

Fig. 1: Angiogenesis process within solid tumor

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 by Eloundou, the field of oncology has been revitalized by anti-angiogenic 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 2-3 mm 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 own. 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. 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, etc., 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 (Fig. 1).

**Anti-angiogenic agent:** In recent years, the focus of cancer treatments has shifted dramatically. Up until the past 10-15 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 (Panchal and Singh, 2019a, b), 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 study are for the anti-angiogenic 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 (Holmes and Sleeman, 2000; Panchal and Singh, 2019a, b; Anderson and Chaplain, 1998).

## MATERIALS AND METHODS

**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), Holmes and Sleeman (2000) and Panchal and Singh (2019a, b). 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 study. 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:

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

Where:

$\alpha$  = The decay rate

$K_o$  = Anti-angiogenic factors reaction constant

$\lambda$  = 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 study builds on the experimental and theoretical work described by Anderson *et al.* (2000).

In this research, the model to govern the development of endothelial cells during anti-angiogenesis is based on diffusion, the chemotactic effect by the tumor angiogenic factors, cell mitosis, endothelial cell-cell adherence through fibronectin, the chemotactic 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 function for tumor angiogenic factors. The function for anti-angiogenic factors is as follows:

$$\mu(H) = \mu_o H \frac{K_o}{(K_o + H)}$$

where  $\mu_o$  (a positive constant coefficient) is the anti-angiogenic chemotactic factor indicating strength of the chemotactic response because of angiostatin and  $K_o$  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:

$$\begin{aligned} \frac{\partial C}{\partial t} = & D_C \nabla^2 C - \nabla \chi_i \frac{K_1}{K_1 + C} C \nabla G - \nabla \rho_1 C \nabla F + \\ & \rho C \left( 1 - \frac{C}{C_o} \right) \left( \frac{G^* - G}{G_o} \right) - \mu_o \frac{K_o \partial^2 H C}{(K_o + H) \partial x^2} - \\ & \mu_o \frac{K_o}{K_o + H} H \frac{\partial C}{\partial x} - \mu_1 C \end{aligned} \quad (4)$$

The boundary conditions for AAF concentration satisfies given below:

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

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 Eq. 4 which is a nonlinear parabolic partial differential equation, the implicit finite difference method have been implemented.

**Non-dimensionalizing the system:** Non-dimensionalization 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 Eq. 4 is been non-dimensionalized by rescaling the distance between the blood vessel and the tumor with  $L$ , time with  $\tau = L^2/D_G$  (where,  $D_G$  is the tumor angiogenic factor diffusion coefficient), endothelial cell density with  $C_o$  and tumor angiogenic factors  $G_o$  and anti-angiogenesis concentrations with  $H_o$ , respectively. So, taking:

$$\begin{aligned} H^* = \frac{H}{H_o}, d_H = \frac{TD_H}{L^2}, \alpha = \frac{T\alpha_1}{L^2}, \\ \varpi = \beta T \text{ and } K_H = \frac{TK_o}{L^2}, l = \frac{TK_o(O)}{L^2} \end{aligned}$$

and other variables as they were set by Panchal and Singh (2019a, b) and for simplicity dropping the bars for notations, then the non-dimensionalised equation of anti-angiogenesis factor becomes:

$$\frac{\partial H}{\partial t} = d_H \frac{\partial^2 H}{\partial x^2} - \lambda H - \varpi \frac{HC}{(1+H)} \quad (5)$$

Endothelial cells concentration becomes:

$$\begin{aligned} \frac{\partial C}{\partial t} = & d_c \frac{\partial^2 C}{\partial x^2} - \chi(l) \frac{K_1 C \partial^2 G}{(K_1 + C) \partial x^2} - \chi(l) \frac{K_1}{K_1 + e} \times \frac{\partial C \partial G}{\partial x^2} - \\ & \rho C \frac{\partial^2 F}{\partial x^2} - \rho \frac{\partial C \partial F}{\partial x^2} + \rho_o C (1 - C) E(G) - \psi C - \\ & \mu_o C \frac{\partial H^2}{\partial x^2} - \mu_o \frac{\partial C \partial H}{\partial x^2} \end{aligned} \quad (6)$$

**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:

$$\begin{aligned} \frac{H_i^{j+1} - H_i^j}{\Delta t} = & dH \frac{H_{i-1}^{j+1} - 2H_i^{j+1} + H_{i+1}^{j+1} + H_{i-1}^j - 2H_i^j + H_{i+1}^j}{2\Delta x^2} - \\ & \beta \frac{(H_i^{j+1} - H_i^j)}{2} - \varpi \frac{(H_i^{j+1} - H_i^j) C_i^j}{2(1+H_i^j)} \end{aligned} \quad (7)$$

where,  $g = \Delta t d_u / 2 \Delta x^2$ ,  $h = \Delta t \lambda / 2$  and  $m_i^j = \Delta t \omega e_i^j / 2(1 + C_i^j)$ , substituting  $g$ ,  $h$  and  $m$  the above equation can be express in a tridiagonal form:

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

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 Eq. 4:

$$\begin{aligned} \frac{\partial C}{\partial t} = d_c \frac{d^2 c}{\partial x^2} - \chi(1) \frac{K_1 C \partial A^2}{(K_1 + C) \partial x^2} - \chi(1) \frac{K_1}{K_1 + e} \times \frac{\partial C \partial A}{\partial x^2} - \rho C \frac{\partial F^2}{\partial x^2} - \rho \frac{\partial C \partial F}{\partial x^2} + \rho_o C(1 - C) E(G) - \\ \psi E - \mu_o \frac{K_o}{K_o + H} C \frac{\partial H^2}{\partial x^2} - \mu_o \frac{K_o}{K_o + H} \frac{\partial C \partial H}{\partial x^2} \end{aligned} \quad (8)$$

Applying the discretization by the finite difference scheme to Eq. 9, we obtain:

$$\begin{aligned} \frac{C_i^{j+1} - C_i^j}{\Delta t} = d_c \frac{(C_{i-1}^{j+1} - 2C_i^{j+1} + C_{i+1}^{j+1} + C_{i-1}^j - 2C_i^j + C_{i+1}^j)}{2(\Delta x)^2} - \chi(1) \frac{K_1 (C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x (K_1 + C_i^j)} \times \\ \frac{\{G_{i+1}^{j+1} - G_{i-1}^{j+1} + G_{i-1}^j\}}{4\Delta x} - \chi(1) \frac{K_1 C_i^j}{K_1 + C_i^j} \times \frac{(G_{i+1}^{j+1} - 2G_i^{j+1} + G_{i+1}^j + G_{i-1}^j - 2G_i^j + G_{i+1}^j)}{2(\Delta x)^2} - \\ \rho \frac{(C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x} \times \frac{(F_{i+1}^{j+1} - F_{i-1}^{j+1} + F_{i+1}^j - F_{i-1}^j)}{4\Delta x} - \rho e_i^j \frac{(F_{i-1}^{j+1} - 2F_i^{j+1} + F_{i+1}^{j+1} + F_{i-1}^j - 2F_i^j + F_{i+1}^j)}{2(\Delta x)^2} \\ \rho_o C_i^j (1 - C_i^j) E(G) + \Psi \left( \frac{C_{i+1}^{j+1} - C_i^{j+1}}{2} \right) - \sigma \frac{K_H}{K_H + H_i^j} \frac{C_i^j (H_{i+1}^{j+1} - 2H_i^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - 2H_i^j - H_{i-1}^j)}{2(\Delta x)^2} - \\ \alpha \frac{K_H}{K_H + H_i^j} \frac{(H_{i+1}^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - H_{i-1}^j)}{4\Delta x} \times \frac{(C_{i+1}^{j+1} - C_{i-1}^{j+1} + C_{i+1}^j - C_{i-1}^j)}{4\Delta x} \end{aligned} \quad (9)$$

By substituting:

$$\begin{aligned} \bar{A} = \frac{\Delta t d_c}{2(\Delta x)^2}, \quad \bar{B}_i^j = \frac{\chi(1)(K_1) \Delta t (G_{i+1}^{j+1} - G_{i-1}^{j+1} + G_{i+1}^j - G_{i-1}^j)}{16(\Delta x)^2 (K_1 + C_i^j)} \\ \bar{C}_i^j = \frac{\chi(1) K_1 \Delta t (G_{i+1}^{j+1} - 2G_i^{j+1} + G_{i+1}^j + G_{i-1}^j - 2G_i^j + G_{i+1}^j)}{2(\Delta x)^2 (K_1 + C_i^j)}, \quad \bar{D}_i^j = \frac{\rho \Delta t (F_{i+1}^{j+1} - F_{i-1}^{j+1} + F_{i+1}^j - F_{i-1}^j)}{16(\Delta x)^2} \\ \bar{E}_i^j = \frac{\rho \Delta t (F_{i+1}^{j+1} - 2F_i^{j+1} + F_{i+1}^j + F_{i-1}^j - 2F_i^j - F_{i+1}^j)}{2(\Delta x)^2}, \quad \bar{F} = \frac{\Psi \Delta t}{2}, \quad \bar{G}_i^j = \rho_o \Delta t (1 - C_i^j) E(G_i^j) \\ \bar{H}_i^j = \Delta t \mu_o \frac{K_H}{K_H + H_i^j} \frac{\{H_{i+1}^{j+1} - 2H_i^{j+1} - H_{i-1}^{j+1} + H_{i+1}^j - 2H_i^j - H_{i-1}^j\}}{2(\Delta x)^2} \\ \bar{I}_i^j = \Delta t \mu_o \frac{K_H}{K_H + H_i^j} \frac{\{H_{i+1}^{j+1} - H_{i-1}^{j+1} - H_{i-1}^j + H_{i+1}^j - 2H_i^j - H_{i-1}^j\}}{16(\Delta x)^2} \end{aligned}$$

and rearranging terms Eq. 9 can be written in a tridiagonal matrix form then becomes:

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

Where:

$$\begin{aligned} P_c &= 1 + 2\bar{A} + \bar{F}, (P_d)_i^j = -\bar{A} + \bar{B}_i^j + \bar{D}_i^j + \bar{I}_i^j, \\ (P_e)_i^j &= -\bar{A} - \bar{B}_i^j - \bar{D}_i^j - \bar{I}_i^j, (P_f)_i^j = 1 - \\ 2\bar{A} - \bar{C}_i^j - \bar{E}_i^j + \bar{G}_i^j + \bar{F}_i^j - \bar{H}_i^j, (P_g)_i^j &= \\ \bar{A} - \bar{B}_i^j - \bar{D}_i^j - \bar{I}_i^j \end{aligned}$$

## 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 by Panchal and Singh (2019a, b).

Figure 2 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 research. The results of the simulation are shown in Fig. 3. Results indicate that as

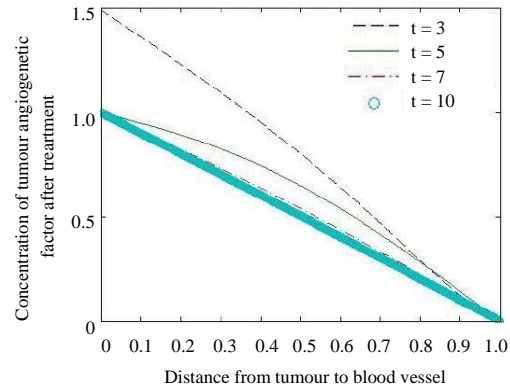


Fig. 2: Concentration of TAF after in present of anti-angiogenic factor

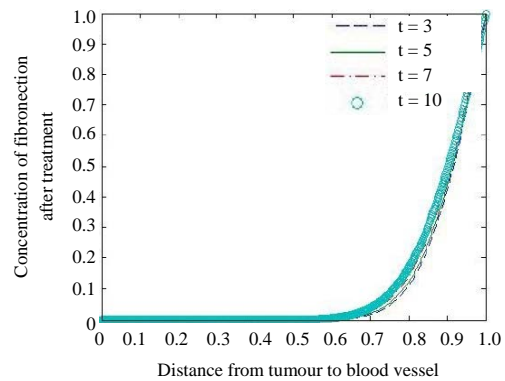


Fig. 3: Fibronectin concentration in present of anti-angiogenic factor

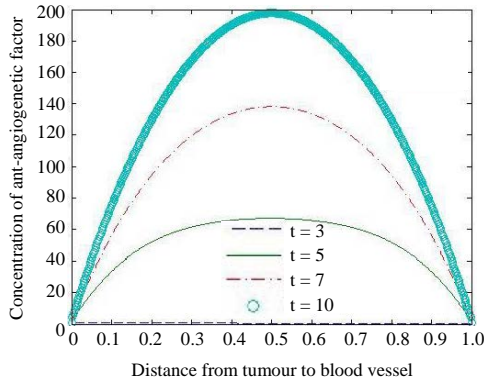


Fig. 4: Anti-Angiogenic Factor (AAF) concentration

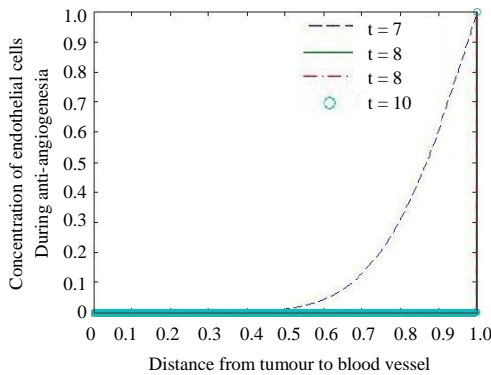


Fig. 5: Endothelial cell concentration in present of anti-angiogenic factor

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. 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 anti-angiogenic factor when the value  $K$  varies are given in Fig. 4. Figure 4 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 Fig. 5 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

Table 1: Parametric values for AAF

|                                                 |         |                       |
|-------------------------------------------------|---------|-----------------------|
| Diffusion coefficient of anti-angiogenic factor | $d_H$   | $1.79 \times 10^{-4}$ |
| Decay rate of anti-angiogenic factor            | $\beta$ | $5.0 \times 10^{-2}$  |
| Anti-angiogenic factor uptake rate              | $r(0)$  | $1.0 \times 10^{-3}$  |
| Anti-angiogenic factor maximum constant rate    | $q$     | $3.0 \times 10^{-1}$  |

anti-angiogenesis as a treatment, the treatment is effective in inhibiting and destroying endothelial cells from reaching the tumor.

## CONCLUSION

During angiogenesis results showed that as time progresses the concentration of tumor angiogenic 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.

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