
<td>M</td>
<td>Death rate of tumor cell</td>
<td>0.05</td>
</tr>
<tr>
<td>R</td>
<td>Capillary Degradation Rates</td>
<td>0.02</td>
</tr>
<tr>
<td>ε</td>
<td>Sensitivity of tumor cells to glucose levels</td>
<td>100</td>
</tr>
<tr>
<td>I</td>
<td>Convective movement</td>
<td>1</td>
</tr>
</tbody>
</table>

3. RESULTS AND DISCUSSION

3.1 Mathematical Model of Compact Tumor

In mathematical model of compact tumor growth cell, motility/migration \( (D_n) \) is equal to zero, and the mass movement/convective movement in the tissue \( (I) \) is not equal to zero. Equation (1) is reduced to an ordinary differential equation by transforming the coordinate plane

\[
z = x - Vt
\]

\( V \) is the tumor growth, represents a parameter that influences the rate of change of \( g \).

Tumor Cell

\[
\frac{\partial n}{\partial t} = Bn \cdot [1 - \sigma(g)] - Mn \cdot \sigma(g) + D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial (In)}{\partial x} ;
\]

\[
Bn \cdot [1 - \sigma(g)] - Mn \cdot \sigma(g) + D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial (In)}{\partial x} = 0
\]

\( D_n = 0 \) represents the nature of the compact tumor and when there was no rate of change in the number of tumor cell \( \left( \frac{\partial n}{\partial t} = 0 \right) \).

Such that from previous equation obtained

\[
Bn \cdot [1 - \sigma(g)] - Mn \cdot \sigma(g) - \frac{\partial (In)}{\partial x} - \frac{\partial n}{\partial t} = 0
\]

(3)

Transform Equation (3) using Equation (2)

\[
\frac{\partial^2 n}{\partial x^2} = \frac{\partial}{\partial x} \left( \frac{\partial n}{\partial x} \right) = \frac{\partial}{\partial x} \left( \frac{\partial n}{\partial z} \frac{\partial z}{\partial x} \right) = \frac{\partial}{\partial z} \left( \frac{\partial n}{\partial z} \right) = \frac{\partial^2 n}{\partial z^2} = \frac{\partial n}{\partial t} \frac{\partial n}{\partial z} = -V \frac{\partial n}{\partial z}
\]

The tumor cell equation is as follows:

\[
Bn \cdot [1 - \sigma(g)] - Mn \cdot \sigma(g) - \frac{\partial (In)}{\partial z} + V \frac{\partial n}{\partial z} = 0
\]

(4)

Necrotic tissue

\[
\frac{\partial m}{\partial t} = Mn \cdot \sigma(g) - \frac{\partial (Im)}{\partial x}
\]

(5)

\[
Mn \cdot \sigma(g) - \frac{\partial (Im)}{\partial x} - \frac{\partial m}{\partial t} = 0
\]

Transform Equation (4) using Equation (2)

\[
\frac{\partial m}{\partial t} = \frac{\partial m}{\partial z} \frac{\partial z}{\partial t} = -V \frac{\partial m}{\partial z}
\]
The necrotic tissue equation is obtained as follows:

\[ M_n \cdot \sigma(g) - \frac{\partial (Im)}{\partial z} + V \frac{\partial m}{\partial z} = 0 \]  

(6)

Glucose

\[ \frac{\partial g}{\partial t} = Pc [1 - g] - Qn \cdot [1 - \sigma(g)] + \frac{D_g (\partial^2 g)}{\partial x^2} ; \]

\[ Pc [1 - g] - Qn \cdot [1 - \sigma(g)] + \frac{D_g (\partial^2 g)}{\partial x^2} - \frac{\partial g}{\partial t} = 0 \]  

(7)

Transform Equation (7) using Equation (2)

\[ \frac{\partial ^2 g}{\partial x^2} = \frac{\partial}{\partial x} \left( \frac{\partial g}{\partial x} \right) = \frac{\partial}{\partial x} \left( \frac{\partial g}{\partial z} \right) \frac{\partial z}{\partial x} = \frac{\partial^2 g}{\partial z^2} \]

The glucose equation is obtained:

\[ Pc [1 - g] - Qn \cdot [1 - \sigma(g)] + \frac{D_g (\partial^2 g)}{\partial x^2} + V \frac{\partial g}{\partial z} = 0 \]  

(8)

Capillary

\[ \frac{\partial g}{\partial t} = -R [n + m] c ; \]

\[ -R [n + m] c - \frac{\partial c}{\partial t} = 0 \]  

(9)

Transform Equation (9) using Equation (2)

\[ \frac{\partial c}{\partial t} = \frac{\partial c}{\partial z} \frac{\partial z}{\partial t} = -V \frac{\partial c}{\partial z} \]

The capillary equation is obtained

\[ -R [n + m] c + V \frac{\partial c}{\partial t} = 0 \]  

(10)

After the transformation process, the compact tumor equation can be expressed as follows:

Tumor cells : \[ B_n \cdot [1 - \sigma(g)] - M_n \cdot \sigma(g) - \frac{\partial (Im)}{\partial z} + V \frac{\partial n}{\partial z} = 0 \]

Necrotic tissue : \[ M_n \cdot \sigma(g) - \frac{\partial (Im)}{\partial z} + V \frac{\partial m}{\partial z} = 0 \]  

(11)

Glucose : \[ Pc [1 - g] - Qn \cdot [1 - \sigma(g)] + \frac{D_g (\partial^2 g)}{\partial z^2} + V \frac{\partial g}{\partial z} = 0 \]

Capillary : \[ -R [n + m] c + V \frac{\partial c}{\partial t} = 0 \]

\[ \sigma(g) = \frac{1}{2} \left[ 1 - \tanh \left( \epsilon \left\{ g - g_{cr} \right\} \right) \right] ; \]

\[ I(z) = \int_{-\infty}^{z} B_n [1 - \sigma(g)] \]

\[ V = \lim_{z \to \pm \infty} I(z) \]

The boundary conditions for compact tumors can be expressed in Equation (12) as follows:
Next, we use this assumption

a. $\epsilon \to \infty$, meaning all tumor cells proliferate or die at specific positions at specific times,

b. $M \to \infty$, meaning tumor cells die instantaneously,

c. $R \to \infty$, meaning there are no capillaries inside the tumor.

Condition (c) is feasible only if the tumor has a clear region where there is no growth or death of tumor cells within the normal tissue area which can be stated as:

$$\exists x_b: \forall x > x_b, n(x) + m(x) = 0,$$

To get the value of $V$ solution for $z \to \pm \infty$ need to solve. By entering the boundary condition value in Equation (12) and condition a-c, we get an ODE system with constant coefficients which can be expressed as follows:

$$n = 0, \text{if } g \leq g_{cr}$$

$$Vn' - (In)' + Bn = 0 \text{ if } g > g_{cr}$$

$$m = \begin{cases} 1, & \text{if } g \leq g_{cr} \\ 0, & \text{if } g > g_{cr} \end{cases}$$

$$D_g g'' + Vg' - Pc[1 - g] - Qn = 0$$

$$c = \begin{cases} 1, & \text{if } n + m = 0 \\ 0, & \text{if } n + m > 0 \end{cases}$$

Condition $g > g_{cr}$ showed that glucose flow was sufficient for tumor cells to proliferate, causing these parameters $\sigma(g)$ approaches zero. This means that there is no transition from proliferation to tumor cell death, thus allowing the cells to continue reproducing, thus promoting continued tumor growth. On the contrary, the conditions $g \leq g_{cr}$ indicating that glucose flow is insufficient for proliferation. As a result, the main tumor cells die $\sigma(g)$ is close to 1. This indicates a transition from proliferation to cell death among tumor cells, thus inhibiting continuous tumor growth.

To find the eigen values of Equation (13), we need to analyze the differential equation involving $g$. For case $g > g_{cr}$, where $m = 0$

$$\lambda_{1,2} = \frac{-V \pm \sqrt{V^2 + 4D_g Pc}} {2D_g}$$

For the stability of the equilibrium points, if both eigenvalues have negative real part, the equilibrium point is stable, meaning that deviation in glucose concentration $g$ will diminish over time, potentially stabilizing tumor growth inhibition. Since tumor cells rely on glucose for proliferation, a decrease in glucose concentration due to antiangiogenic therapy can lead to a decrease in tumor growth rate or even tumor shrinkage if glucose levels drop sufficiently low.

Using parameter on Table 1, we can plot Equation (13) with variation of conditions.
Figure 2. Numeric Plot of (a) Glucose with $g > g_{cr}$ and, (b) Tumor cell with $V = 1$.

Figure 3. Numeric Plot of (a) Glucose with $g > g_{cr}$ and, (b) Tumor cell with $V = 100$.

Figure 2 and Figure 3 show that high level of glucose that is more than critical threshold values, support tumor growth. In Figure 3, the tumor cell increases more sharply with increasing glucose levels, indicating that tumor cells proliferate more rapidly when glucose is readily available.

Figure 4. Numeric Plot of (a) Glucose with $g \leq g_{cr}$ and, (b) Tumor cell.

In Figure 4, there is insufficient glucose to support optimal tumor growth. Tumor cell density (n) does not increase significantly and may even decrease, indicating constrained tumor growth under low glucose conditions.
4. CONCLUSIONS

It can be concluded that the mathematical model of compact tumor, the number of changes in tumor cells over time will be influenced by the processes of proliferation, death, and migration. Proliferation of tumor cells will occur if the glucose concentration level is sufficient. If the glucose concentration level decreases, the proliferation rate will slow down so that tumor cells cause death. The process of proliferation and death of tumor cells is regulated by a sigmoid function $\sigma(g)$, the sigmoid function is the glucose level for proliferation. Effective antiangiogenic therapy might involve maintaining glucose levels at or below $g_{cr}$, especially in tumors with high $V$, to inhibit tumor cell proliferation. This strategy could include dietary restrictions, glucose metabolism inhibitors, or enhancing glucose consumption by normal tissues.

REFERENCES

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