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Continuous Models of Tumor Induced Angiogenesis and Anti-Angiogenesis Strategy

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Abstract Continuous models of tumor-induced angiogenesis have been discussed and numerical simulations of one model have been carried out and the figures corresponding to various types of behaviors of the biological event have been shown. Actual dynamics of the biological process can be visualized with the help of figures generated. We also discussed the anti-angiogenesis strategy by identifying factors responsible for angiogenesis, and targeting such factors to control the process. The prevalent drugs along with their mathematical parameters have been discussed.

Keywords: Angiogenesis; TAF; Tip Density; Elimination constant.

1. INTRODUCTION

Cancer is one of the major reasons of mortality and morbidity all over the world. The developed countries are spending huge amount of money in cancer research. It is estimated that 1 out of 8 persons in the developed countries and 1 out of 20 persons in the developing countries are suffering from cancer. Several eminent personalities including Edward Lorenz, the Father of Chaos, and Steve Jobs, founder of i-phone, lost their life to cancer. In India alone, nearly 11 lakh people suffer from cancer and about 5 lakh people die due to it every year. Scientists are working hard to find a pattern of cell behavior and proliferation of transformed cells in different types of cancers.

It is noteworthy that besides many scientific tools, the subject of mathematical modeling and numerical analysis have also played a significant role in cancer research. Balding and McElwain (1985) developed a mathematical model for tumor-induced capillary growth. Chaplain and Stuart (1991) modeled diffusion of chemical secreted by tumor into the surrounding tissue. A noteworthy contribution to tumor modeling was made by Sachs et al. (2001), wherein they

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discussed some classical growth equations and interplay between tumor and surrounding tissue during cancer growth and therapy. Sheratt and Chaplain (2001) extensively discussed the early development of solid tumor using mathematical modeling. Swanson (2003) reviewed mathematical modeling of brain tumors both untreated and treated after having undergone chemotherapy or surgical resection. Gerisch and Chaplain (2008) formulated a continuum model of cancer cell invasion of tissue which incorporates the processes of cell-cell and cell-matrix invasion.

Bryne and Chaplain (1995) developed a mathematical model for tumor angiogenesis, wherein a tumor recruits blood vessels from the neighboring vasculature, thereby getting nutrients and a mode for metastasis.

Balding and McElwain (1985) solved this model which was developed by the method of lines, which converts the modeled equations into a larger system of ordinary differential equations. Bryne and Chaplain (1995) solved the model with the help of NAG FORTRAN routine DO3PGF.

In this paper, we discuss three models of tumor induced angiogenesis and carry out the numerical simulations of tumor angiogenesis model of Bryne and Chaplain (1995) using the Mathematica software. We have shown the figures in case of successful angiogenesis, unsuccessful angiogenesis and slow angiogenesis. We further discuss anti – angiogenesis strategy, by identifying the various factors responsible for angiogenesis, and targeting these factors to control and slow down neo-vascularization.

2. THE TUMOR ANGIOGENESIS MODELS

Cancer is a complicated phenomenon, which arises due to interactions between cells and several biochemical substances. Tumor growth may be studied in two different phases: Avascular phase-the initial phase, and the Vascular phase-in which the tumor tries to recruit blood supply from the main blood stream. This process of formation of blood vessels is called angiogenesis, which is necessary for cancer cells to proliferate and spread to various body parts. The tumor secretes a chemical into the surrounding host tissue, which causes the formation of blood capillaries. This chemical is called Tumor Angiogenesis Factor (TAF). Edelstein (1982) developed a fungal growth model, based on which Bryne and Chaplain (1995) developed their model for tumor induced neovascularisation. Here we discuss this model in detail, followed by a quick summary of the other two models.

MODEL-I

The process of angiogenesis takes place in the following three stages:

1. The basal lamina degrades in response to TAF.
2. The blood vessels are formed and are moved towards the tumor.
3. The blood vessels penetrate the tumor.

The second stage of angiogenesis is most crucial for a tumor to obtain nutrients, proliferate and metastasize, and here we concentrate on this stage. This model describes the process of angiogenesis in terms of the following three variables.

c : representing the chemical substance that is secreted into the surrounding tissue by the tumor, also known as TAF.

ρ : denoting the vessel density. In response to TAF, the basal lamina degrades and capillary vessels are formed, which advance towards the tumor.
n : representing the tip density, i.e. the number of tips per unit cross sectional area in a plane perpendicular to the direction of motion. The vessels join together to form a closed network, for the blood circulation to occur. Tips are formed at the leading front. The tips advance further and finally penetrate the tumor after which this model is no longer valid.

We next describe the system of differential equations governing the model.

The equation for vessel density:

It is assumed that vessel density can increase only by the movement of the tips, so that

$$\frac{\partial \rho}{\partial t} = - n(x, t)\nu(x, t) - d(\rho)$$

where $\rho(x, t)$ is the capillary density in units of capillary length per unit area, $n(x, t)$ is the tip density in units of tips per unit area, $\nu(x, t)$ is the velocity of the tips, and $d(\rho)$is the death rate of capillaries in units of capillary length per unit area per unit time.

Vascular decay is also a feature of tumor induced vascularization. Eddy and Cassarett (1973) observed that some of the debris from the breakdown of established vessels may be used to provide material for growth elsewhere. If it is assumed that a fixed proportion γ_1 of branches are broken down in each time unit, then

$$d = \gamma_1 \rho$$

The equation for tip density n(x, t): is given by

$$\frac{\partial n}{\partial t} = \frac{\partial (n,\nu)}{\partial t} + \sigma$$

where σ is the net tip creation rate in units of tips per unit area per unit time; the net tip creation rate is a balance between tip creation σ_c and tip annihilation σ_a, in units of tips per unit area per unit time

In undisturbed state, the limbal vasculature consists of interconnected vessels with no free tips. Tips are produced when the vessels are stimulated by

TAF. Tip proliferation arises from secondary branching behind the leading tip density front. Once the migrating vasculature has advanced towards the tumor, tip proliferation at the leading vascular edge multiplies rapidly. We assume the existence of a critical TAF concentration c_P such that when $c > c_P$ the tip proliferation occurs. Following Bryne and Chaplain (1995), we have taken tip creation rate proportional to the TAF concentration and the tip density. Hence, $\sigma_c \propto \alpha_1 H(c - c_P) nc$, where α_1 is the rate of secondary tip proliferation, per unit TAF concentration, per tip, when the TAF concentration is sufficiently large, and H(.) is the Heaviside step function given by

$$H(x) = \begin{cases} 1, & \text{if } x > 0 \\ 0, & \text{if } x \leq 0 \end{cases}$$

$$\therefore \ \sigma_c = \alpha_0 c \rho + \alpha_1 H(c - c_p) n c,$$

The first term of above equation is the contribution of secondary branching, with α_0 the rate of appearance of tips per unit area per unit TAF concentration for a unit length of branch.

In the literature, three models of tip annihilation have been proposed, viz., tip-to-tip anastomosis, tip-to-branch anastomosis, and tip death due to over-crowding.

Tip-to-branch anastomosis is necessary to create an interconnected network of vessels, for the blood flow to occur. Also, tip annihilation is dominant in area of high capillary density so as to prevent unnecessary growth.

Here we consider tip annihilation, due to tip-to-branch anastomosis, modeled as

$$\sigma_a = -\beta_1 \rho n$$

where β_1 is a constant, and has units of tips fused per unit density per unit length of branch perunit time.

Thus,

$$\sigma = \sigma_c + \sigma_a$$
$$= \alpha_0 c \rho + \alpha_1 H(c - c_p) n c - \beta_1 \rho n$$

According to Edelstein (1982) model for fungal growth, the tip speed v is constant. However, there are evidences that the tip extension is influenced by the presence of TAF, see Balding and McElwain (1985). Therefore, the cell flux J consists of two terms, due to random motion and due to chemotaxis

$$J(x,t) = J_{\text{random}} + J_{\text{chemotactic}}$$
$$= -\mu_1 \frac{\partial n}{\partial x} + \chi_1 n \frac{\partial c}{\partial x},$$

where μ_1 is the motility coefficient, χ_1 is the chemotactic coefficient. Thus, $J = n\,\nu$ implies

$$\nu = -\mu_1 \frac{1}{n}\frac{\partial n}{\partial x} + \chi_1 \frac{\partial c}{\partial x},$$

We finally have

$$\frac{\partial \rho}{\partial t} = \mu_1 \frac{\partial n}{\partial x} - n\chi_1 \frac{\partial c}{\partial x} - \gamma_1 \rho,$$

$$\frac{\partial n}{\partial t} = \mu_1 \frac{\partial^2 n}{\partial x^2} - \chi_1 \frac{\partial}{\partial x}\left(n \frac{\partial c}{\partial x}\right) + \alpha_0 c\,\rho + \alpha_1 H(c - c_p) n\,c - \beta_1 \rho n$$

To use above equations, we need an expression for the TAF concentration c(x, t). We assume that

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \lambda_1 c - \alpha_1 H(c - c_p) n\,c$$

where D is the diffusion coefficient of TAF and λ_1 is the natural decay rat.

We get the following system of equations to solve

$$\frac{\partial \rho}{\partial t} = \mu_1 \frac{\partial n}{\partial x} - n\,\chi_1 \frac{\partial c}{\partial x} - \gamma_1 \rho$$

$$\frac{\partial n}{\partial t} = \mu_1 \frac{\partial^2 n}{\partial x^2} - \chi_1 \frac{\partial}{\partial x}\left(n \frac{\partial c}{\partial x}\right) + \alpha_0\, c\,\rho + \alpha_1\, H(c - c_p) n\,c - \beta_1 \rho n$$

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \lambda_1\, c - \alpha_1\, H(c - c_p) n\,c$$

To close the system defined above, we introduce boundary and initial conditions. At the tumor, TAF concentration = c_0, tip density = 0. At the limbus, TAF concentration = 0, tip density decays exponentially to 0, vessel density decays exponentially to ρ_{min} at the rate k s^{-1}.

The vessel density at the limbus does not fall to zero, because from experiments in Paweletz and Knierim (1989), Stokes and Lauffenburger (1991), it is suggested that if the front advancing towards the tumor has to maintain contact with the limbus, then the vessel density at limbus must not fall below some value ρ_{min}.

Consequently, the boundary and initial conditions are as follows:

$$\rho(L,t) = \rho_{min} + (\rho_L - \rho_{min})e^{-kt}, \rho(x,0) = 0 \quad \text{for } 0 \le x \le L,\ \rho(L,0) = \rho_L$$

$$n(0,t) = 0, n(L,t) = n_L e^{-kt}, n(x,0) = 0 \quad \text{for} \quad 0 \le x \le L, n(L,0) = n_L$$

$$c(0,t) = c_0, c(L,t) = 0,\ c(x,0) = 0 \quad \text{for} \quad 0 \le x \le L$$

where ρ_L is the density of the limbal vessels, and L is the distance between the tumor and the nearest limbal vessels.

Further, this system is non – dimensionalised and for this purpose, the reference variables are L and $\tau = \frac{L^2}{D}$, which is the time for TAF to diffuse from the tumor to the limbus.

The governing equations transform to:

$$\frac{\partial \rho}{\partial t} = \mu \frac{\partial n}{\partial x} - \chi n \frac{\partial c}{\partial x} - \gamma \rho,$$

$$\frac{\partial n}{\partial t} = \mu \frac{\partial^2 n}{\partial x^2} - \chi \frac{\partial}{\partial x}\left(n \frac{\partial c}{\partial x} \right) + \alpha_0 \rho c + \alpha_1 H(c - c_P) n c - \beta \rho n$$

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} - \lambda c - \alpha_1 H(c - c_p) n c$$

subject to

$$\rho(1,t) = \rho_{min} + (1 - \rho_{min}) e^{-kt}, \rho(x,0) = 0 \quad \text{for} \quad 0 \le x \le 1, \ \rho(1,0) = 1$$

$$n(0,t) = 0, \ n(1,t) = n_L \ e^{-kt}, n(x,0) = 0 \quad \text{for} \quad 0 \le x \le 1, \ n(1,0) = n_L$$

$$c(0,t) = 1, c(1,t) = 0, c(x,0) = 0 \quad \text{for } 0 \le x \le 1.$$

According to Balding and McElwain (1985) and Folkman (1976), 14 days is the average time for vascularization to occur. Hence, following Bryne and Chaplain (1995), we take $\tau \sim 3.5$ days. If the distance between tumor and limbus is 3 mm, then this leads to an estimate of diffusion coefficient $D \sim 2.9 \times 10^{-7}$ cm^2 s^{-1}.

The model discussed above takes into account the effect of TAF on the basal lamina and describes motion of capillary sprouts as a directed response towards the tumor.

MODEL II

The model of tumor induced angiogenesis, described above, however does not take into account the role of extracellular matrix in capillary formation. Further improvement in this work was made by Anderson and Chaplain (1998), and they developed the model of angiogenesis with focus on 3 variables : endothelial cells, TAF and fibronectin.

Fibronectin is a protein of the extracellular matrix and it plays an important role in cell adhesion (binding of a cell to a surface, extracellular matrix or another cell), growth, migration and differentiation.

Interactions between the endothelial cells and the extracellular matrix are very important and directly affect cell migration.

Haptotaxis is the directed response of endothelial cells in a fibronectin field.

Thus, the motion of endothelial cells is influenced by 3 factors: random motility, haptotaxis and chemotaxis (in response to TAF).

$\therefore$ The endothelial cell flux J_n is given by:

$$J_n = J_{random} + J_{chemo} + J_{hapto}$$

Here, n denotes the endothelial cell density per unit area, c, the TAF concentration, and f, the fibronectin concentration.

$J_{random} = -D_n \nabla n$, where D_n is a positive constant, the cell random motility coefficient.

$J_{chemo} = \chi(c) n \nabla c$, where $\chi(c)$ is a chemotactic function and $\chi(c) = \chi_0 \dfrac{k_1}{k_1 + c}$

In Model-I, $\chi(c)$ was taken as a constant. The form of $\chi(c)$ here suggests that chemotactic sensitivity decreases when concentration of TAF increases.

The effect of fibronectin on the endothelial cells is modeled by the haptotactic flux:

$$J_{hapto} = \rho_0 \, n \nabla f, \text{ where } \rho_0 > 0$$

The conservation equation for the endothelial cell density is given by:

$$\frac{\partial n}{\partial t} + \nabla . J_n = 0$$

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \nabla . (\chi(c) n \nabla c) - \nabla . \rho_0 n \nabla f)$$

The complete system describing the interactions of the endothelial cells, TAF and fibronectin is given by:

$$\frac{\partial n}{\partial t} = \overbrace{D_n \nabla^2 n}^{\text{random motility}} - \overbrace{\nabla . \left(\frac{\chi_0 k_1}{k_1 + c} n \nabla c \right)}^{\text{chemotaxis}} - \overbrace{\nabla . (\rho_0 n \nabla f)}^{\text{haptotaxis}}$$

$$\frac{\partial f}{\partial t} = \overbrace{\omega n}^{\text{production}} - \overbrace{\mu n f}^{\text{uptake}}$$

$$\frac{\partial c}{\partial t} = \overbrace{\lambda n c}^{\text{uptake}}.$$

The capillary sprouts remain within the domain of tissue under consideration, and so the boundary condition takes the form:

$\underline{\zeta}.(-D_n \nabla n + n(\chi(c)\nabla c + \rho_0 \nabla f)) = 0$, where $\underline{\zeta}$ is outward unit normal vector.

The initial conditions have been taken as:

(a) If the tumor is approximately circular and TAF diffuses into the extracellular matrix, then the TAF concentration field may be of the form:

$$c(x,y,0) = \begin{cases} 1 & 0 \le r \le 0.1 \\ \dfrac{(v-r)^2}{v-0.1} & 0.1 < r \le 1 \end{cases}$$

where ν is a positive constant and r is given by

$$r = \sqrt{(x-1)^2 + (y-\frac{1}{2})^2}$$

assuming the tumor is centered on (1,1/2), with a radius of 0.1.

It is worth mentioning that the equation and initial condition for TAF is essentially the same in the previous model and this model. In the previous model, the diffusion of TAF in the extracellular matrix was taken care of in the equation itself and in this model, it is assumed that the TAF has already diffused into the extracellular matrix, and initial TAF profile is as given above. The initial TAF profile for a larger tumor implant is:

$c(x,y,0) = e^{-\frac{(1-x)^2}{\varepsilon_1}}, (x,y) \in [0,1]\times[0,1]$ where ε_1 is a positive constant.

Both these forms of initial TAF concentration represent decrease in TAF concentration as the distance from the tumor increases.

It is assumed that presence of TAF field leads to rupturing of basal lamina, and plasma fibronectin leaks into the extracellular matrix, and thus, there is high concentration of fibronectin near the parent basal lamina. Thus, the initial fibronectin concentration is taken as:

$f(x,y,0) = ke^{\frac{x^2}{\varepsilon_2}}, (x,y) \in [0,1]\times[0,1]$ where $k < 1$, ε_2 are positive constants.

The initial position of capillary wall is described by:

$$e^{-\frac{x^2}{\varepsilon_3}} \sin^2(6\pi y)$$

This model takes into consideration TAF and fibronectin (a Matrix Metallo Protein), and under the effect of these two, the directional migration of capillaries towards the tumor occurs.

MODEL -III

In another recent work by Travasso *et al.* (2011), the authors have considered the effect of all pro-angiogenic and anti-angiogenic factors, and have modeled the equation for such factors as:

$$\frac{\partial c_i}{\partial t} = \nabla.(D_i(r)\nabla c_i) - \beta_c c_i \rho H(\rho),$$

where c_i represents a growth factor, which is the balance between pro and anti-angiogenesis factors.

The first term of this equation represents migration of growth factor c_i as a result of diffusion.

β_c is the rate of consumption by endothelial cells of c, the sum of the concentrations of all angiogenic factors considered.

H is the Heavyside function.

ρ describes the cells capable of proliferation, but not activated as yet. It takes the value -1 outside the capillary and $+1$ inside it. In areas of high proliferation of endothelial cells, the value of ρ is greater than one.

It is assumed that capillaries are formed as a result of endothelial cell proliferation (in response to c_i) and as a result of directed migration towards the tumor (here termed as interface dynamics).

$\therefore$ Position of capillary = Interface Dynamics + Endothelial cell proliferation.

$$\text{i.e.} \qquad \frac{\partial \rho}{\partial t} = M\nabla^2[-\rho + \rho^3 - \varepsilon\nabla^2\rho] + \alpha_p(c)\rho H(\rho),$$

where M is the mobility coefficient of the endothelial cells.

There is a critical value of c, here denoted by c_p i.e. above which proliferation occurs at a maximum rate $\alpha_P c_P$

For $c < c_P$, the proliferation rate is $\alpha_P c$.

$$\therefore \qquad \alpha_p(c) = \begin{cases} \alpha_p c & \text{for} \quad c < c_p \\ \alpha_p c_P & \text{for} \quad c > c_p \end{cases}$$

ε denotes the width of the capillary vessels.

Tip Velocity: Velocity of the activated cells is modeled as:

$$\nu = \chi\nabla c\left[1 + \left(\frac{G_M}{G} - 1\right) H(G - G_M)\right], \; G \equiv \nabla c,$$

where χ is the chemotactic response of the endothelial cells.

For $G > G_{M,}$ the cells attain their maximum velocity $\chi\ G_{M}$, G_{M}, being a critical value of gradient of c.

Endothelial cell activation occurs at points with large values of both c and ρ.

For activated cells to move, there must be some minimum value of G above which the cell motion occurs.

Based on experimental evidence and mathematical calculations, the authors made the observation that the increase of endothelial cell proliferation leads to an increase of the branch density and vessel density. For low proliferation rates, the vessels are very thin and rarely thick enough for a tip cell to emerge.

Thus, the process of angiogenesis is the result of a delicate balance between proliferation and chemotaxis, and various patterns observed in different experiments is due to variations in concentrations of TAF and MMPs in the ECM.

Here, we have discussed three models of tumor-induced angiogenesis, and all these models describe the process of neovascularization under the effect of three essential components viz. Tumor Angiogenesis Factor(TAF); Matrix Metalloproteins(MMPs),present in the ECM that stimulate angiogenesis, fibronectin being one of them; and directed response of endothelial cells towards the tumor, being modeled as random flux in the above models.

All models depict essentially the same features of the process with minor differences. The third model also takes into account the microscopic details of vessel thickness and capillary diameter in cases of high and low proliferation.

Model-I also discusses in detail secondary branching and secondary tip proliferation, above a critical value of TAF, which is necessary for neovascularization.

We feel that Model-I captures all the macroscopic features of the process of angiogenesis. We perform numerical simulations of this model.

3 NUMERICAL SIMULATIONS

We have carried numerical simulations of this system of equations using Mathematica 7.0. In all figures presented below, the tumor is located at x = 0 and limbus at x = 1.

In figures 1(a), (b), (c), we have shown tip density and vessel density responding to TAF, in case of successful angiogenesis.

We have taken parameters as:

$$\mu = 0.001, \chi = 0.4, \beta = 50, c_p = 0.2, \lambda = 1, \alpha_1 = 10, \alpha_0 = 50, \gamma = 0.25.$$

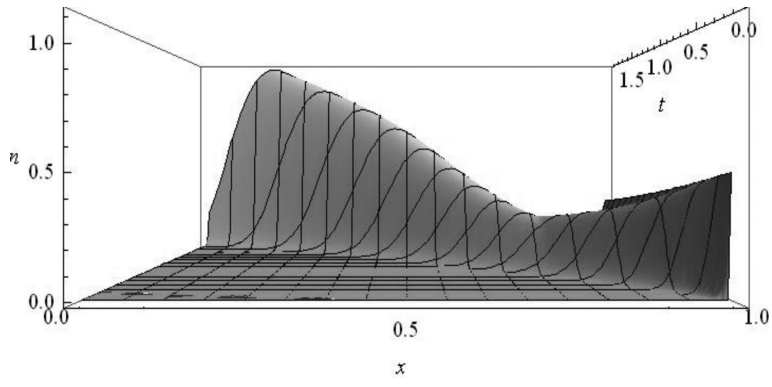


Figure 1(a): Tip density in case of successful angiogenesis

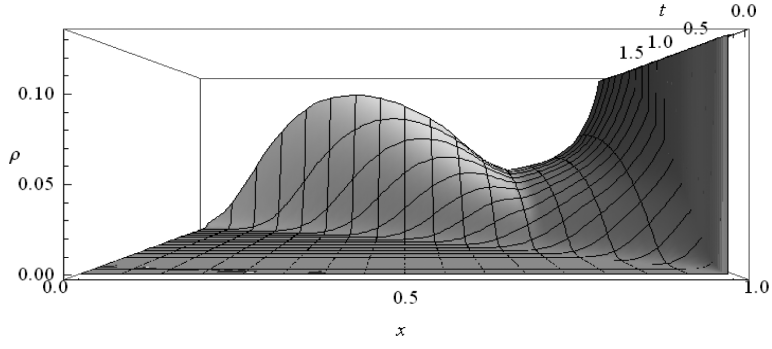


Figure 1(b): Vessel density in case of successful angiogenesis

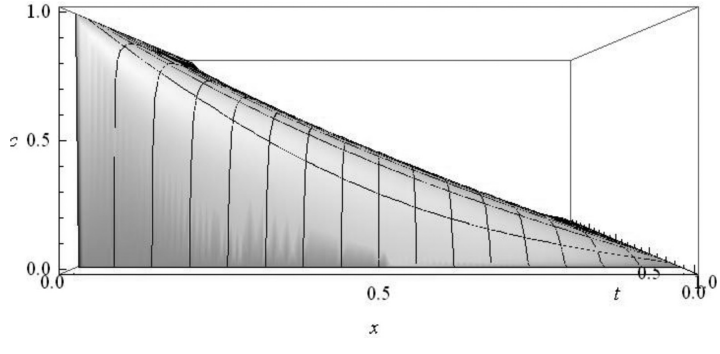


Figure 1(c): TAF concentration

In these figures, we have considered secondary tip proliferation which is necessary for angiogenesis.

In figures 2(a), (b) we have shown tip density profile and vessel density profile in case the parameters λ and c_P are increased to $\lambda = 10$ and $c_P = 0.5$, other parameters remaining the same.

Note that c_P is the critical TAF concentration, such that secondary tip proliferation occurs when $c > c_P$. As is clear from the figures below, neovascularization does not take place in this case.

These figures indicate that the presence of TAF plays a significant role in neovascularization.

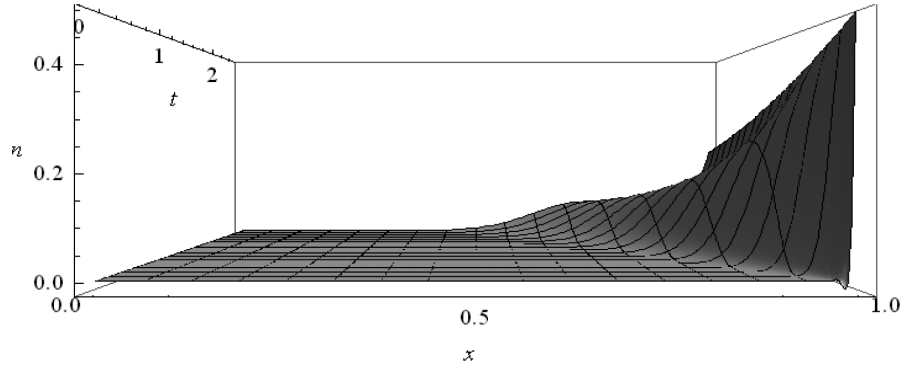


Figure 2(a): Tip density in case of unsuccessful angiogenesis

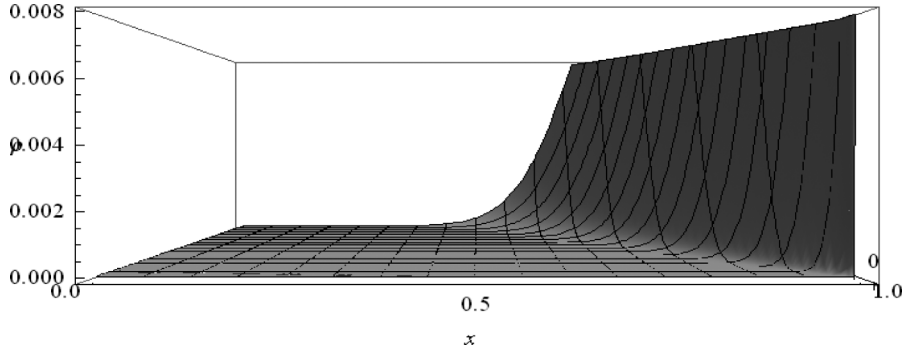


Figure 2(b): Vessel density in unsuccessful angiogenesis

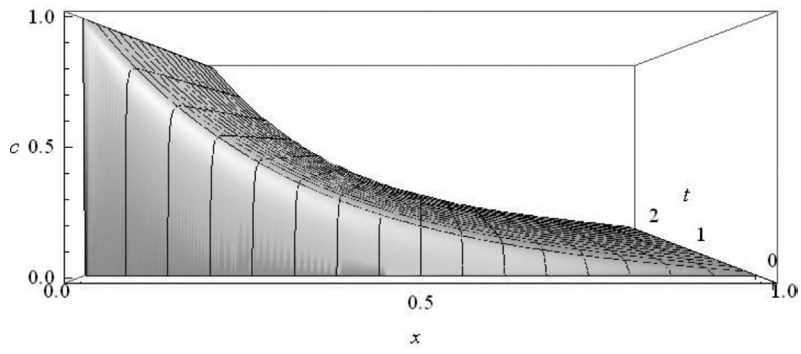


Figure 2(c): TAF concentration in unsuccessful angiogenesis

In next simulations, we have taken secondary tip proliferation rate $\alpha_1 = 0$, taking other parameters as in Figure 1. We note that in this case vascularization does take place, although at a slower rate.

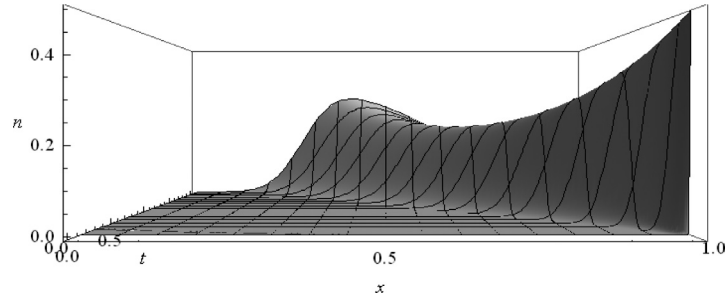


Figure 3(a): Tip density without secondary tip proliferation

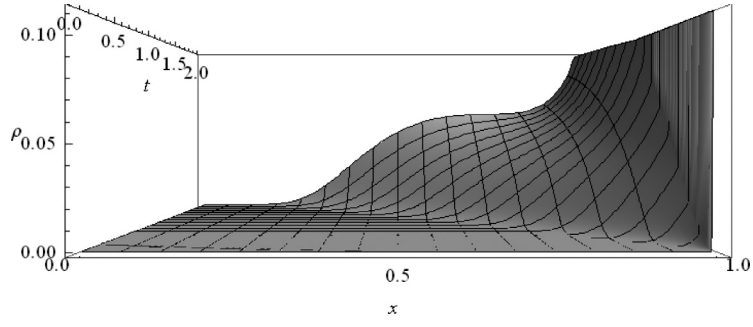


Figure 3(b): Vessel density with $\alpha_1 = 0$

All the figures shown above explain the behavior of vasculature in three different cases of successful angiogenesis, unsuccessful angiogenesis, and slow angiogenesis. In figure 1(a), we see the tip profile advancing towards the tumor at x = 0. The tip number multiplies very fast at the leading edge, as the vasculature advances towards the tumor. The vessel density in figure 1(b) also follows a similar pattern. Thus, the strong presence of a TAF field, and secondary tip proliferation leads to successful angiogenesis.

In figure 2(b), the effect of a weak TAF field is evident, with tip density decaying very fast, as is the case with vessel density in figure 2(b). Clearly, the tips and the vessels do not reach tumor at x = 0, resulting in an unsuccessful angiogenesis. The increase in decay rate of TAF from $\lambda_1 = 1$ in figure 1(c) to $\lambda 1 = 10$ in figure 2(c) led to weakening of the underlying TAF field, which is responsible for unsuccessful angiogenesis. An increase in critical TAF concentration c_P from 0.2 in figures 1(a), 1(b), and 1(c), to $c_P = 0.5$ in figures 2(a), 2(b), and 2(c), is also responsible for the unsuccessful angiogenesis. For $c < 0.5$, there was no secondary tip - proliferation. These two factors combined together resulted in the tumor not getting the blood supply.

Figure 3(a) and 3(b) show slow angiogenesis. This corresponds to the case when we have taken rate of secondary tip proliferation $\alpha_1 = 0$. Comparing figure 1(a) and figure 3(a), we find that secondary tip proliferation in 1(a) led to very fast vascularisation, while in absence of secondary tip proliferation, in figure 3(a), (b) the tips and vessels do reach the tumor at x = 0, but at a very slow rate, and the vessel density and tip density is also less when compared to 1(a) and 1(b). Thus, secondary tip proliferation acts as a catalyst in the process of angiogenesis.

4 ANTI-ANGIOGENESIS STRATEGY

Having studied the process of angiogenesis in detail, we will now discuss the anti- angiogenesis methods. We know that angiogenesis is critical for tumor development, growth and metastasis. There are several proteins in the body that stimulate angiogenesis, viz. The Vascular Endothelial Growth Factor(VEGF), Fibroblast Growth Factor(FGF) and Platelet Derived Growth Factor (PDGF) and their tyrosine kinase receptors are major regulators of angiogenesis.

VEGF is a signal protein produced by cells that stimulates angiogenesis. VEGF's function is to create new blood vessels during embryo development, wound healing and formation of new blood vessels to compensate for blocked vessels. Expression of VEGF is necessary for a tumor to achieve neo-vascularization.

FGF and PDGF are also growth factors that play a significant role in the process of angiogenesis.

Tyrosine kinase is an enzyme, that acts as a regulator in many cellular functions. Tyrosine kinase phosphorylation and dephosphorylation regulate many cellular pathways.

Drugs have been made that target the process of angiogenesis. Anti-angiogenesis strategy plays a crucial role in cancer treatment. While chemotherapy has side effects as it affects normal cells since most chemotherapeutic drugs are DNA synthesis inhibitors resulting in side-affects, anti-angiogenesis treatment has no major known side effects, provided the level of drug in the blood does not exceed the prescribed safe limit.

The drugs are taken either orally, or intravenously.

Drug- decay from blood is a first order process, with decay rate being:

$\frac{dC}{dt} = -k\,C$ where C(t) is the concentration of drug at time t, and k is the elimination constant

The elimination constant *k* is related to the half- life $T_{1/2}$ of the drug by the relation:

$$k = \frac{1n2}{T_{1/2}}$$

Hence, drugs with longer half life stay in the blood stream for longer durations.

These facts may help in designing effective dose amount and schedule.

Several drugs have been identified for their anti-angiogenesis activity.

Here, we discuss 4 recent drugs that are being investigated for their role in cancer treatment:

a) SU6668 : SU6668 is a tyrosine kinase inhibitor which targets VEGF, FGF and PDGF.
   The drug is given orally, and its half-life is approximately 1 hour in humans (Britten et al. 2002).
   The drug is well tolerated at 200 mg/m^2 .
   SU6668 was found to display significant anti-angiogenesis potential in a study (Klenke and Abdollahi, 2007) performed on 10 male severe immunodeficient mice. The authors concluded that SU6668 can induce growth inhibition of various primary tumors.

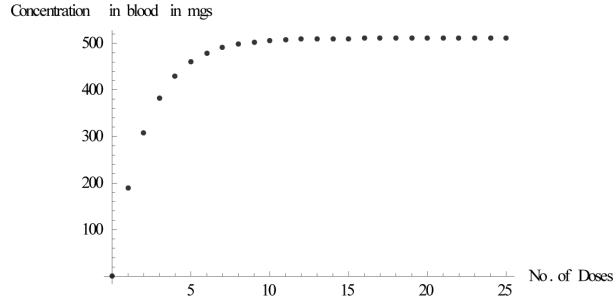
b) Vandetanib (ZD6474) : Vandetanib is a dual inhibitor of VEGF and Epidermal Growth Factor Receptor (EGFR) (Morabito, 2009). It is taken orally, and it inhibits intracellular signaling pathways involved in tumor growth, progression and angiogenesis.
   Maximum tolerated dose is 300 mg.
   ZD6474 has half life of more than 100 hours and a minimum of 28 days of continuous dosing is required to achieve steady state plasma concentration.

It has been found that Vandetanib is a selective inhibitor of VEGF and EGF- stimulated cell proliferation.

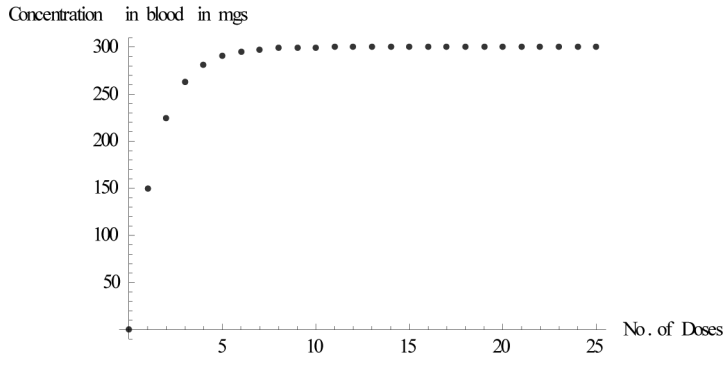
c) BMS-690514: It is a VEGFR and EGFR tyrosine kinase inhibitor, and it has been observed that combining it with radiation could improve the prognosis of tumor (Bahleda, 2008).
Maximun tolerated dose is 200 mg.
Half – life is approximately 11 hours.

d) Bevacizumab (Avastin): It is the most widely used drug for slowing down the process of angiogenesis. It inhibits VEGF-A, a chemical that stimulates angiogenesis. It is licensed to treat various kinds of metastatic cancers (Wikipedia).
Recommended dose is 5mg/kg to 10mg/kg every 2 weeks, or 7.5 mg/kg to 15 mg/kg to be given once every 3 weeks.
It is given intravenously.
It has a long half life of 20 days (range 11-50 days).
It is important to note that elimination constant of a drug varies according to age, and is smaller for old or sick people. When a drug is introduced, it is first tested on animals, followed by clinical trials. We suggest the use of mathematical modeling and simulations in designing effective dose schedule. Such simulations may be patient specific, taking into account their age, sex and any other ailments. The aim of a effective dose schedule is to keep the level of drug in the blood above a effective level and below the safety threshold.

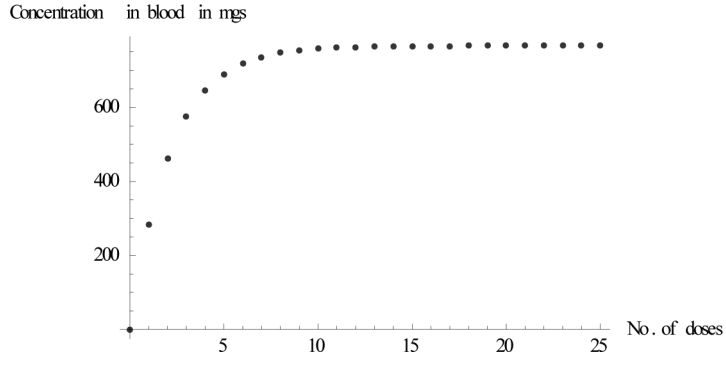
Here we have performed simulations for the drug Avastin, for a 60 Kg male. In all the figures above, the level of drug settles to a constant concentration after about 7-8 doses. It is also to be noted that the amount of drug that reaches the blood stream depends on the mode of drug delivery. For a drug



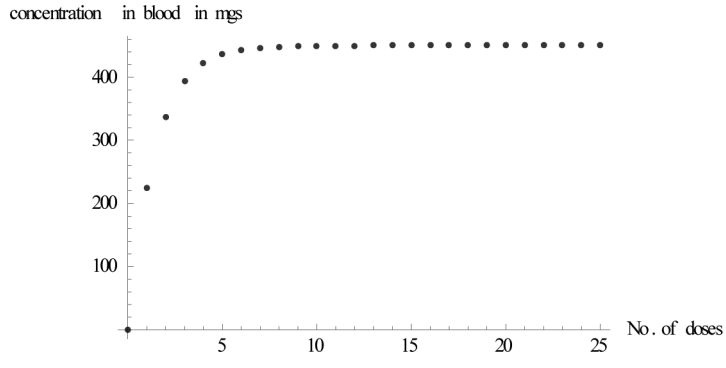
(a) Concentration of Avastin in blood when 5mg/Kg are given after every 2 weeks



(b) Concentration of Avastin in blood when 5mg/Kg are administered after every 3 weeks



(c) Concentration of Avastin in blood when 7.5 mg/Kg are given after every 2 weeks



(d) Concentration of Avastin when 7.5 mg/Kg are given after every 3 weeks

given intravenously, the entire drug reaches the blood stream instantly. In oral delivery, some amount of the drug is lost in absorption while passing through the food tract system. Effective and optimal drug delivery schedules may be designed with the help of these facts.

5. CONCLUSIONS

While making models for biological or physical processes, two important points that need to be worked out are the parameters estimation and of course, the solution (analytical or numerical) of the resultant mathematical model. While parameters estimation requires experimental evidence, obtaining the solution of the model correctly has been an area of active research where the obvious aim is to solve the system effectively. Here, we have studied three models of angiogenesis and solved one such model using Mathematica. We have carried out numerical simulations in three cases: successful angiogenesis, with secondary tip proliferation, unsuccessful angiogenesis, and angiogenesis without secondary tip proliferation. The figures presented earlier clearly demonstrate these cases. The presence of a powerful graphical interface helped us to visualize the behavior of tips and vessels in a very clear way, such that one needed no expertise to understand, something which was not possible in earlier studies reported in literature. We further identified the signaling factors of angiogenesis, and the drugs that target these factors. It is suggested that optimal drug dose, schedule and mode of delivery can be worked out for different kinds of tumors and for individual patients for better results along with radiation etc. with the help of mathematical simulations.

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