

Original Article

**Numerical Analysis of Mathematical Model of Tumor Treatment
by Anti-Angiogenesis**

Mihir Panchal^{1*} and Twinkle Singh²

¹ Department of Applied Mathematics and Humanities, Sardar Vallabhbhai National Institute of Technology, Surat 395007, India

²Department of Mathematics, Uka Tarsadia University, Bardoli 394601, India

Abstract

Explanation of cell movement and cell population in biology is one of the most interesting themes of the mathematical oncology. This study targets to produce numerical solutions of system of equation produced by the process of angiogenesis in development of tumor from vascular to avascular and then metastasis. We consider a situation in which anti-angiogenesis treatment is administered before a tumor is vascularized. This involve the treatment by preventing the angiogenesis by anti angiogenic agent namely said an anti-angiogenic factors (AAF). We developed the governing equations for the conservation of endothelial cells, tumor angiogenic factors and fibronectin concentrations. To solve these equations a finite Difference

Corresponding Author: Mihir Panchal < mihirpanchal45@gmail.com >

How to Cite this Article: Panchal, M., & Singh, T. (2019). Numerical Analysis of Mathematical Model of Tumor Treatment by Anti-Angiogenesis. *The Journal of Applied Sciences Research*, 6(4):48-59.

Retrieved from <http://www.journals.wsrpublishing.com/index.php/tjasr/article/view/467>

Article History: Received: 2019-09-13 Accepted: 2019-11-12

Copyright © 2019, World Science and Research Publishing. All rights reserved



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](https://creativecommons.org/licenses/by-nc-nd/4.0/).

method is applied. Which is consider to be very reliable and stable for parabolic partial differential equations. After the discretization process of equations we get the matrices which solve by Matlab simulations. we have used the previously published parametric values which are chosen to suit this study. Results obtained designate that when we applied the antiangiogenic term to the equation for endothelial cell concentration, endothelial cells concentration declines identically. This can make huge inferences for cancer treatment.

Keywords: Tumor angiogenesis, Anti-angiogenesis, Finite difference method

Introduction

Cancer is a disease that occurs as a result of genetic mutations in cells due to any number of causes. It is the culmination of these mutations being passed on through the generations of a cell's progeny that leads to tumor formation. A cell population is referred to as being cancerous when these mutations lead to their uncontrolled proliferation and intrusion on nearby tissues. These cancer cells interfere with the normal functioning of cells and are detrimental to the organism's survival. While some forms of cancer do not form a solid mass (such as leukemia), the most common quality associated with cancer is the ability to form an aggressive tumor. The report indicated that they are in the need of a speedy implementation of efficient prevention strategies.

We can distinguish three main face of tumor development, the avascular phase (benign) which is said to a primary stage in which tumor have no blood supply, the vascular phase in which tumor angiogenesis happens and tumor get the bold as well as other nutrition from veins and the malignant phase (cancer) that is consider as a final stage in which tumor spread from its primary location to different part of the body. There are various different strategy developed to cure the invasion of cancer. One of the approach to treat cancer is involves anti-angiogenesis to break the angiogenesis process. This approach attaches a naturally occurring process in tumor growth and uses it to prevent tumor angiogenesis.

Ever since the extremely important connection between angiogenesis and tumor growth was established in [3], the field of oncology has been revitalized by antiangiogenic treatments. When a tumor begins to form, its existence and growth depend on the diffusion of oxygen and nutrients in its immediate vicinity. However, tumor growth is diffusion-limited, that is, after it reaches a certain size, approximately 2-3mm in diameter, the center of this cell cluster can no longer be sustained by the amount of oxygen attainable via simple diffusion. In response to this, the effected cells begin to release hypoxia-induced factors (HIFs).

Tumor Angiogenesis

These processes compound and are very effective in causing blood vessels to sprout from nearby existing vasculature, however, unlike the normal process of angiogenesis, this process is hasty and unregulated. Tumor vasculature is most often highly tortuous and inefficiently structured leading to spatially and temporally heterogeneous blood flow. In addition they have large fenestrations leading to leaky vessels and highly compromised nutrient delivery. The cancer cells that originally triggered the angiogenic switch rarely see the benefit of their efforts since these incoming vessels usually penetrate only the tumor rim, leaving the bulk of the tumor lacking any consistent oxygen supply. As a result, the center of a tumor often develops into a necrotic core and the hypoxic cells that surround this core maintain constant angiogenic signalling. As the tumor grows the very dense blood vessels and tumor cells become compacted leading to collapsed blood vessels, restricted blood flow and high interstitial fluid pressure.

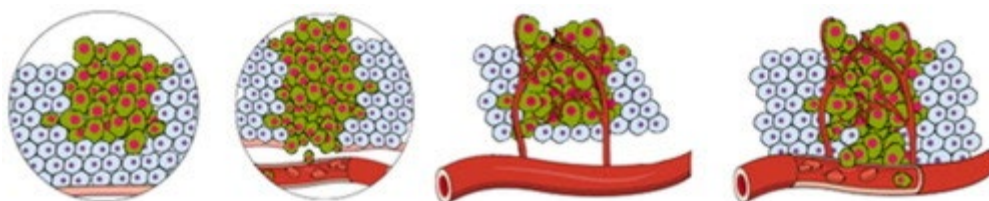


Fig. 1: Angiogenesis process within solid tumor

Anderson et al. (2000) pondered an experiment on mice in which Anti-angiogenesis was indicated where many types of tumor were inculcate in mice and were allowed to develop. Levine et al. define anti-angiogenesis as a process whereby anti-angiogenic factors (AAF) are applied to hamper the development of a tumor. Similarly Ledzewicz and Schattler (2008) explained anti-angiogenesis as a cancer treatment that aims to delay or halt a tumor vascularization. Anderson et al. (2000) reflect anti-angiogenesis to be a normal tumor induced procedure.

Anti Angiogenic Agent

In recent years the focus of cancer treatments has shifted dramatically. Up until the past 10 to 15 years, the central concern was killing the cells which comprised the tumor bulk. However, with the realization that angiogenesis was a crucial part of sustained tumor growth, much energy and effort has been expended on the development of antiangiogenic drugs. Originally the rationale was that destroying all tumor vasculature would lead to the tumor being starved of essential nutrients and oxygen leading to tumor cell death. When endothelial cell killing drugs such as combretastatin were first injected into a tumor, the antiangiogenic effects were deemed to be significant and fast-acting, yet the majority of tumor cells remained unaffected. This is due to a number of factors but most importantly, many forms of cancer can survive under hypoxic conditions. Not only does the tumor survive, it also implies that a source of angiogenic signalling remains. New models that will be offered in this paper are for the anti-angigenic factors and the conservation of endothelial cells being the features that influence and are a response to the cure. Models for tumor angiogenic factors and for fibronectin will be used as they were earlier published in Panchal and Singh (2019).

Mathematical Model

The equations that will be presented in this paper for tumor angiogenic factors and fibronectin is constructed on previously published models of Anderson and Chaplain (1998), Eleondou (2011), Holmes and Sleeman (1990) and Panchal and Singh (2019).

The governing equation of conservation of the tumor angiogenic factors will be used as follows:

$$\frac{\partial G}{\partial t} = D_G \nabla^2 G - f(G)g(C) - h(G) \quad (1)$$

The equation governing fibronectin will be expressed as:

$$\frac{\partial F}{\partial t} = D_F \nabla^2 F + \frac{\sigma_F CF}{\omega + F} - s_F CF - \beta_F F \quad (2)$$

The anti-angiogenic factor as the treatment administered in this paper. It will be supplement to the region of interest. The conservation equation of AAF will be based on diffusion, uptake of the factor by endothelial cells and its loss due to decay as had been expected with the tumor angiogenic factors. Therefore its equation will be as follows:

$$\frac{\partial H}{\partial t} = D_H \frac{\partial^2 H}{\partial x^2} - \alpha H - \lambda \frac{He}{(K_0 + H)}, \quad (3)$$

Where α represents the decay rate, K_0 is anti-angiogenic factors reaction constant and λ is the anti-angiogenesis factor reaction rate. Due to administration of AAF, Model of endothelial cells for the duration of treatment is changes to some extent. It is important that the biological experiments and mathematical models complement each other. In particular, this paper builds on the experimental and theoretical work described by Anderson et al. (2000).

In this work the model to govern the development of endothelial cells during anti-angiogenesis is based on diffusion, the chemotatic effect by the tumor angiogenetic factors, cell mitosis, endothelial cell-cell adherence through fibronectin, the chemotatic effect by anti-angiogenic factors and endothelial cell lost due to decay. it is presumed that the function describing conservation of anti-angiogenic factors follows a simple logistic form just similar the funtion for tumor angiogenic factors. The function for anti-angiogenic factors is as follows: $\mu(H) = \mu_0 H \frac{K_0}{(K_0 + H)}$, where μ_0 (a positive constant coefficient) is the anti-angiogenic chemotatic factor indicting strength of the chemotactic response because of angiostatin and K_0 is also positive constant of the desensitization of endothelial cell due to anti-angiogenic factors. The

equation governing the conservation of endothelial cell when the term for the anti-angiogenic factor is added, it becomes:

$$\frac{\partial C}{\partial t} = D_c \nabla^2 C - \nabla \chi_1 \frac{K_1}{K_1 + C} C \nabla G - \nabla \rho_1 C \nabla F + \rho C \left(1 - \frac{C}{C_0} \right) \left(\frac{G^* - G}{G_0} \right) - \mu_0 \frac{K_0 \partial^2 HC}{(K_0 + H) \partial x^2} - \mu_0 \frac{K_0}{K_0 + H} H \frac{\partial C}{\partial x} - \mu_1 C \quad (4)$$

The boundary conditions for AAF concentration satisfies given below:

$$H = H_m, \quad x = L, \quad H = 0 \quad \text{and} \quad x = 0.$$

Here, depending on the dose applied the concentration of anti angiogenic factor at the blood vessel fluctuates. The dose that is added to the region during each time interval is given by H_k for $0 \leq k \leq t$. To solve Equation (4), which is a nonlinear parabolic partial differential equation, the implicit finite difference method have been implemented.

Non-dimensionalizing the system

Nondimensionalization is the partial or full removal of units from an equation involving physical quantities by a suitable substitution of variables. This technique can simplify and parameterize problems where measured units are involved. So we have Equation (4) is been non-dimensionalized by rescaling the distance between the blood vessel and the tumor with L , time with $\tau = \frac{L^2}{D_G}$, (where D_G , is the tumor angiogenic factor diffusion coefficient), endothelial cell density with C_0 , and tumor angiogenetic factors G_0 and anti-angiogenesis concentrations with H_0 , respectively. So, taking: $H^* = \frac{H}{H_0}$, $d_H = \frac{TD_H}{L^2}$, $\alpha = \frac{T\alpha_1}{L^2}$, $\varpi = \beta T$ and $K_H = \frac{TK_0}{L^2}$, $l = \frac{TK_0(0)}{L^2}$ and other variables as they were set in Panchal and Singh [5], and for simplicity dropping the bars for notations, then the non-dimensionalised equation of anti-angiogenesis factor becomes:

$$\begin{aligned} & \alpha \frac{K_H}{K_H + H_i^j} \frac{(H_{i+1}^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - H_{i-1}^j)}{4\Delta x} \times \frac{(C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x} \\ & g = \frac{\Delta t d_\alpha}{2\Delta x^2}, h = \frac{\Delta t \lambda}{2} \\ & m_i^j = \frac{\Delta t \varpi e_i^j}{2(l + C_i^j)} \end{aligned} \quad (5)$$

Endothelial cells concentration becomes:

$$\frac{\partial C}{\partial t} = d_c \frac{d^2 C}{\partial x^2} - \chi(1) \frac{K_1 C \partial^2 G}{(K_1 + C) \partial x^2} - \chi(1) \frac{K_1}{K_1 + e} \times \frac{\partial C \partial G}{\partial x^2} - \rho C \frac{\partial^2 F}{\partial x^2} - \rho \frac{\partial C \partial F}{\partial x^2} + \rho_0 C (1 - C) E(G) - \psi C - \mu_0 C \frac{\partial H^2}{\partial x^2} - \mu_0 \frac{\partial C \partial H}{\partial x^2} \quad (6)$$

1. Finite Difference Discretization of Model Equation and their solutions

Equation (5) stands for the non-dimensionalized anti-angiogenic factors equation. We apply the Finite difference method to this equation then the discretization can be written as :

$$\frac{H_i^{j+1} - H_i^j}{\Delta t} = d_H \frac{H_{i-1}^{j+1} - 2H_i^{j+1} + H_{i+1}^{j+1} + H_{i-1}^j - 2H_i^j + H_{i+1}^j}{2\Delta x^2} - \beta \frac{(H_i^{j+1} - H_i^j)}{2} - \varpi \frac{(H_i^{j+1} - H_i^j)C_i^j}{2(l + H_i^j)} \tag{7}$$

where $g = \frac{\Delta t d_a}{2\Delta x^2}, h = \frac{\Delta t \lambda}{2}$ and $m_i^j = \frac{\Delta t \varpi e_i^j}{2(l + C_i^j)}$ Substituting g, h, and m the above equation can

be express in a tridiagonal form,

$$\begin{pmatrix} (P_a)_i^j & -g & 0 & 0 & 0 & 0 \\ -g & (P_a)_i^j & -g & 0 & 0 & 0 \\ 0 & -g & (P_a)_i^j & -g & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & -g & (P_a)_i^j & -g \\ 0 & 0 & 0 & 0 & -g & (P_a)_i^j \end{pmatrix} \begin{pmatrix} H_1^{j+1} \\ H_2^{j+1} \\ H_3^{j+1} \\ \cdot \\ \cdot \\ H_{i-1}^{j+1} \\ H_i^{j+1} \end{pmatrix} = \begin{pmatrix} (P_b)_i^j & g & 0 & 0 & 0 & 0 \\ g & (P_b)_i^j & g & 0 & 0 & 0 \\ 0 & g & (P_b)_i^j & g & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & g & (P_b)_i^j & g \\ 0 & 0 & 0 & 0 & g & (P_b)_i^j \end{pmatrix} \begin{pmatrix} H_1^j \\ H_2^j \\ H_3^j \\ \cdot \\ \cdot \\ H_{i-1}^j \\ H_i^j \end{pmatrix} + \begin{pmatrix} 2g \times H_1^j \\ 0 \\ 0 \\ 0 \\ \cdot \\ 0 \\ 2g \times H_{n+1}^j \end{pmatrix}$$

Where, $(P_a)_i^j = 1 + 2g + h + m_i^j$, $(P_b)_i^j = 1 - 2g + h + m_i^j$.

The Solution of the Model for Endothelial Cells Conservation during Anti-angiogenesis from equation (4),

$$\frac{\partial C}{\partial t} = d_c \frac{d^2 C}{\partial x^2} - \chi(1) \frac{K_1 C \partial A^2}{(K_1 + C) \partial x^2} - \chi(1) \frac{K_1}{K_1 + e} \times \frac{\partial C \partial A}{\partial x^2} - \rho C \frac{\partial F^2}{\partial x^2} - \rho \frac{\partial C \partial F}{\partial x^2} + \rho_0 C(1 - C)E(G) - \psi E - \mu_0 \frac{K_0}{K_0 + H} C \frac{\partial H^2}{\partial x^2} - \mu_0 \frac{K_0}{K_0 + H} \frac{\partial C \partial H}{\partial x^2} \tag{8}$$

Applying the discretization by the Finite Difference scheme to equation (9) we obtain:

$$\begin{aligned} \frac{C_i^{j+1} - C_i^j}{\Delta t} = & d_c \frac{(C_{i-1}^{j+1} - 2C_i^{j+1} + C_{i+1}^{j+1} + C_{i-1}^j - 2C_i^j + C_{i+1}^j)}{2(\Delta x)^2} - \chi(1) \frac{K1(C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x(K_1 + C_i^j)} \times \\ & \frac{\{G_{i+1}^{j+1} - G_{i-1}^{j+1} + G_{i+1}^j - G_{i-1}^j\}}{4\Delta x} - \chi(1) \frac{K_1 C_i^j}{K_1 + C_i^j} \times \frac{(G_{i+1}^{j+1} - 2G_i^{j+1} + G_{i+1}^j + G_{i-1}^j - 2G_i^j + G_{i+1}^j)}{2(\Delta x)^2} - \\ & \rho \frac{(C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x} \times \frac{(F_{i+1}^{j+1} - F_{i-1}^{j+1} + F_{i+1}^j - F_{i-1}^j)}{4\Delta x} - \rho e_i^j \frac{(F_{i-1}^{j+1} - 2F_i^{j+1} + F_{i+1}^j + F_{i-1}^j - 2F_i^j + F_{i+1}^j)}{2(\Delta x)^2} + \\ & \rho_0 C_i^j (1 - C_i^j) E(G) + \psi \frac{(C_{i+1}^{j+1} - C_i^j)}{2} - \sigma \frac{K_H}{K_H + H_i^j} \frac{C_i^j (H_{i+1}^{j+1} - 2H_i^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - 2H_i^j - H_{i-1}^j)}{2(\Delta x)^2} \end{aligned}$$

$$\alpha \frac{K_H}{K_H + H_i^j} \frac{(H_{i+1}^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - H_{i-1}^j)}{4\Delta x} \times \frac{(C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x} \tag{9}$$

By substituting, $\bar{A} = \frac{\Delta t d_c}{2(\Delta x)^2}$, $\bar{B}_i^j = \frac{\chi(1)K_1\Delta t(G_{i+1}^{j+1} - G_{i-1}^{j+1} + G_{i+1}^j - G_{i-1}^j)}{16(\Delta x)^2 (K_1 C_i^j)}$,

$$\bar{C}_i^j = \frac{\chi(1)k_1\Delta t(G_{i+1}^{j+1} - 2G_i^{j+1} + G_{i-1}^{j+1} + G_{i+1}^j - 2G_i^j + G_{i-1}^j)}{2(\Delta x)^2 (K_1 C_i^j)}, \quad \bar{D}_i^j = \frac{\rho\Delta t(F_{i+1}^{j+1} - F_{i-1}^{j+1} + F_{i+1}^j - F_{i-1}^j)}{16(\Delta x)^2}$$

$$\bar{E}_i^j = \frac{\rho\Delta t(F_{i-1}^{j+1} - 2F_i^{j+1} + F_{i+1}^{j+1} + F_{i-1}^j - 2F_i^j + F_{i+1}^j)}{2(\Delta x)^2}, \quad \bar{F} = \frac{\Psi\Delta t}{2}, \quad \bar{G}_i^j = \rho_0\Delta t(1 - C_i^j)E(G_i^j)$$

$$\bar{H}_i^j = \Delta t\mu_0 \frac{K_H}{K_H + H_i^j} \frac{\{H_{i+1}^{j+1} - 2H_i^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - 2H_i^j - H_{i-1}^j\}}{2(\Delta x)^2}, \quad \bar{I}_i^j = \Delta t\mu_0 \frac{K_H}{K_H + H_i^j} \frac{\{H_{i+1}^{j+1} - H_{i-1}^{j+1} - H_{i+1}^j - H_{i-1}^j\}}{16(\Delta x)^2}, \text{ and}$$

rearranging terms equation (9) can be written in a tridiagonal matrix form then becomes:

$$\begin{pmatrix} P_c & (P_d)_i^j & 0 & 0 & 0 & 0 \\ (P_e)_i^j & P_c & (P_d)_i^j & 0 & 0 & 0 \\ 0 & (P_e)_i^j & P_c & (P_d)_i^j & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & (P_e)_i^j & P_c & (P_d)_i^j \\ 0 & 0 & 0 & 0 & (P_e)_i^j & P_c \end{pmatrix} \begin{pmatrix} C_1^{j+1} \\ C_2^{j+1} \\ C_3^{j+1} \\ \cdot \\ \cdot \\ C_{i-1}^{j+1} \\ C_i^{j+1} \end{pmatrix} = \begin{pmatrix} (P_f)_i^j & (P_g)_i^j & 0 & 0 & 0 & 0 \\ (P_h)_i^j & (P_f)_i^j & (P_g)_i^j & 0 & 0 & 0 \\ 0 & (P_h)_i^j & (P_f)_i^j & (P_g)_i^j & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & (P_h)_i^j & (P_f)_i^j & (P_g)_i^j \\ 0 & 0 & 0 & 0 & (P_h)_i^j & (P_f)_i^j \end{pmatrix} \times \begin{pmatrix} C_1^j \\ C_2^j \\ C_3^j \\ \cdot \\ \cdot \\ C_{i-1}^j \\ C_i^j \end{pmatrix} + \begin{pmatrix} 2\bar{A} \times C_1^j \\ 0 \\ 0 \\ 0 \\ \cdot \\ \cdot \\ 0 \\ 2\bar{A} \times C_{n+1}^j \end{pmatrix} \tag{10}$$

Where, $P_c = 1 + 2\bar{A} + \bar{F}$, $(P_d)_i^j = -\bar{A} + \bar{B}_i^j + \bar{D}_i^j + \bar{I}_i^j$, $(P_e)_i^j = -\bar{A} - \bar{B}_i^j - \bar{D}_i^j - \bar{I}_i^j$,

$$(P_f)_i^j = 1 - 2\bar{A} - \bar{C}_i^j - \bar{E}_i^j + \bar{G}_i^j + \bar{F}_i^j - \bar{H}_i^j, \quad (P_g)_i^j = \bar{A} - \bar{B}_i^j - \bar{D}_i^j - \bar{I}_i^j,$$

Results and Discussion

The results for the concentration of the endothelial cells when the antiangiogenic factor is added to the equation, to model that becomes with treatment. Results are acquired from a MATLAB simulation. The process of angiogenesis is assumed to take 10 days. Results are shown for previously generated fibronectin concentration, tumor angiogenic factor and endothelial cells concentration as anti-angiogenic factors is added to the equation for endothelial cells during angiogenesis.

In the simulation, the anti-angiogenic factor is added 3 days after when the process of angiogenesis started, which had been taken at $t = 0$. Results are then generated for $t = 3, 5, 7$ and 10 days after angiogenesis. These values were chosen randomly. Parametric values for the model governing the tumor angiogenic factor are the same as those used in [4].

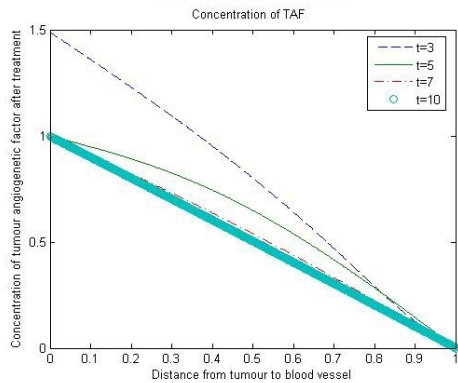


Figure 1: Concentration of TAF after in present of of Anti-angiogenic Factor

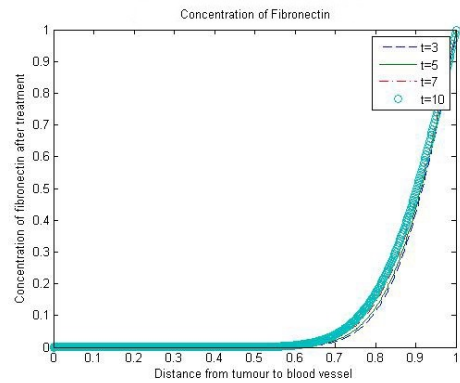


Figure 2: Fibronectin Concentration in present of Anti-angiogenic Factor

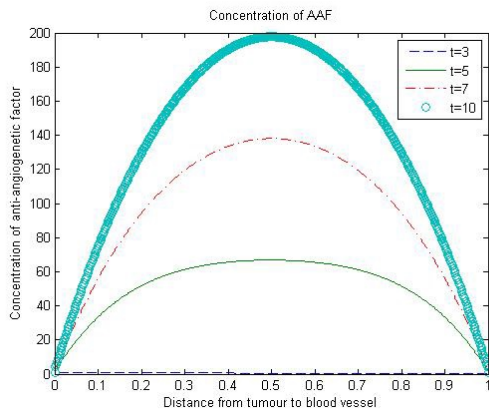


Figure 3: Anti-angiogenic Factor(AAF) Concentration

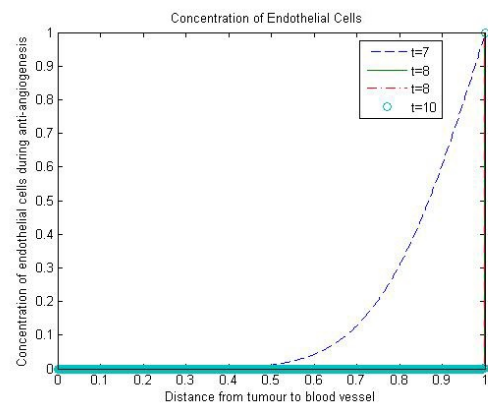


Figure 4: Endothelial Cell Concentration in present of Anti-angiogenic Factor

Figure 1 shows that after the addition of anti-angiogenic factors although the concentration of the tumor angiogenic factor decreases, it remains above zero. This means that the tumor angiogenic factor is available for degrading the basement membrane of the blood vessel so as to allow the migration of endothelial cells as was discussed before.

Parametric values for fibronectin are the same as those used in previous work Panchal and Singh (2019). The results of the simulation are shown in Figure 2. Results indicate that as time increases the fibronectin concentration increases by a small amount over its value during initial stages of no treatment. This shows that the treatment does not completely stop the growth of endothelial cells, because they are the source of fibronectin. However, the concentration of fibronectin is much reduced, which suggests that endothelial cell concentration is also reduced.

Table 1: Parametric Values for AAF

Diffusion coefficient of Anti-angiogenetic factor	d_H	1.79×10^{-4}
Decay rate of Anti-angiogenetic factor	β	5.0×10^{-2}
Anti-angiogenetic factor Uptake rate	$r(0)$	1.0×10^{-3}
Anti-angiogenetic factor Maximum constant rate	q	3.0×10^{-1}

Parametric Values for the Anti-Angiogenic Factor is given in table 1. The simulation to show the consequence of varying level on the concentration of the antiangiogenic factor when the value K varies, are given in Figure 3. The figure shows that as time progresses the concentration of anti-angiogenic factor rises, as is exposed for the increasing values of K .

That density of endothelial cells when the treatment is added after 3 days are displayed in Figure 4, and is taken as the initial condition for anti-angiogenesis process. The effect of anti-angiogenic factor is investigated by observing endothelial cells behavior as initiated at two different stages of angiogenesis. From these observations we can therefore conclude that according to our new model, which included anti-angiogenesis as a treatment, the treatment is effective in inhibiting and destroying endothelial cells from reaching the tumor. Inhibiting angiogenesis could be a most effective way of preventing tumors progressing to the malignant stage.

Conclusion

During angiogenesis results showed that as time progresses the concentration of tumor angiogenetic factor decreased from the boundaries of the tumor. At the same time

endothelial cells migrated towards the tumor. Then anti-angiogenic factor was introduced to the region. Initial, boundary and zero flux boundary conditions were imposed and simulations were applied, after discretizing the models, using Matlab. Results for anti-angiogenesis process showed that endothelial cells responded chemotactically to two opposing gradients. Results indicated that the anti-angiogenic factor does delay the growth of endothelial cells, and also destroy endothelial cells appearing in the region.

Results also indicated that anti-angiogenic factor is the effective treatment for inhibiting and destroying endothelial cells from reaching the tumor. Inhibiting angiogenesis could be one of the most effective way of preventing tumors progressing to the malignant stage. The results generated by our numerical simulations, that are in agreement with the experimental observations obtained by Anderson et al. (2000), who concluded that anti-angiogenic factors reduce the tumor cell development. Results obtained here are in line with the three types of anti-angiogenesis given by Orme and Chaplain (1997). Our results indicate the effectiveness of anti-angiogenesis as a treatment to prevent vascularization of non-cancerous tumors.

References

- A. Stephanou, S.R. McDougall, A.R.A. Anderson, M.A.J. Chaplain. (2005). Mathematical modelling of flow in 2D and 3D vascular networks: Applications to antiangiogenic and chemotherapeutic drug strategies. *Mathematical and Computer Modelling*. 41, (10), 1137–1156.
- A.R.A. Anderson, and M.A.J. Chaplain. (1998). Continuous and Discrete Mathematical Models of Tumor-induced Angiogenesis. *Bulletin of Mathematical Biology*, 60, (5), 857–900.
- A.R.A. Anderson, M.A.J. Chaplain, C. Garcia-Reimbert and C.A. Vargas (2000). Gradient Driven Mathematical Model of Anti-Angiogenesis. *Mathematical and Computer Modelling*. 32, (10), 1141–1152.

- J.M.O. Eloundou.(2011). Mathematical Modelling of the Stages of the Tumor Growth and Non Local Interactions in Cancer Invasion.Master Thesis, University of Stellenbosch.
- M. M. Panchal and T. R. Singh (2019). Finite Difference Schemes to Nonlinear Parabolic System of Cancer Invasion and Interaction of Cancer Cell with Surrounding Tissues. *Int. Journal Of Advanced technology in Engineering and sciences*, 7 (2),01-11.
- M. M. Panchal and T. R. Singh (2019). Numerical solution of the mathematical modelling of tumor growth during the process of angiogenesis. *Int. Journal of Recent Scientific Research*. 2 (4c), 38010-38014. DOI: <http://dx.doi.org/10.24327/ijrsr.2019.1004.3341>
- M.E. Orme and M.A.J. Chaplain. (1997). Two-dimensional models of tumor angiogenesis and anti-angiogenesis strategies. *IMA Journal of Mathematics Applied in Medicine Biology*. 14, (3), 189–205.
- M.J. Holmes and B.D. Sleeman. (1999). A Mathematical Model of Tumor Angiogenesis Incorporating Cellular Traction and Viscoelastic Effects. *Journal of Theoretical Biology*. Volume 202, Issue 2, 21 January 2000, Pages 95-112.
- S. Sanga, J.P. Sinek, H. B. Frieboes, M. Ferrari, J.P. Fruehauf and V. Cristini. (2006). Mathematical modeling of cancer progression and response to chemotherapy. *Expert Rev. Anticancer*. 6, (10), 1361—1376.
- T. Alarcon, H. Byrne , P. Maini and J. Panovska. (2005). Mathematical Modelling of Angiogenesis and Vascular Adaptation. In R Paton and L McNamara (Eds). *Multidisciplinary Approaches to Theory in Medicine*. Elsevier. Amsterdam. 3, 369–387
- U. Ledzewicz, and H. Schattler. (2008). Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis. *Journal of Theoretical Biology*. 252, (2), 295–312
- World Cancer Report. (2014). Global battle against cancer won't be won with treatment alone. *Epidemiology/Etiology/Cancer Prevention*. European Society for Medical Oncology.