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Computational Modeling Of Tumor Angiogenesis

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Computational Modeling of Tumor Angiogenesis

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BY

Santanu Chatterjee

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Computational Modeling of Tumor Angionegesis

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Master's Thesis
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Thesis Advisor : Dr. Suhrit K. Dey

Abstract

Every cancerous tumors generates many number of blood vessels, which are capillary tubes, to draw nutrients and grow. This is angiogenesis. If angiogenesis is inhibited, the tumor dies. It often works like a magic bullet for many cancer patients. Since an infinite number of blood vessels, generated by the tumor, is possible, and some of these vessels may die because of the resistence imparted by the body, genetically, we have assumed that gene expressions from cancer cells as a flux of fluid in the xyz-cartesian frame for mathematical modeling. In this work, a mathematical model for the growth/decay of angiogenesis (developed by Dr. Suhrit K. Dey) has been solved using numerical techniques.

Acknowledgements

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1 Introduction.

Cancer is a collection of disease with a common feature of uncontrolled cell growth[10]. Most tissues in the body can give rise to cancer and might yield several different types of cancer with unique features. The body of a human being maintains homeostasis, a state of dynamic equilibrium. Because of homeostasis, each cell in an organ, after its birth, gets oxygen, food and nutrients to grow and works for the betterment of the whole body and dies at a fixed time. This natural death of body cells is known as apoptosis.The salient feature of the cancer cells is that apoptosis is disrupted, because of the mutation of the cells. The p53 imbalance is one of the inmportant factors for which the control on cell proliferation fails. P53 is a protein present in each cell and it controls the growth and death of a cell during mitosis. In other words, cancer cells escape the usual controls for cell proliferation that is present for each and every cell in the body of a human being. Human body has its own mechanism of tracking down these mutated cells and destroying them. This is done by the immune system of the body. But, when the immune system becomes weak, these mutated cells gain strength, grows uncontrollably and forms tumor.

In the beginning, tumors formed by the cancer cells are avascular, i. e., they do not have their own blood supply and rely upon diffusion from the neighboring vessels for the supply of oxygen and nutrients and the removal of waste products. As the tumor grows, thr demand for the nutrients increase until the flux of nutrients to the tumor is too small to supply entire mass of cells. In response to the shortage of oxygen, some gene expressions take place which code for signalling molecules that are used to induce nearby vessels to grow new capillaries to vascularize the tumor through a process called angiogenesis. These are known as growth factors(e. g. primary vascular endothelial growth factor(VEGF) and basic fibroblast growth factor(b/FGF)). These growth factors diffuse from the tumor cells to the nearby primary vessels, and initiate a cascade of processes, including the activation of endothelial cells that line the blood

vessel walls, inducing them to proliferate and migrate chemotactically towards the tumor. This results in capillary network from the tumor to the nearby primary vessels, thereby bringing essential nutrients to the tumor and providing a shorter route for the spread of cancer cells to the other parts of the body.

Although angiogenesis is crucial to tumor growth, it's not a unique process. During the development of embryo, angiogenesis refines the unstructured capillary network and produce a complex system of large and small vessels. Under normal physiological conditions angiogenesis is regulated by a balance between angiogenesis promoting and angiogenesis inhibiting factors. In normal tissue, angiogenesis is largely absent, except in ovary, throughout the menstrual cycle, during wound healing and during the formation of placenta. It does also occur during a variety of pathological conditions, such as diabetic retinopathy, arthritis etc. Success of tumor angiogenesis provides a plentiful supply of nutrients to the tumor and the tumor grows in size containing a large number of cancer cells.

Other than helping the tumor to grow, angiogenesis also provides the crucial link for the cancer cells to migrate to the other parts of the body. This is called metastasis of cancer. The phenomenon makes many cancers very lethal, as without the metastasis, cancer remains localized and somewhat easily controllable (e. g. without metastasis the cancer may be controllable by removing the tumor by surgery). So, in essence, if angiogenesis can be stopped, the tumor will die. Here, in our model, angiogenesis is considered as a process used for the flux of mass as a tumor grows. The primary objective is the development and subsequent computational study of the mathematical model so that the flux of mass, all around the tumor may be prevented.

Mathematical modeling can provide some significant insights to the process of angiogenesis. So far, many authors have developed mathematical models incorporating the detailed biochemical and physiological information available regarding angiogenesis. In this work, the aim is to solve numerically the continuum model developed by

Dr. S. K. Dey for the growth/decay of angiogenesis in the presence of a mathematical drug.

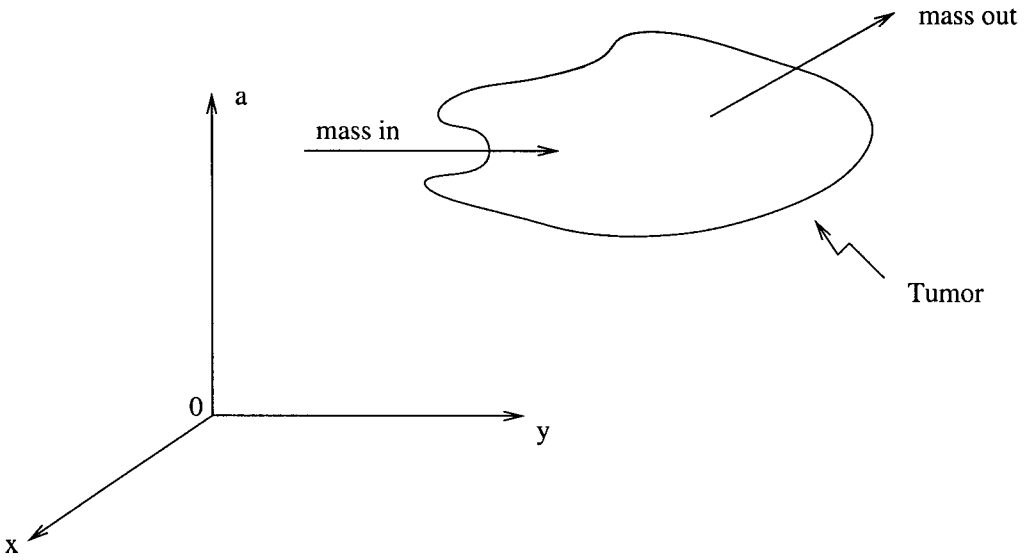


Figure 1: Flow of mass in and out of area surrounding tumor

2 Mathematical Model(Dey)

In this work, we are studying Dey's continuum model. In this model the tumor itself and the growing capillaries are modeled by a slowly developing flux of mass in the field. The human body is a three dimensional configuration[Figure 1]. Thus any in vivo model requires three dimensional geometry. All human body cells are considered as biochemicals and the unit to measure their concentration is same for different kind of cells.

Let f be the flux per unit mass. Let dm = an infinitesimal mass = $\rho\ dV$, where ρ = density of the mass in the tumor and dV = an infinitesimal volume. clearly here $f = f(x,y,z,t)$.

Consider a small change in f as $\Delta f = f(x+\Delta x, y+\Delta y, z+\Delta z, t+\Delta t)$ - $f(x, y, z, t)$.

Then we can write :

$$\frac{df}{dt} = \frac{\partial f}{\partial t} + \frac{\partial f}{\partial x}\frac{dx}{dt} + \frac{\partial f}{\partial y}\frac{dy}{dt} + \frac{\partial f}{\partial z}\frac{dz}{dt} \tag{2.1}$$

Now the flux developing in three dimensional space is proportional to the velocity

of biochemical fluid. So we can argue that

$$f_{alongx} = a_1 \frac{dx}{dt}$$

and

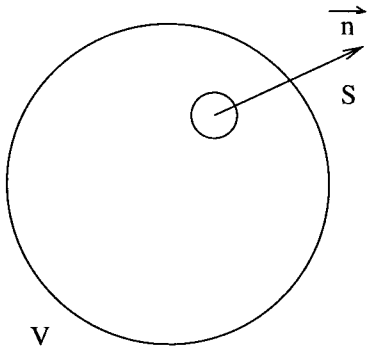
$$f_{alongy} = a_2 \frac{dy}{dt}$$

and

$$f_{alongz} = a_3 \frac{dz}{dt}$$

where a_1, a_2, a_3 are the constants of proportionality. For simplicity the proportionality constants have been taken to be equal to unity. Then (1) can be rewritten as :

$$\frac{df}{dt} = \frac{\partial f}{\partial t} + f\frac{\partial f}{\partial x} + f\frac{\partial f}{\partial y} + f\frac{\partial f}{\partial z} \tag{2.2}$$



Now consider a control volume V enclosed by a surface area S. Let q be the concentration of the biochemical in V. Let $\vec{n}$ be the unit outward normal vector to S. Clearly

$$q = f\,dm = f\rho dV$$

The principle of conservation of mass gives us the following relationship :

$$\frac{d}{dt}\iiint_V f\rho\,dV = \quad \text{Change in the growth of the tumor} \quad - \iint_S \vec{J}\cdot\vec{n}\,dS \tag{2.3}$$

where $\vec{J}$ = flux of f $\vec{n}$ = outward unit normal.

By the divergence theorem

$$\iint_S \vec{J} \cdot \vec{n} \; ds = \iiint_V \vec{\nabla} \; JdV \tag{2.4}$$

Fick's law for the flux of biomass is given by

$$\vec{J} = -\nu \vec{\nabla} f \tag{2.5}$$

Substituting J with (2.5) into (2.4), we get:

$$\iiint_V JdV = -\nu \iiint_V \nabla^2 f dV. \tag{2.6}$$

This gives us

$$\frac{df}{dt} = c + \nu \nabla^2 f \tag{2.7}$$

If, by medication, this change in the growth of the tumor is rendered negative, tumor should shrink, depending on the value of f. Here we must note that the property of the malignant cell is to grow with whatever food it may get from the boundary.

Now our assumption is that the medication is trying to destroy the flux linearly, i.e., the reduction in the growth of the flux is linearly proportional to the amount of flux. Consider μ be the rate at which the medication is trying to reduce the flux per unit time. Then from (6), we can find that the rate of change of flux(assuming the constant c = 0) :

$$\frac{df}{dt} = -\mu f + \nu \nabla^2 f \tag{2.8}$$

Now, if we combine equations (2.2) and (2.8) we get our complete model :

$$\frac{\partial f}{\partial t} + f\frac{\partial f}{\partial x} + f\frac{\partial f}{\partial y} + f\frac{\partial f}{\partial z} = -\mu f + \nu \nabla^2 f \tag{2.9}$$

This is a nonlinear hyperbolic partial differential equation. The term $\nu \nabla^2 f$ denotes the dispersion of the biomass fluid from the primary site and the term $f(\frac{\partial f}{\partial x} +$

$\frac{\partial f}{\partial y} + \frac{\partial f}{\partial z}$) represents the convection phenomena. Here ν = coefficient of dispersion, which means that the biomass are moving from the "more" concentration to the less concentration area.

2.1 Dimension Analysis

The dimension of the flux f is length/time. Therefore, the dimension of the quantity $\frac{\partial f}{\partial t}$ is $length/(time)^2$. The dimension of the convection component is $length/(time)^2$, since the dimension of $\frac{\partial f}{\partial x}$ is $1/(time)$. Now the parameter μ represents the destruction of the flux f over unit time. The dimension of μ is 1/(time). So the dimension of the element $-\mu f$ is $length/(time)^2$. Also the dimension of the dispersion component is $length/(time)^2$. Let L stands for length and T stands for time here. Then the dimension equation is given by :

$$\frac{\frac{L}{T}}{T} + \frac{L}{T}\frac{\frac{L}{T}}{L} + \frac{L}{T}\frac{\frac{L}{T}}{L} + \frac{L}{T}\frac{\frac{L}{T}}{L} = -\frac{1}{T}\frac{L}{T} + \frac{L^2}{T}\frac{L}{T}\frac{1}{L^2}$$

which by simplification yields :

$$\frac{L}{T^2} = \frac{L}{T^2}$$

3 The Numerical Algorithm

In this work the mathematical model has been solved numerically by using a hybrid numerical algorithm consisting of two step predictor-corrector scheme and simpson's rule developed by Dey and Dey[5,6]. The original predictor-corrector scheme [1] is being used in 2 steps and then the simpson's rule subsequently in order to achieve better stability property. In the next section, stability of three dimensional predictor corrector scheme has been studied. This hybrid model was chosen with the consideration that the biological systems are moderately stiff and need algorithms with better stability properties. In the predictor-corrector scheme forward explicit finite difference formula for extrapolation is used as a predictor along with a convex formula as a corrector. The time derivative has been represented using forward difference approximation whereas the space derivatives in the convection components have been approximated using backward difference approximation. The space derivatives in the diffusion components have been approximated using central difference scheme.

The predictor in step 1 is the following:

$$\begin{aligned}\hat{F}_{i,j,k} &= F^n_{i,j,k} + \alpha_1({F^n_{i-1,j,k}}^2 - {F^n_{i,j,k}}^2) + \alpha_2({F^n_{i,j-1,k}}^2 - {F^n_{i,j,k}}^2) \\ &+\alpha_3({F^n_{i,j,k-1}}^2 - {F^n_{i,j,k}}^2) - rF^n_{i,j,k} + \beta_1(F^n_{i-1,j,k} - 2F^n_{i,j,k} + F^n_{i+1,j,k}) \\ &+\beta_2(F^n_{i,j-1,k} - 2F^n_{i,j,k} + F^n_{i,j+1,k}) + \beta_3(F^n_{i,j,k-1} - 2F^n_{i,j,k} + F^n_{i,j,k+1})\end{aligned} \tag{3.1}$$

where, $\alpha_1 = \dfrac{\Delta t}{4\Delta x}$, $\alpha_2 = \dfrac{\Delta t}{4\Delta y}$, $\alpha_3 = \dfrac{\Delta t}{4\Delta z}$, $r = \mu\dfrac{\Delta t}{2}$, $\beta_1 = \dfrac{\nu\Delta t}{2\Delta x^2}$, $\beta_2 = \dfrac{\nu\Delta t}{2\Delta y^2}$, $\beta_3 = \dfrac{\nu\Delta t}{2\Delta z^2}$

and

$$i = 1, 2, \cdots NX, j = 1, 2, \cdots NY, k = 1, 2, \cdots NZ$$

The corrector at step 1 is given by

$$
\begin{aligned}
F_{i,j,k}^{n+\frac{1}{2}} &= (1-\gamma_1)\hat{F}_{i,j,k} + \gamma_1(F_{i,j,k}^{n} + \alpha_1(\hat{F}_{i-1,j,k}^{2} - \hat{F}_{i,j,k}^{2}) + \alpha_2(\hat{F}_{i,j-1,k}^{2} - \hat{F}_{i,j,k}^{2}) \\
&\quad + \alpha_3(\hat{F}_{i,j,k-1}^{2} - \hat{F}_{i,j,k}^{2}) - r\hat{F}_{i,j,k} + \beta_1(\hat{F}_{i-1,j,k} - 2\hat{F}_{i,j,k} + \hat{F}_{i+1,j,k}) \\
&\quad + \beta_2(\hat{F}_{i,j-1,k} - 2\hat{F}_{i,j,k} + \hat{F}_{i,j+1,k}) + \beta_3(\hat{F}_{i,j,k-1} - 2\hat{F}_{i,j,k} + \hat{F}_{i,j,k+1}))
\end{aligned} \tag{3.3}
$$

where γ_1 is a convex parameter such that $0 < \gamma_1 < 1$.

The predictor 2 is given by :

$$
\begin{aligned}
\hat{\hat{F}}_{i,j,k} &= F_{i,j,k}^{n+\frac{1}{2}} + \alpha_1({F_{i-1,j,k}^{n+\frac{1}{2}}}^{2} - F_{i,j,k}^{n+\frac{1}{2}2}) + \alpha_2({F_{i,j-1,k}^{n+\frac{1}{2}}}^{2} - F_{i,j,k}^{n+\frac{1}{2}2}) \\
&\quad + \alpha_3({F_{i,j,k-1}^{n+\frac{1}{2}}}^{2} - F_{i,j,k}^{n+\frac{1}{2}2}) - rF_{i,j,k}^{n+\frac{1}{2}} + \beta_1(F_{i-1,j,k}^{n+\frac{1}{2}} - 2F_{i,j,k}^{n+\frac{1}{2}} + F_{i+1,j,k}^{n+\frac{1}{2}}) \\
&\quad + \beta_2(F_{i,j-1,k}^{n+\frac{1}{2}} - 2F_{i,j,k}^{n+\frac{1}{2}} + F_{i,j+1,k}^{n+\frac{1}{2}}) + \beta_3(F_{i,j,k-1}^{n+\frac{1}{2}} - 2F_{i,j,k}^{n+\frac{1}{2}} + F_{i,j,k+1}^{n+\frac{1}{2}})
\end{aligned} \tag{3.4}
$$

The corrector 2 is given by :

$$
\begin{aligned}
F_{i,j,k}^{nc} &= (1-\gamma_2)\hat{\hat{F}}_{i,j,k} + \gamma_2(F_{i,j,k}^{n+\frac{1}{2}} + \alpha_1(\hat{\hat{F}}^{2}_{i-1,j,k} - \hat{\hat{F}}^{2}_{i,j,k}) + \alpha_2(\hat{\hat{F}}^{2}_{i,j-1,k} - \hat{\hat{F}}^{2}_{i,j,k}) \\
&\quad + \alpha_3(\hat{\hat{F}}^{2}_{i,j,k-1} - \hat{\hat{F}}^{2}_{i,j,k}) - r\hat{\hat{F}}_{i,j,k} + \beta_1(\hat{\hat{F}}_{i-1,j,k} - 2\hat{\hat{F}}_{i,j,k} + \hat{\hat{F}}_{i+1,j,k}) \\
&\quad + \beta_2(\hat{\hat{F}}_{i,j-1,k} - 2\hat{\hat{F}}_{i,j,k} + \hat{\hat{F}}_{i,j+1,k}) + \beta_3(\hat{\hat{F}}_{i,j,k-1} - 2\hat{\hat{F}}_{i,j,k} + \hat{\hat{F}}_{i,j,k+1}))
\end{aligned} \tag{3.5}
$$

where γ_2 is again a convex parameter such that $0 < \gamma_2 < 1$.

In order to compute simpson's rule, the approximation of functions at the following 3 points has been computed :

$$
\begin{aligned}
s_n \;=\; & \Big(\frac{({F^n_{i-1,j,k}}^2 - {F^n_{i+1,j,k}}^2)}{2\Delta x} + \frac{({F^n_{i,j-1,k}}^2 - {F^n_{i,j+1,k}}^2)}{2\Delta y} + \frac{({F^n_{i,j,k-1}}^2 - {F^n_{i,j,k+1}}^2)}{2\Delta z} \\
& -\mu F^n_{i,j,k} + \nu\Big(\frac{(F^n_{i-1,j,k} - 2F^n_{i,j,k} + F^n_{i+1,j,k})}{\Delta x^2} \\
& + \frac{(F^n_{i,j-1,k} - 2F^n_{i,j,k} + F^n_{i,j+1,k})}{\Delta y^2} + \frac{(F^n_{i,j,k-1} - 2F^n_{i,j,k} + F^n_{i,j,k+1})}{\Delta z}\Big)
\end{aligned}
\tag{3.6}
$$

$$
\begin{aligned}
s_{n+\frac{1}{2}} \;=\; & \Big(\frac{({F^{n+\frac{1}{2}}_{i-1,j,k}}^2 - {F^{n+\frac{1}{2}}_{i+1,j,k}}^2)}{2\Delta x} + \frac{({F^{n+\frac{1}{2}}_{i,j-1,k}}^2 - {F^{n+\frac{1}{2}}_{i,j+1,k}}^2)}{2\Delta y} + \frac{({F^{n+\frac{1}{2}}_{i,j,k-1}}^2 - {F^{n+\frac{1}{2}}_{i,j,k+1}}^2)}{2\Delta z} \\
& -\mu F^{n+\frac{1}{2}}_{i,j,k} + \nu\Big(\frac{(F^{n+\frac{1}{2}}_{i-1,j,k} - 2F^{n+\frac{1}{2}}_{i,j,k} + F^{n+\frac{1}{2}}_{i+1,j,k})}{\Delta x^2} \\
& + \frac{(F^{n+\frac{1}{2}}_{i,j-1,k} - 2F^{n+\frac{1}{2}}_{i,j,k} + F^{n+\frac{1}{2}}_{i,j+1,k})}{\Delta y^2} + \frac{(F^{n+\frac{1}{2}}_{i,j,k-1} - 2F^{n+\frac{1}{2}}_{i,j,k} + F^{n+\frac{1}{2}}_{i,j,k+1})}{\Delta z}\Big)
\end{aligned}
\tag{3.7}
$$

$$
\begin{aligned}
s_{nc} \;=\; & \Big(\frac{({F^{nc}_{i-1,j,k}}^2 - {F^{nc}_{i+1,j,k}}^2)}{2\Delta x} + \frac{({F^{nc}_{i,j-1,k}}^2 - {F^{nc}_{i,j+1,k}}^2)}{2\Delta y} + \frac{({F^{nc}_{i,j,k-1}}^2 - {F^{nc}_{i,j,k+1}}^2)}{2\Delta z} \\
& -\mu F^{nc}_{i,j,k} + \nu\Big(\frac{(F^{nc}_{i-1,j,k} - 2F^{nc}_{i,j,k} + F^{nc}_{i+1,j,k})}{\Delta x^2} \\
& + \frac{(F^{nc}_{i,j-1,k} - 2F^{nc}_{i,j,k} + F^{nc}_{i,j+1,k})}{\Delta y^2} + \frac{(F^{nc}_{i,j,k-1} - 2F^{nc}_{i,j,k} + F^{nc}_{i,j,k+1})}{\Delta z}\Big)
\end{aligned}
\tag{3.8}
$$

Then

$$F^{n+1}_{i,j,k} = F^n_{i,j,k} + \frac{\Delta t}{6}(s_n + 4s_{n+\frac{1}{2}} + s_{nc})$$

This gives the value in the field at the point i,j,k .

4 Stability Analysis

This section is devoted to the stability of numerical algorithm. For simplicity, we are only analyzing the stability of the three dimensional model using single step predictor-corrector scheme. The stability of this scheme when applied to one dimensional system can be found in [1]. The non-linear system is linearized for stability and convergence analysis using Taylor's formula. The linearized model can be represented as :

$$\frac{\partial f}{\partial t} + \theta \bigtriangledown f = -\mu f + \nu \bigtriangledown^2 f. \tag{4.1}$$

where θ is a constant.

The linear system in (4.1) has to be represented using matrix notations. In order to achieve that, we define the following set of matrix notations. The field of computation is three dimensional space is given by,

$$i = 1, 2, \cdots NX \qquad and \qquad j = 1, 2, \cdots NY \qquad and \qquad k = 1, 2, \cdots NZ$$

The similar analysis can be found in [2] for three dimensional Heat conduction equation. The author adopted the matrix notations from [2]. Let R be a normed linear space of dimension (NX)x(NY)x(NZ). Define the following I-order matrices :

$(F_{j,k})_{i,s} = \delta_{i,s} f_{i,j,k}$,

$(I_I)_{i,s} = \delta_{i,s}$, $(L_I) = \delta_{i-1,s}$ and $(L_I^T)_{i,s} = \delta_{i+1,s}$

where

$$i = 1, 2, \cdots NX, j = 1, 2, \cdots NY, k = 1, 2, \cdots NZ$$

and $\delta_{i,s} = 1$ if $i = s$ and 0 otherwise.

Now let us define the following J-order square matrices with I-order square matrices as elements:

$(F_k)_{j,s} = \delta_{j,s}F_{j,k}$, $(I_J) = \delta_{j,s}I_I$

$(L_J)_{j,s} = \delta_{j,s}L_I$

$(B_J)_{j,s} = \delta_{j-1,s}I_I$ and $(B_J^T)_{j,s} = \delta_{j+1,s}I_I$

where $j = 1, 2, \cdots NY$, $s = 1, 2, \cdots NY$

Then let us define the following k-order square matrices with J-order matrices as elements :

$(F)_{k,s} = \delta_{k,s}F_k$, $(I)_{k,s} = \delta_{k,s}I_I$, $(L)_{k,s} = \delta_{k,s}L_J$,

$(B)_{k,s} = \delta_{k,s}$,

$(H)_{k,s} = \delta_{k,s}I$ so that $(H^T)_{k,s} = \delta_{k+1,s}I$

where $k = 1, 2 \cdots NZ, s = 1, 2, \cdots NZ$.

Now assume that the boundary conditions are all zero. Then the finite difference formula for the predictor of (4.1) can be represented as :

$$\begin{aligned}[\hat{F}]_{k,s} &= [(\alpha_1 + \beta_1)(LF^nL^T) + (\alpha_2 + \beta_2)(BF^nB^T) + (\alpha_3 + \beta_3)(HF^nH^T) \\ &+(1 - \alpha_1 - \alpha_2 - \alpha_3 - r - 2\beta_1 - 2\beta_2 - 2\beta_3)F^n \\ &+\beta_1(L^TF^nL) + \beta_2(B^TF^nB) + \beta_3(H^TF^nH)]_{k,s}\end{aligned} \tag{4.2}$$

where α_i, r , β_i , $i = 1, 2, 3$ are given as :
$\alpha_1 = \dfrac{\theta\Delta t}{\Delta x}$, $\alpha_2 = \dfrac{\theta\Delta t}{\Delta y}$, $\alpha_3 = \dfrac{\theta\Delta t}{\Delta z}$, $r = \mu\Delta t$, $\beta_1 = \dfrac{\nu\Delta t}{x^2}$, $\beta_2 = \dfrac{\nu\Delta t}{y^2}$, $\beta_3 = \dfrac{\nu\Delta t}{z^2}$.
Now let us define the following Ix1 order square matrix:

$$(F_{j,k}^n) = F_{i,j,k}^n, i = 1, 2, \cdots I$$

and let us define the following Jx1 column matrices using Ix1 matrices as the elements:

$$(F_k)_j = F_{j,k}, j = 1, 2 \cdots J$$

and define the following K order column matrices with J order column matrices as elements:

$$(F)_k = F_k, k = 1, 2, \cdots K$$

Using these column matrices (4.2) reduces to

$$\hat{F} = A.F \tag{4.3}$$

where

$$\begin{aligned} A &= (\alpha_1 + \beta_1)L + (\alpha_2 + \beta_2)B + (\alpha_3 + \beta_3)H \\ &+(1 - \alpha_1 - \alpha_2 - \alpha_3 - r - 2\beta_1 - 2\beta_2 - 2\beta_3)I \\ &+\beta_1 L^T + \beta_2 B^T + \beta_3 H^T. \end{aligned}$$

The matrix A can be represented as $A = I + C$ where I is the identity matrix and

$$\begin{aligned} C &= (\alpha_1 + \beta_1)L + (\alpha_2 + \beta_2)B + (\alpha_3 + \beta_3)H \\ &+(1 - \alpha_1 - \alpha_2 - \alpha_3 - r - 2\beta_1 - 2\beta_2 - 2\beta_3)I \\ &+\beta_1 L^T + \beta_2 B^T + \beta_3 H^T. \end{aligned}$$

Similarly the corrector can be represented as:

$$F^{n+1} = \Gamma F^n + I \cdot \hat{F} - \Gamma \cdot \hat{F} + \Gamma C \cdot \hat{F}$$

where $\Gamma = diag(0, \gamma, 0)$. This, by simplification yields

$$F^{n+1} = (I + C + \Gamma C^2)F^n \tag{4.4}$$

Let $M = (I + C + \Gamma C^2)$. Then, if we denote the eigenvalues of C by λ^C, then the eigenvalues of M will be

$$\lambda^M = (1 + \lambda^C + \gamma(\lambda^C)^2). \tag{4.5}$$

For stability, we need,

$$\|\lambda^M\| < 1 \tag{4.6}$$

which gives us

$$-1 < (1 + \lambda^C + \gamma\lambda^{C^2}) < 1. \tag{4.7}$$

Our aim is to optimize λ^M with respect to γ. Since (4.5) is linear with γ, the stability condition is achieved if (4.7) is satisfied. By simplification of (4.7), we get

$$-\frac{(2+\lambda^C)}{\lambda^{C^2}} < \gamma < -\frac{1}{\lambda^C} \tag{4.8}$$

Let us discuss the bound on γ we got in (4.8). Clearly, if $\lambda^C > 0$, we can't get $0 < \gamma < 1$.

From appendix A, and from [4] we can find out for three dimensional case,

$$\begin{aligned}\lambda^C &= 2(\sqrt{(\alpha_1+\beta_1)\beta_1}\cos\phi_1 + \sqrt{(\alpha_2+\beta_2)\beta_2}\cos\phi_2 + \sqrt{(\alpha_3+\beta_3)\beta_3}\cos\phi_3) \\ &\quad -(\alpha_1+\alpha_2+\alpha_3+r+2\beta_1+2\beta_2+2\beta_1).\end{aligned} \tag{4.9}$$

Here all the α_is, β_is, $i = 1, 2, 3$ and r are positive. Then , to minimize, we choose

$$\cos\phi_1 = \cos\phi_2 = \cos\phi_3 = -1$$

Then (4.9) becomes

$$\begin{aligned}\lambda^C &= -2[\sqrt{(\alpha_1+\beta_1)\beta_1} + \sqrt{(\alpha_2+\beta_2)\beta_2} + \sqrt{(\alpha_3+\beta_3)\beta_3}] \\ &\quad -(\alpha_1+\alpha_2+\alpha_3+r+2\beta_1+2\beta_2+2\beta_1).\end{aligned} \tag{4.10}$$

Computational experiment showed us that the range of γ when λ^C as given by (4.10) is within the limit $0 < \gamma < 1$. In fact, numerical calculation showed that for a choice of $t = .001$, $\Delta x = \Delta y = \Delta z = .02$, $NX = NY = NZ = 50$, $\mu = 2.0$, $\nu = .00001$ and for $\theta = .005, \cdots 4$, γ could be any value within 0 to 1.

5 Truncation Error

In this section the truncation error due to explicit finite difference approximation is analyzed. The truncation error caused due to the approximation of the time derivative

$$\left[\frac{\partial f}{\partial t}\right]^n_{i,j,k} = \frac{1}{\Delta t}\left[\triangle_t(f)\right]^n_{i,j,k} + E_t. \tag{5.1}$$

Also by definition of forward difference operator,

$$\Delta t\left[\frac{\partial f}{\partial t}\right]^n_{i,j,k} = [ln(I+\Delta t)f] = (\Delta_t - {\Delta_t}^2 + {\Delta_t}^3 - \cdots)f. \tag{5.2}$$

Comparing (5.1) and (5.2), and approximating the Taylor's series for logarithm to the first term, we get,

$$\Delta t E_t = \Delta t f'(t) - [f(t+\Delta t) - f(t)]$$

which gives

$$\Delta t E_t = \Delta t f'(t) - [f(t) + \Delta t f'(t) + \frac{\Delta t^2}{2!}f''(t_1) + \cdots]$$

where $t < t_1 < t + \Delta t$. This gives, by simplification,

$$E_t = -\frac{\Delta t}{2!}f''(t_1). \tag{5.3}$$

So the error due to approximation of time derivative is of $O(\Delta t)$.

The truncation error in the space derivative in the convection component along x direction is given by:

$$\left[\frac{\partial f}{\partial x}\right]^n_{i,j,k} = [-ln(1-\triangledown_x)f]^n_{i,j,k} = [(\triangledown_x + \frac{{\triangledown_x}^2}{2} + \cdots)f]^n_{i,j,k}$$

which , upon approximation to the first term of the Taylor's series gives us

$$\left[\frac{\partial f}{\partial x}\right]^n_{i,j,k} = \frac{1}{\Delta x}[\triangledown_x f]^n_{i,j,k} + E_x$$

This gives

$$E_x = f'(x) - [f(x) - f(x-\Delta x)].$$

The Taylor series expansion of $f(x-\Delta x)$ is $f(x-\Delta x) = [f(x)-\Delta x f'(x)+\frac{\Delta x^2}{2!}f''(x_1)+ \cdots]$ which upon application to the last equation and subsequent simplification yields

$$E_x = \frac{\Delta x}{2!}\left[\frac{\partial f}{\partial x}\right]^n_{i,j,k}. \tag{5.4}$$

Thus the error is $O(\Delta x)$.Smililarly we can find,

$$E_y = \frac{\Delta y}{2!}\left[\frac{\partial f}{\partial y}\right]^n_{i,j,k}. \tag{5.5}$$

and

$$E_z = \frac{\Delta z}{2!}\left[\frac{\partial f}{\partial z}\right]^n_{i,j,k}. \tag{5.6}$$

The error in space derivative along x-axis in the diffusion componet is given by :

$$\left[\frac{\partial^2 f}{\partial x^2}\right]^n_{i,j,k} = \frac{1}{\Delta x^2}[(\delta_x - \frac{{\delta_x}^3}{24} + \cdots)(\delta_x - \frac{{\delta_x}^3}{24} + \cdots)f]^n_{i,j,k}.$$

Upon approximation to the first term of the series, we get

$$\left[\frac{\partial^2 f}{\partial x^2}\right]^n_{i,j,k} = \frac{1}{\Delta x^2}[f(x-\Delta x) - 2f(x) + f(x+\Delta x)] + E_{x^2}.$$

Approximating $f(x-\Delta x)$ and $f(x+\Delta x)$ by it's Taylor series expansion and subsequent simplification yields

$$E_{xx} = \frac{\Delta x^2}{4!}f''''(\tau). \tag{5.7}$$

Thus the truncation error is of order $O(\Delta x^2)$. Similarly the truncation error along y-axis and z-axis could be found as $O(\Delta y^2)$ and $O(\Delta z^2)$. Then we can find the total truncation error as :

E_{total} = Differential equation - Difference Equation,

which gives,

$$\begin{aligned} E_{total} &= [f_t + ff_x + ff_y + ff_z - \nu f_{xx} - \nu f_{yy} - \nu f_{zz}] \\ &-[(f_t - E_t) + f(f_x - E_x) + f(f_y - E_y) + f(f_z - E_z) \\ &-\nu(f_{xx} - E_{xx}) - \nu(f_{yy} - E_{yy}) - \nu(f_{zz} - E_{zz})] \end{aligned}$$

which gives

$$E_{total} = [E_t + fE_x + fE_y + fE_z - \nu E_{xx} - \nu E_{yy} - \nu E_{zz}] \tag{5.8}$$

Since $E_t \approx O(t)$,$E_x \approx O(\Delta x)$, $E_y \approx O(\Delta y)$,$E_z \approx O(\Delta z)$, $E_{xx} \approx O(\Delta x^2)$, $E_{yy} \approx O(\Delta y^2)$, $E_{zz} \approx O(\Delta z^2)$, the system of equations is first order accurate.

6 Discussions

In this section, we are going to discuss in detail, the computational aspect of the model. We have used two different set of boundary and initial conditions and solved the model numerically. First, we have considered free boundary[7]. The assumption is that dispersion of all the biochemicals can take place through both the boundaries $i = 0, j = 0, k = 0$ and $i = NX + 1, j = NY + 1, k = NZ + 1$ in three dimensional solution space. It is already stated that human body is three dimensional and if we consider a part of the human body within a three dimensional block, body fluids are constantly flowing in and out of that part. The free boundary assumption is based upon that consideration. If U represents biochemicals then, applying extrapolation, the boundary conditions are given by

$$\begin{aligned} U_{0,j,k} &= 2.5 \cdot U_{1,j,k} - 0.5 \cdot U_{2,j,k} + 0.5 \cdot U_{3,j,k}; \\ U_{i,0,k} &= 2.5 \cdot U_{i,1,k} - 0.5 \cdot U_{i,2,k} + 0.5 \cdot U_{i,3,k}; \\ U_{i,j,0} &= 2.5 \cdot U_{i,j,1} - 0.5 \cdot U_{i,j,2} + 0.5 \cdot U_{i,j,3}; \end{aligned}$$

Also

$$\begin{aligned} U_{NX+1,j,k} &= 2.5 \cdot U_{NX,j,k} - 0.5 \cdot U_{NX-1,j,k} + 0.5 \cdot U_{NX-2,j,k}; \\ U_{i,NY+1,k} &= 2.5 \cdot U_{i,NY,k} - 0.5 \cdot U_{i,NY-1,k} + 0.5 \cdot U_{i,NY-2,k}; \\ U_{i,j,NZ+1} &= 2.5 \cdot U_{i,j,NZ} - 0.5 \cdot U_{i,j,NZ-1} + 0.5 \cdot U_{i,j,NZ-2}; \end{aligned}$$

The tumor is assumed to be present in the region close to the point $i = 0, j = 0, k = 0$. Our assumption is that f is a flux of biomass which is changing(growing/decaying) at a very slow rate. A large value of f implies that the angiogenesis have developed, i.e., blood vessels have been created from the tumor to the nearby primary blood vessels and the extra supply of oxygen, food and nutrients reaching the tumor. We have assumed that the flux f starts from a very small value and that's why we have set the initial flux $f = .005$ over the entire space in the beginning of the computation. The

value of ν, the rate of dispersion has been chosen $\nu = .00001$. This choice is made based on the information in [8]. The solution space has been taken to be equal to 50x50x50(i.e. $NX = NY = NZ = 50$) and $\Delta x = \Delta y = \Delta z = 0.02$. Also $\Delta t = .001$ we solved the model for 1000 steps so that the time goes from 0 to 1. Note that, this is purely logical timesteps. We are yet to correlate this with any actual time period. The numerical results for the model is studied for $\mu = 1.5, 2.0, 3.0$. Note that μ is a conceptual mathematical drug and so the rate of growth/decay of the flux is studied for different values of μ. The idea is that the values of μ might give the inkling of the dose of some real world medication suitable to control the growth of angiogenesis. We found that for $mu = 1.5$ angiogenesis could not be stopped at all[Figure 2]. For $mu = 2.0$ f first decreases and then increases. This is a very interesting situation. With longer simulation, it has been found that f eventually grows. So , angiogenesis could be deceiving[Figure 3]. For $mu = 2.5$, f decreases steadily[Figure 4]. In another execution,we initialized a larger f near the tumor and smaller elsewhere, with the assumption that f could be more neat the tumor. But we got almost the same result as earlier for $mu = 1.5, 2.0$[Figure 5 and 6].

The numerical solution of the model is also studied for a smaller field size ($NX = NY = NZ = 25$ and subsequently $\Delta x = \Delta y = \Delta z = 0.04$. It has been found that, depending on the values of the parameters, if the flux is in a growth phase, larger field size produces faster growth. This is not a biological phenomena, rather a computational one. Larger solution space gives larger condition number for the system of equations. We did the linearized stability analysis, using θ as a constant. Since, we are actually solving nonlinear equations, we can think of theta as a variable, varying in each step. By computation, it is found that the condition number of the system of equations in one dimension for $\theta = 2$ is nearly 65 for larger field($NX = NY = NZ = 50$), and 33.3 for smaller field($NX = NY = NZ = 25$). The condition number is much smaller for smaller values of θ(for $\theta = 0.1$, the condition number for

the large field is 6 and for smaller field, it is 3.5). This shows us that with a larger field and with increase in θ (flux f), the system of equations becomes moderately stiff.

In case of closed boundary, the tumor is assumed to be present in the middle of the field. The flux at the boundary $i = 0, j = 0, k = 0$ and $i = NX + 1, j = NY + 1, k = NZ + 1$ are all 0. The flux, f is set to .005 in the middle of the field and smaller towards to the boundary. The computation is done with the same set of parameters as in the free boundary case. It is found out that in this case, the flux is decaying faster than that of free boundary case. Intuitively, this implies that if the flow of the biomass could be stopped throughout the boundary, the flux of malignant cell will starve and decay[Figure 7]. This is evident, since with the decay of supply of oxygen, nutrients and food, the tumor will die eventually and angiogenesis will be inhibited.

7 Parallelization of the code

Since the code for this problem involves extensive numeric computation, the numerical code has been implemented to run in parallel cluster for faster execution. We've used MPI platform in a distributed memory cluster for this purpose. The cluster implementation is done using same technique as in [4]. Our total field of computation consists of NXxNYxNZ points. This complete field has been split along the x-axis, depending on the number of processors being used for the execution of the code. After the execution of each step, the ghost planes in the boundary are exchanged among the neighboring processors to ensure consistency of data in each processor. This is achieved with a minimum number of send-receive calls(i.e., by buffering the data and sending the complete plane in one call.), to ensure that the cost of send-receive calls doesn't render the parallel implementation undesirable. At the receiving end, this large buffer is decoded and remapped into the respective points. This particular parallelization technique was developed by [9]. This method helps to convert nonparallel codes to parallel codes with minimum changes. Also maintaining the parallel code is easier. The parallel code is ru using 8 processors on a space of $NX = NY = NZ = 50$. It has been found that the result of the parallel code matches completely with serial code.

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A Appendix

A.1 Stability in one dimension

In one dimension the linearized model is :

$$\frac{\partial f}{\partial t} + \theta \frac{\partial f}{\partial x} = -\mu f + \nu \frac{\partial^2 f}{\partial x^2} \qquad A.1$$

Then the finite difference formula for the predictor could be written as :

$$Fh_i = \alpha_1(F^n_{i-1} - F^n_{i+1}) - \mu F^n_i + \beta_1(F^n_{i-1} - 2F^n_i + F^n_{i+1}) \qquad A.2$$

The finite difference formula for the convex corrector is given by :

$$F^{n+i}_i = (1-\gamma)Fh_i + \gamma(F^n_i + \alpha_1(Fh_{i-1} - Fh_{i+1}) - rFh_i + \beta_1(Fh_{i-1} - 2Fh_i + Fh_{i+1})) \qquad A.3$$

In matrix-vector notation (A.2) can be written as :

$$FHAT = (I + C)F^n \qquad A.4$$

where I is identity matrix and

$$C = diag(b, a, d)$$

is a tridiagonal matrix[3]. Here

$$b = \alpha_1 + \beta_1$$

and

$$a = (-\alpha_1 - r - \beta_1)$$

and

$$d = \beta_1$$

Here $FHAT = [Fh_i], i = 1, 2, \cdots NX$ and $F^n = [F^n_i], i = 1, 2, \cdots NX$ are column vectors.

The equation (A.3) can be simplified as :

$$F_i^{n+1} = \gamma F_i^n + Fh_i - \gamma Fh_i + \gamma(\alpha_1+\beta_1)Fh_{i-1} + \gamma(-\alpha_1 - r - 2\beta_1)Fh_i + \beta_1 Fh_{i+1} \quad (A.5)$$

which, in matrix form could be written as

$$F^{n+1} = \Gamma F^n + I.FH - \Gamma FH + \gamma C.FH \quad (A.6)$$

where

$$\Gamma = diag(0, \gamma, 0)$$

and I is identity matrix. Both Γ and I are of order NX.

Using (A.4) to replace FH at (A.6) we get

$$F^{n+1} = \Gamma F^n + I.(I+C)F^n - \Gamma(I+C)F^n + \gamma C(I+C)F^n$$

or

$$F^{n+1} = (I + C + \gamma C^2)F^n \quad (A.7)$$

If we assume

$$M = (I + C + \gamma C^2)$$

then the convergence of the solution is achieved when

$$\|M\| < 1 \quad (A.8)$$

The condition (A.8) is satisfied if the matrix M is convergent, i.e.,

$$-1 < \lambda_i^M < 1$$

where $\lambda_i^M, i = 1, 2, \cdots NX$ are the eigenvalues of M. But how the eigenvalues of M looks like? To answer this question, we need the following lemma :

Lemma 1 *If λ is an eigenvalue of a N dimensional square matrix A , then λ^2 is the eigenvalue of the matrix A^2.*

Let λ be an eigenvalue of A and v be the correcponding eigenvector of the N dimensional square matrix A. Then

$$Av = \lambda v$$

by the definition of eigenvalues and eigenvectors of a square matrix. If we multiply both side of the equation by matrix A, we get,

$$A.Av = A.\lambda v$$

or

$$A^2v = \lambda Av,$$

since λ is a scalar. Then we get,

$$A^2v = \lambda(\lambda)v = \lambda^2 v.$$

So the eigenvalue of A^2 is λ^2 .

The dimension of I is same as that of C and so the eigenvectors of I can be taken same as that of C.

Before proceeding further, we need the following lemma:

Lemma 2 *If $Q = diag(p, q, r)$ is a tri-diagonal matrix of order N then the eigenvalues of Q are given by*

$$\lambda_i = q + 2\sqrt{pr}\cos\frac{ni\pi}{(N+1)}.$$

Let $V = [v_i]^T, i = 1, 2, \cdots N$ be the eigenvectors of Q. Now from the definition of Q, we get,

$$pv_{i-1} + qv_i + rv_{i+1} = \lambda_j v_i \tag{A.9}$$

where we are considering the jth eigenvalue. Let$v_i = \xi^i$. Then (A.9) can be written as

$$p\xi^{i-1} + q\xi^i + r\xi^{i+1} = \lambda_j \xi^i$$

which implies

$$p + (q - \lambda_j)\xi + r\xi^2 = 0. \tag{A.10}$$

Solving (A.10) for ξ yields

$$\xi = \frac{(\lambda_j - q) \pm \sqrt{(\lambda_j - q)^2 - 4pr}}{2p} \tag{A.11}$$

Let $\frac{(\lambda_j - p)}{2q} = \sqrt{\frac{r}{p}} \cos\phi$. Then (A.11) becomes

$$\xi = \sqrt{\frac{r}{p}} e^{\pm i\phi}$$

which gives

$$\lambda_j = q + 2\sqrt{pr}\cos\phi, j = 1, 2, \cdots N \tag{A.12}$$

By definition, $v_j = r_1\xi_1^j + r_2\xi_2^j$, considering two different values of ξ. Then

$$v_j = (\sqrt{\frac{r}{p}})^j (r_1 e^{ij\phi} + r_2 e^{-ij\phi}) \quad ,$$

from which we get, by simplification

$$v_j = (\frac{r}{p})^{\frac{j}{2}} (\hat{A}\cos j\phi + \hat{B}\sin j\phi). \tag{A.13}$$

Taking zero boundary into account we get :

$$\phi = \frac{n\pi}{(J+1)}.$$

By substitution of this result to (A.12), we get

$$\lambda_j = q + \sqrt{pr}\cos\frac{nj\pi}{(J+1)} \tag{A.14}$$

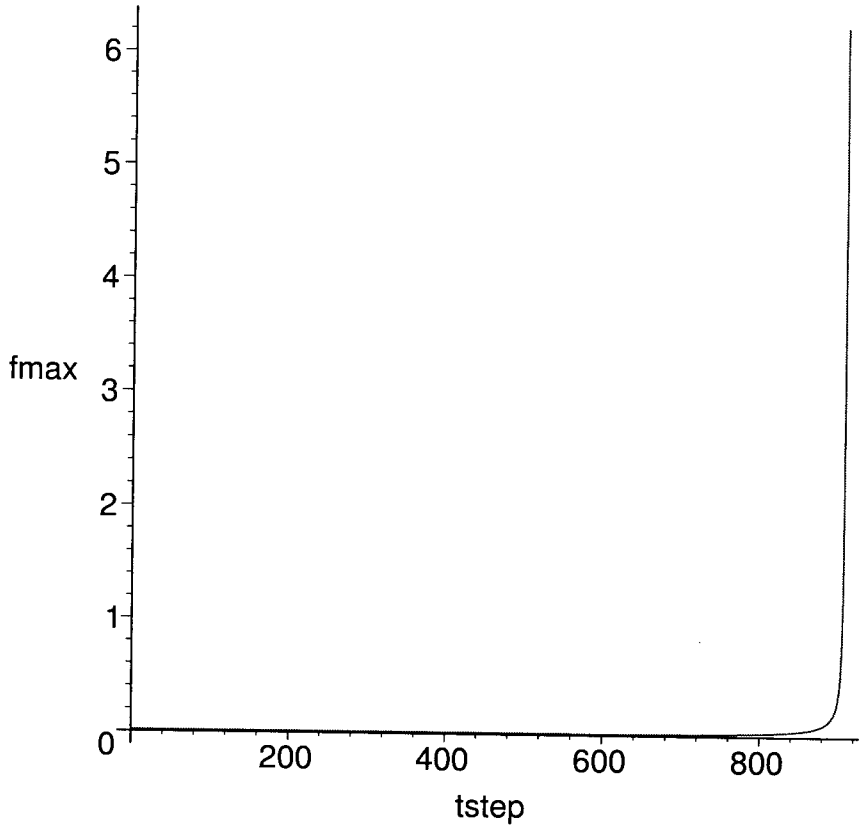

Figure 2: mu=1.5,free boundary

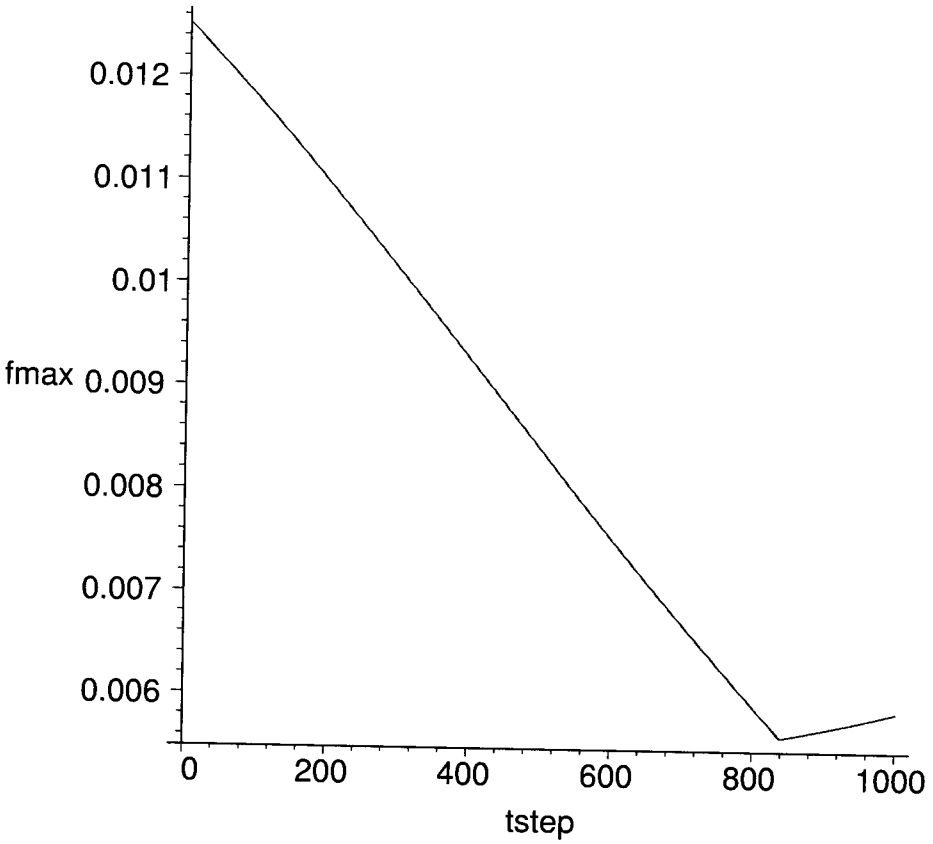

Figure 3: mu=2.0,free boundary

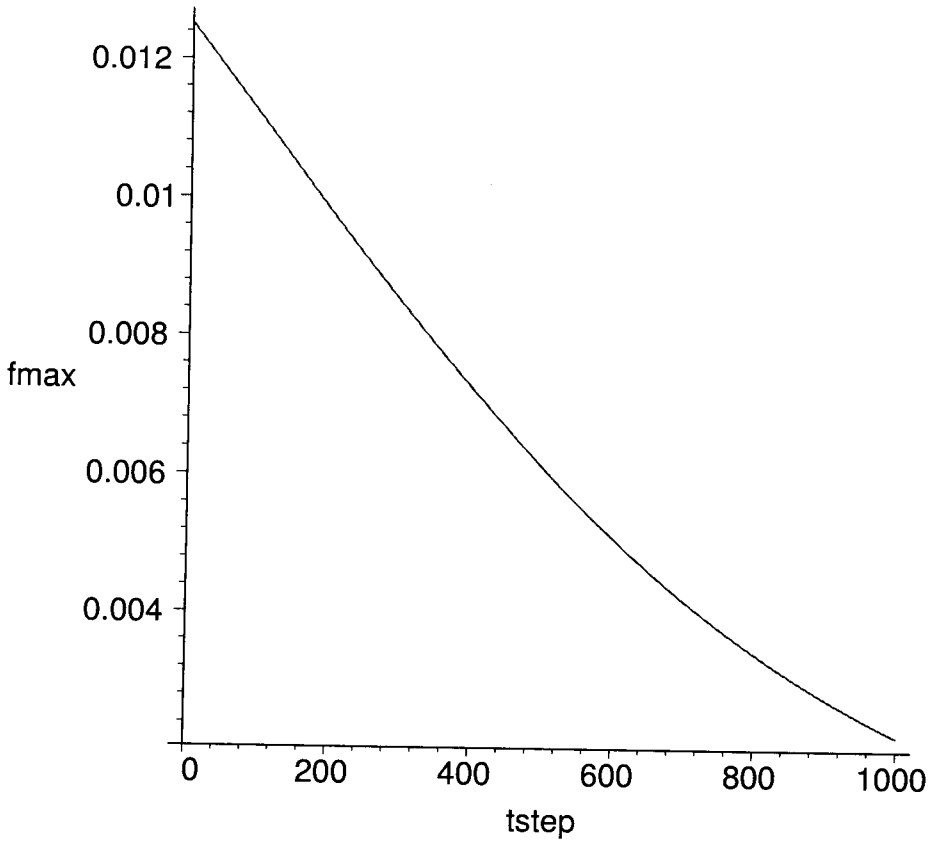

Figure 4: mu=2.5,free boundary

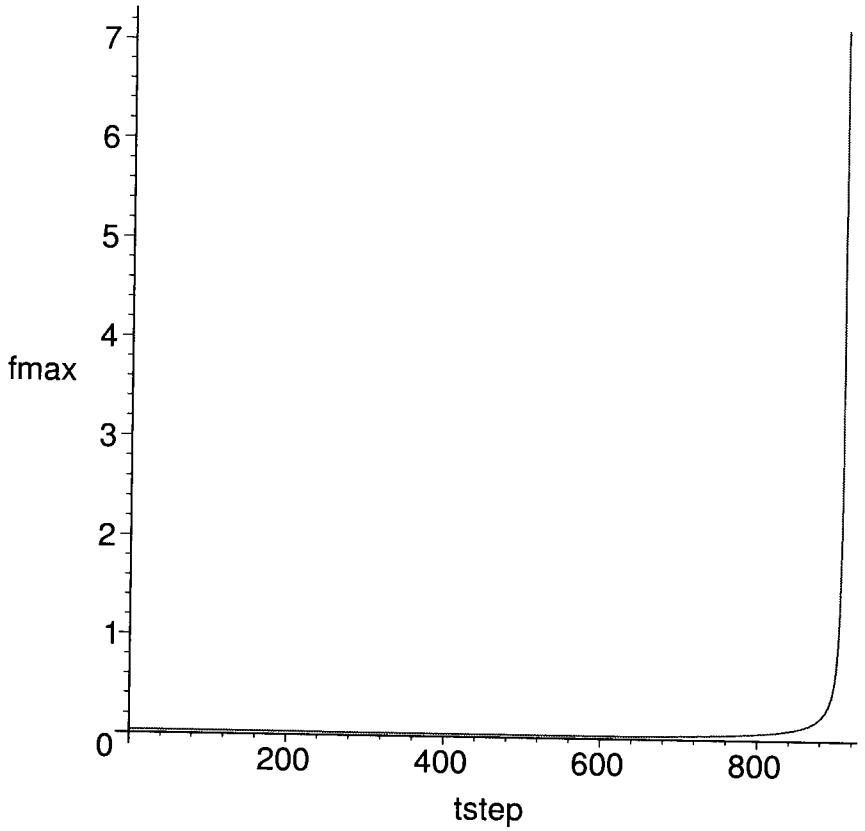

Figure 5: mu=1.5,free boundary with initial flux larger near the tumor

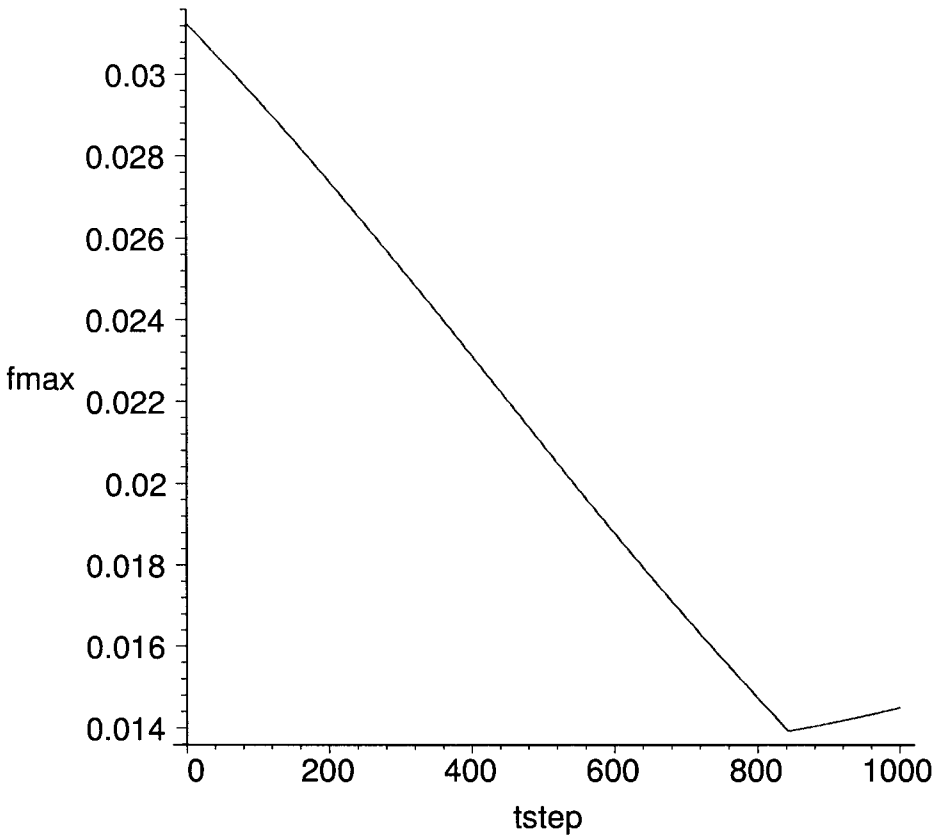

Figure 6: mu=2.0,free boundary with initial flux larger near the tumor

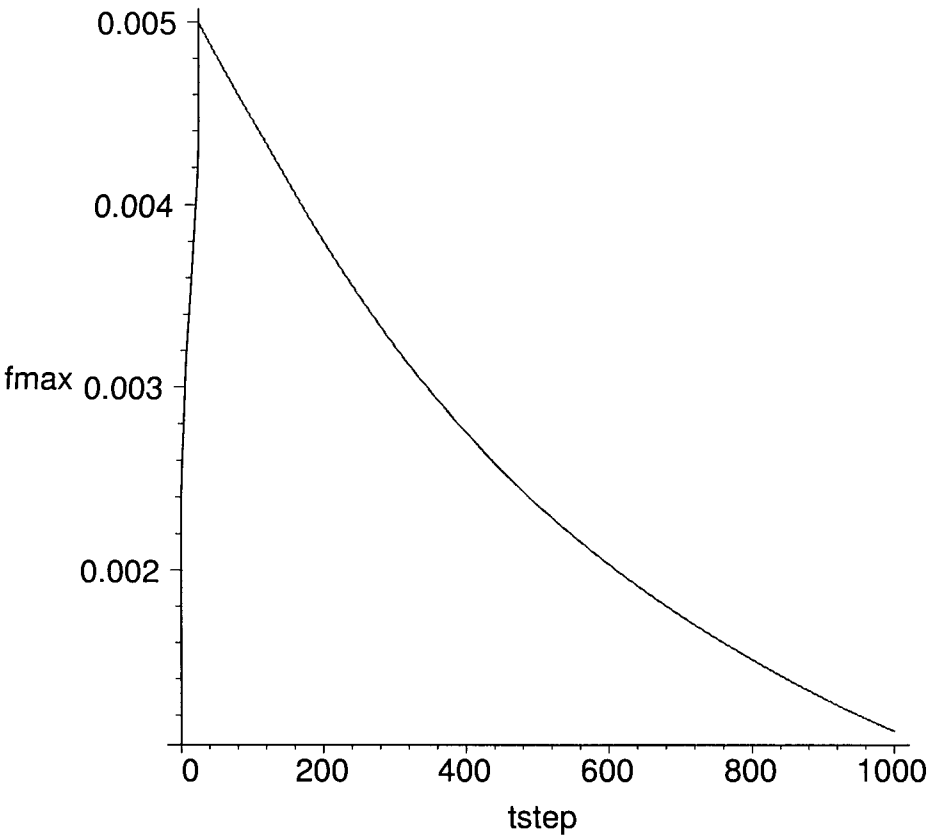

Figure 7: mu=2.5,closed boundary