REU Report Outline

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Abstract

In this paper, the numerical approximation of a one-dementional mathematical model of tumor angiogenesis originally was developed by Levine, Nilsen-Hamilton, and Sleeman [2] and later modified in [3]. The finite element method is employed to discretize the equations in space and a backward Euler discretization is used in time. Numerical results were then used to describe various biological phenomena.

1 Introduction

The biological setting for this model is based on the ideas of tumor angiogenesis and growth as proposed by Dr. Folkmann [1]. Once tumors reach a certain stage of growth, they can begin emitting angiogenic factor, which is the first step towards vascularization. Vascularization often results in the tumor spreading rapidly both locally and throughout the body.

The mathematical model used in this project is derived from the work of Levine, Nilsen-Hamilton, and Sleeman [3]. The equations are based on the chemical reactions that occur between various cells and factors. Mathematical analysis of these reactions results in a system of coupled time-dependent nonlinear ordinary and partial differential equations which represent the interactions of cells in and around a capillary near a tumor.

One of the major goals of this project is to approximate the solution of these equations using the finite element method to discretize in space and a backward Euler approximation to discretize in time. This discretization differs from previous numerical simulations [3] which used an explicit finite difference scheme on a uniform mesh.

This finite element approximation to the model is used to simulate two situations in which the angiostatin acts as an inhibitor or an inhibitor generator. In addition, the original model given in [3] was later modified in [4] and this project is the first to incorperate this change.

Section 2 briefly describes the biological setting and terminology for the model. For further details, the reader is referred to the original work by Dr. Levine and associates [2], [3], and [4].

Section 3 discusses the biological kinematics of tumor angiogenesis. It also presents the system of one-dimensional coupled non-linear ordinary and partial differential equations with which these kinematics are modelled.

Section 4 introduces the finite element and Backward Euler methods used to solve the system presented in § 3. The finite element method is used to discretize the system spatially, while the Backward Euler method addresses the time dependency of the model.

Section 5 explains the procedure by which this project was implemented. It also makes note of some of the more technical aspects of this project.

Section 6 graphically presents the numerical results obtained by this project. It also discusses the implications of these figures.

Section 7 concludes the findings of this project. In addition, it proposes some possibilities for future research.

2 The Biological Setting

The subject of this project is tumor angiogenesis. A *tumor* is a growth of cancerous cells. Cancerous cells occur when a cell mutates during its reproduction and is unable to fix the error. Tumors then form by the reproduction of these cancerous cells. Normally, a tumor can only grow to about 2mm in diameter due to the rate of oxygen diffusion through the body's tissues; once this diameter has been reached, the center of the tumor often begins to suffocate and die. At or before this point, it is generally possible to safely remove the tumor with surgery.

Angiogenesis is the formation of capillaries from existing vessels. Examples of this include the healing process (e.g. repairing a scrape or cut), reproduction, inflammation, and arthritis. There are two types of angiogenesis with respect to the rate of growth. *Rapid growth* angiogenesis is characterized by the swift formation of new capillaries to a wounded area and the subsequent cessation and regression of these new capillaries. If the new capillaries continue to grow unchecked, it is referred to as *uncontrolled* angiogenesis, as demonstrated by arthritis, emphysema, psoriasis, diabetic retinopathy, and tumor growth.

Tumor angiogenesis occurs if, when the tumor reaches its unvascularized potential, it begins to secrete tumor angiogenic factor (TAF). Also, due to the fact that the core of the tumor becomes necrotic at this point, it may begin to emit tumor necrotic factor (TNF). If either of these occurs, the tumor eventually develops a network of capillaries and becomes malignant. Malignancy is characterized by rapid growth of the tumor, now possible due to the ready supply of oxygen from the new capillary network. This network also allows the tumor to send tumor cells into the blood or lymphatic systems to other parts of the body in a process known as *metastasis*. These tumors, however, do not usually vascularize due to the fact that the main tumor also emits an angiostatin (angiogenesis inhibiting agent). This accounts for the fact that sometimes when a patient has a tumor removed, another cancerous tumor will appear in a totally different part of the body. The new tumor is able to vascularize and thus grow due to the removal of the angiostatin producing tumor.

A capillary is composed of three main parts. The outermost part is the extracellular matrix (ECM) which encircles and supports the cellular components. It is composed primarily of fibronectin and is also referred to as the basement lamina or basement membrane. Next are the endothelial cells (EC), which form a single layer of flattened and extended cells lining the basement lamina. Finally, the pericytes form a periendothelial cellular network throughout the basement membrane.

When a tumor begins to release TAF into the ECM, it diffuses through the basement lamina until it comes to a capillary wall, where it binds with receptors on the endothelial cells. This causes the endothelial cells to aggregate within the capillary and begin producing proteolytic enzymes (proteases). The proteases then degrade the basement lamina and ECM, allowing the formation of a new capillary sprout. As the EC aggregate, they change form by developing pseudopodia that enable them to move into the gap formed by the degradation of the ECM. The movement of the endothelial cells is due both to chemotaxis (movement up a concentration gradient) and haptotaxis (movement up an adhesive gradient). The concentration of TAF in the ECM increases as the endothelial cells approach the tumor, and the fibronectin in the ECM enhances endothelial cell adhesion to the matrix. In other words, these factors cause the capillary sprout to grow towards the tumor. One reason that tumors are especially deadly is that they utilize the body's own defense system against it. An example of this is the tumor's usage of macrophage cells. When a macrophage cell ingests a TNF molecule, it releases vascular endothelial growth factor (VEGF). VEGF, like TAF, binds to receptors on the endothelial cells, resulting in the formation of additional proteases which further degrade the ECM.

This model is based on the idea that the endothelial cells have random migration defined by a persistent random walk, while chemotactically they move according to a biased persistent random walk. For a more in depth discussion on this topic, see Grier's work [5].

3 The Mathematical Model

The mathematical model which forms the basis of this work is due to Levine, Nilsen-Hamilton, and Sleeman [3]. It couples the ideas of endothelial cell movement with respect to enzyme kinematics and reinforced random walks. While the human body is a three dimensional object, the geometry of this project has been simplified to a one dimensional problem as a foundation for further research. This project focuses on the concentration or density of various biological elements along a one-dimensional section of the ECM in close approximation to the capillary wall.

The enzyme kinematics are given in detail in [3]. Since this model incorporates a modification suggested later by Levine, et al. this project presents the kinematics of this modification:

$$
\begin{aligned}
V + R &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [RV] \\
[RV] &\overset{k_2}{\rightarrow} C_A + R \\
C_A \; + \; F &\overset{k_3}{\rightarrow} [C_A F] \\
[C_A F] &\overset{k_4}{\rightarrow} C_A \; + \; F',
\end{aligned} \tag{1}
$$

where the k_is represent the rates of reaction with the corresponding definitions:

$V =$ a molecule of angiogenic factor,
$R =$ a receptor on an endothelial call,
$RV =$ the intermediate complex formed when V binds to R,
$C_A =$ the active proteolytic enzyme,
$F =$ a molecule of fibronectin,
$C_A F =$ an active proteolytic enzyme bound to a fibronectin molecule,
$F' =$ a degraded molecule of fibronectin.

It is important to note that if I is a protease inhibitor produced by the endothelial cells in response to the angiostatic agent, then when I and C_A are combined, I acts as a direct inhibitor with ν_e as the equilibrium constant:

$$C_A \; + \; I \; \overset{\nu_e}{\rightleftharpoons} \; C_I,$$

C_I represents an inhibited proteolytic enzyme which can no longer act as the catalyst for the fibronectin degradation. Finally in terms of concentration:

$$[C] \; = \; [C_A] \; + \; [C_I] \; + \; [C_A F].$$

From the biolchemical kinetics and system of time dependent differential equations are obtained; again see [3] for details. The notation used to mathematically describe this model is:

$u =$ concentration of chemotatic agent,
$u_r =$ rate that chemotatic agent is supplied,
$\upsilon =$ concentration of angiogenic factor V,
$\upsilon_r =$ rate that angiogenic factor is supplied,
$c =$ concentration of proteolytic enzyme,
$f =$ density of capillary wall, represented here by fibronectin,
$a =$ concentration of angiostatic agent (anti-angiogenic) factor,
$a_r =$ rate that angiostatic agent factor is supplied,
$\imath_a =$ protease inhibitor density,
$c_a =$ active proteolytic enzyme density.
$c_i =$ inhibited proteolytic enzyme density.
$\eta =$ endothelial cell density,
$\sigma =$ pericyte cell density,
$m =$ magcrophage cell density,

The differential equationsfor the model given in [3] with the modification resulting from are:

We also have, in case that angiostatin is the inhibitor,

$c = c_a + c_i,$
$c_i = \nu_e a c_a + \nu_4 f c_a$

so that
$c_a = \frac{c}{1+\nu_e a+\nu_4 f}$

This definition of c_a differs from the one given in [4].

$$
\begin{aligned}
\frac{\partial u}{\partial t} &= -\frac{\lambda_2 u m}{1+\nu_2 u} + u_r(x,t),\\
\frac{\partial \upsilon}{\partial t} &= \frac{\lambda_2 u m}{1+\nu_2 u} - \frac{\lambda_1 \upsilon \eta}{1+\nu_1 \upsilon} + \upsilon_r(x,t),\\
\frac{\partial c}{\partial t} &= \frac{\lambda_1 \upsilon \eta}{1+\nu_1 \upsilon},\\
\frac{\partial f}{\partial t} &= \beta(f_M - f) f \eta - \frac{\lambda_4 c_a f}{1+\nu_4 f},\\
\frac{\partial a}{\partial t} &= -\frac{\lambda_3 a \eta}{1+\nu_3 a} + a_r(x,t),
\end{aligned}
$$

$$
(2) \qquad \begin{aligned}
\frac{\partial \imath_a}{\partial t} &= \frac{\lambda_3 a \eta}{1 + \nu_3 a}, \\
c_a &= \frac{c}{1 + \nu_e \imath_a + \nu_4 f} \\
\frac{\partial \eta}{\partial t} &= D_1 \frac{\partial}{\partial x}\Big(\eta \frac{\partial}{\partial x}\Big(\ln \frac{\eta}{\tau_1}\Big)\Big), \\
\frac{\partial \sigma}{\partial t} &= D_2 \frac{\partial}{\partial x}\Big(\sigma \frac{\partial}{\partial x}\Big(\ln \frac{\sigma}{\tau_2}\Big)\Big), \\
\frac{\partial m}{\partial t} &= D_3 \frac{\partial}{\partial x}\Big(m \frac{\partial}{\partial x}\Big(\ln \frac{m}{\tau_3}\Big)\Big),
\end{aligned}
$$

$$
\tau_1(c_a, f) = \Big(\frac{c_a + \alpha_1}{c_a + \alpha_2}\Big)^{\gamma_1} \Big(\frac{f + \beta_1}{f + \beta_2}\Big)^{\gamma_2}
$$

Where $0 < \alpha_1 \ll 1 < \alpha_2$ and $\beta_1 > 1 \gg \beta_2 > 0$.

$$
\tau_2(f) = \Big(\frac{f + \alpha_3}{f + \alpha_4}\Big)^{\gamma_3}
$$

Where $0 < \alpha_3 \ll 1 \ll \alpha_4$.

$$
\tau_3(u) = \Big(\frac{u + \beta_3}{u + \beta_4}\Big)^{\gamma_4}
$$

Where $0 < \beta_3 \ll 1 \ll \beta_4$.

The boundary conditions are given by:

$$
\eta \frac{\partial}{\partial x}\Big(\ln \frac{\eta}{\tau_1}\Big)\Bigg|_{x=0,L} = \sigma \frac{\partial}{\partial x}\Big(\ln \frac{\sigma}{\tau_2}\Big)\Bigg|_{x=0,L} = m \frac{\partial}{\partial x}\Big(\ln \frac{m}{\tau_3}\Big)\Bigg|_{x=0,L} = 0
$$

Where L is length of the section of capillary, and the initial conditions chosen:

$$
\begin{array}{lll}
\eta(x,0) = 1, & \sigma(x,0) = 1, & m(x,0) = 1, \\
u(x,0) = 0, & \upsilon(x,0) = 0, & c(x,0) = 0, \\
a(x,0) = 0, & \imath_a(x,0) = 0, & f(x,0) = 1.
\end{array}
$$

Note that a normalization has been incorporated so that this project may choose such initial conditions.

Here λ_i are biological constants while α_i, β_i, and γ_i are empirical constants; again see [3] for details. When angiostatin acts as an inhibitor, the above system simplifies to the following:

$$
(3)\qquad
\begin{aligned}
\frac{\partial u}{\partial t} &= -\frac{\lambda_2 u m}{1+\nu_2 u} + u_r(x,t),\\
\frac{\partial \upsilon}{\partial t} &= \frac{\lambda_2 u m}{1+\nu_2 u} - \frac{\lambda_1 \upsilon \eta}{1+\nu_1 \upsilon} + \upsilon_r(x,t),\\
\frac{\partial c}{\partial t} &= \frac{\lambda_1 \upsilon \eta}{1+\nu_1 \upsilon},\\
\frac{\partial f}{\partial t} &= \beta(f_M - f) f \eta - \frac{\lambda_4 c_a f}{1+\nu_4 f},\\
\frac{\partial a}{\partial t} &= a_r(x,t),\\
c_a &= \frac{c}{1+\nu_e a + \nu_4 f}\\
\frac{\partial \eta}{\partial t} &= D_1 \frac{\partial}{\partial x}\Big(\eta \frac{\partial}{\partial x}\Big(\ln \frac{\eta}{\tau_1}\Big)\Big),\\
\frac{\partial \sigma}{\partial t} &= D_2 \frac{\partial}{\partial x}\Big(\sigma \frac{\partial}{\partial x}\Big(\ln \frac{\sigma}{\tau_2}\Big)\Big),\\
\frac{\partial m}{\partial t} &= D_3 \frac{\partial}{\partial x}\Big(m \frac{\partial}{\partial x}\Big(\ln \frac{m}{\tau_3}\Big)\Big),
\end{aligned}
$$

$$\tau_1(c_a, f) = \Big(\frac{c_a + \alpha_1}{c_a + \alpha_2}\Big)^{\gamma_1} \Big(\frac{f + \beta_1}{f + \beta_2}\Big)^{\gamma_2}$$

Where $0 < \alpha_1 \ll 1 < \alpha_2$ and $\beta_1 > 1 \gg \beta_2 > 0$.

$$\tau_2(f) = \Big(\frac{f + \alpha_3}{f + \alpha_4}\Big)^{\gamma_3}$$

Where $0 < \alpha_3 \ll 1 \ll \alpha_4$.

$$\tau_3(u) = \Big(\frac{u + \beta_3}{u + \beta_4}\Big)^{\gamma_4}$$

Where $0 < \beta_3 \ll 1 \ll \beta_4$.

With analogous boundry and initial conditions.

4 Discrete Problem

The model given in § 3 is discretized in space by the finite element method. The first step in the finite element method is to write the weak solution of the equations. This is accomplished by multiplying each equation by an appropriate test function, integrating over a domain, and integrating the appropriate term by parts. For the model given in [3] we use the following weak form:

$$
(4) \quad
\begin{aligned}
&\int_0^L \frac{\partial u}{\partial t}\phi\,dx \;+\; \int_0^L \frac{\lambda_2 u m}{1\,+\,\nu_2 u}\,\phi\,dx \;=\; \int_0^L u_r(x,t)\,\phi\,dx\\
&\int_0^L \frac{\partial \upsilon}{\partial t}\phi\,dx \;-\; \int_0^L \frac{\lambda_2 u m}{1\,+\,\nu_2 u}\,\phi\,dx \;+\; \int_0^L \frac{\lambda_1 \upsilon \eta}{1\,+\,\nu_1 \upsilon}\,\phi\,dx \;=\; \int_0^1 \upsilon_r(x,t)\,\phi\,dx\\
&\int_0^L \frac{\partial c}{\partial t}\phi\,dx \;-\; \int_0^L \frac{\lambda_1 \upsilon \eta}{1\,+\,\nu_1 \upsilon}\,\phi\,dx = 0\\
&\int_0^L \frac{\partial f}{\partial t}\phi\,dx \;-\; \int_0^L \beta f(f_M\,-\,f)\eta\,\phi\,dx \;+\; \int_0^L \frac{\lambda_4 c_a f}{1\,+\,\nu_4 f}\,\phi\,dx \;=\; 0,\\
&\int_0^L \frac{\partial a}{\partial t}\phi\,dx \;+\; \int_0^L \frac{\lambda_3 a \eta}{1\,+\,\nu_3 a}\,\phi\,dx \;=\; \int_0^L a_r(x,t)\,\phi\,dx\\
&\int_0^L \frac{\partial \imath_a}{\partial t}\phi\,dx \;-\; \int_0^L \frac{\lambda_3 a \eta}{1\,+\,\nu_3 a}\,\phi\,dx \;=0,\\
&\int_0^L \frac{\partial \eta}{\partial t}\phi\,dx \;+\; D_1 \int_0^L \frac{\partial \eta}{\partial x}\,\frac{\partial \phi}{\partial x}\,dx \;-\; D_1 \int_0^L \eta\frac{\tau_1 x}{\tau_1}\,\phi\,dx \;=\; 0,\\
&\int_0^L \frac{\partial \sigma}{\partial t}\phi\,dx \;+\; D_2 \int_0^L \frac{\partial \sigma}{\partial x}\,\frac{\partial \phi}{\partial x}\,dx \;-\; D_2 \int_0^L \sigma\frac{\tau_2 x}{\tau_2}\,\phi\,dx \;=\; 0,\\
&\int_0^L \frac{\partial m}{\partial t}\phi\,dx \;+\; D_3 \int_0^L \frac{\partial m}{\partial x}\,\frac{\partial \phi}{\partial x}\,dx \;-\; D_3 \int_0^L m\frac{\tau_3 x}{\tau_3}\,\phi\,dx \;=\; 0,
\end{aligned}
$$

where the model has assumed that D_i $i\;=\;1,\,2,\,3$ are constants. Here it is tacitly assumed these functions are sufficiently smooth for the weak formulation to be defined.

The boundary conditions for η are natural because:

$$
\begin{aligned}
\int_0^L D_1\frac{\partial}{\partial x}\Big(\eta\frac{\partial}{\partial x}\Big(\ln\frac{\eta}{\tau_1}\Big)\Big)\,\phi\,dx \;&=\; -D_1\int_0^1 \eta\frac{\partial}{\partial x}\Big(\ln\frac{\eta}{\tau_1}\Big)\,\frac{\partial \phi}{\partial x}\,dx \;+\; \Big[D_1\,\eta\frac{\partial}{\partial x}\Big(\ln\frac{\eta}{\tau_1}\Big)\phi\Big]_0^1,\\
&=\; -\,D_1\,\eta_x\,\phi_x \;+\; D_1\,\eta\,\frac{\tau_{1_x}}{\tau_1}\,\phi_x.
\end{aligned}
$$

In a completely analogous manner, the boundry conditions for σ and m are satisfied by the chosen weak formulatioin.

Discretization in space using the finite element method is accomplished by passing the weak problem over a finite-dimentional subspace of the underlying infinite-dimentional space. This paper will denote the finite element discretization by a subscript of h. After this discretization the problem has not been fully discretized. Since the equations are time dependent the backward Euler method is used to approximate the time derivative:

$$u_t(t,x) \approx \frac{u(t,x) - u(t - \Delta t, x)}{\Delta t}.$$

Let $u^n(x)$ denote some approximate solution at time t_n and let $\phi_i(x)$ represent the basis functions for the finite dementional space; then $u_h^n = \sum_{i=1}^{p} c_i^n(t)\phi_i$, where p is the number of elements. The fully discrete problem using backward Euler at the nth timestep then becomes for all $i = 1, \ldots, p$:

$$\begin{aligned}
&\int_0^1 u_h^n \phi_i \, dx + \Delta t \int_0^1 \frac{\lambda_2 u_h^n \, m_h^n}{1 + \nu_2 u_h^n} \phi_i dx \\
&\qquad = \int_0^1 u_h^{n-1} \phi_i \, dx + \int_0^1 u_r^n \phi_i \, dx, \\
&\int_0^1 \upsilon_h^n \phi_i \, dx - \Delta t \int_0^1 \Big(\frac{\lambda_2 u_h^n \, m_h^n}{1 + \nu_2 u_h^n} - \frac{\lambda_1 \upsilon_h^n \, \eta_h^n}{1 + \nu_1 \upsilon_h^n} \Big) \phi_i dx \\
&\qquad = \int_0^1 \upsilon_h^{n-1} \phi_i dx + \int_0^1 \upsilon_r^n \phi_i dx \\
&\int_0^1 c_h^n \phi_i \, dx - \Delta t \int_0^1 \frac{\lambda_1 \upsilon_h^n \, \eta_h^n}{1 + \nu_1 \upsilon_h^n} \phi_i dx \\
&\qquad = \int_0^1 c_h^{n-1} \phi_i \, dx, \\
&\int_0^1 f_h^n \phi_i \, dx - \Delta t \int_0^1 \left(\beta f_h^k \, (f_{M_h} - f_h^n) \eta_h^n - \frac{\lambda_4 c_{a_h}^n f_h^n}{1 \, \nu_4 f_h^n} \right) \phi_i dx \\
&\qquad = \int_0^1 f_h^{n-1} \phi_i \, dx, \qquad\qquad (5) \\
&\int_0^1 a_h^n \phi_i \, dx + \Delta t \int_0^1 \frac{\lambda_3 a_h^n \eta_h^n}{1 + \nu_3 a_h^n} \phi_i \, dx \\
&\qquad = \int_0^L a_h^{n-1} \phi_i \, dx + \int_0^L a_r^n \phi_i \, dx, \\
&\int_0^1 \imath_{a_h}^n \phi_i \, dx - \Delta t \int_0^1 \frac{\lambda_3 a_h^n \eta_h^n}{1 + \nu_3 a_h^n} \phi_i \, dx \\
&\qquad = \int_0^L \imath_a^{n-1} \phi_i \, dx, \\
&\int_0^1 \eta_h^n \phi_i \, dx + D_1 \Delta t \int_0^1 (\eta_h^n)_x (\phi_i)_x \, dx - \int_0^1 \Big(\frac{\eta_h^n}{\tau_{1_h}^n} (\tau_{1_h}^n)_x \Big) (\phi_i)_x \, dx \\
&\qquad = \int_0^1 \eta_h^{n-1} \phi_i \, dx, \\
&\int_0^1 \sigma_h^n \phi_i \, dx + D_2 \Delta t \int_0^1 (\sigma_h^n)_x (\phi_i)_x \, dx - \int_0^1 \Big(\frac{\sigma_h^n}{\tau_{2_h}^n} (\tau_{2_h}^n)_x \Big) (\phi_i)_x \, dx
\end{aligned}$$

$$= \int_0^1 \sigma_h^{n-1} \phi_i \, dx,$$

$$\int_0^1 m_h^n \phi_i \, dx \, + \, D_3 \Delta t \int_0^1 (m_h^n)_x (\phi_i)_x \, dx \, - \int_0^1 \Big(\frac{m_h^n}{\tau_{3_h}^n} (\tau_{3_h}^n)_x \Big) (\phi_i)_x \, dx$$

$$= \int_0^1 m_h^{n-1} \phi_i \, dx.$$

This is a coupled system of nine nonlinear equations. The sustem can be linearized in the usual manner by using a Newton or quasi-Newton method. However, when the model is extended to two or three dimensions the system of equations becomes prohibitively large. For this reason, this project considers an alternative apporach to handling the nonlinearity.

To solve this system of coupled nonlinear equations, this project is linearized by lagging the nonlinear terms and iterating at each timestep. This implies having an initial guess for the nonlinear parts and shifting them to the right hand sides of the equations. Specifically, let $(u_h^n)^k$ denote the k-th iterate at the n-th timestep. The system for $i = 1, \ldots, p$ and $k = 0, \ldots, m$ becomes:

$$\int_0^1 u_h^{n,k+1} \phi_i \, dx$$

$$= - \Delta t \int_0^1 \frac{\lambda_2 u_h^{n,k} m_h^{n,k}}{1 + \nu_2 u_h^{n,k}} \phi_i dx \, + \int_0^1 u_h^{n-1} \phi_i \, dx \, + \int_0^1 u_r^{n,k} \phi_i \, dx,$$

$$\int_0^1 \upsilon_h^{n,k+1} \phi_i \, dx$$

$$= \Delta t \int_0^L \Big(\frac{\lambda_2 u_h^{n,k+1} m_h^{n,k}}{1 + \nu_2 u_h^{n,k+1}} - \frac{\lambda_1 \upsilon_h^{n,k} \eta_h^{n,k}}{1 + \nu_1 \upsilon_h^{n,k}} \Big) \phi_i dx \, + \int_0^L \upsilon_h^{n-1} \phi_i dx \, + \int_0^L \upsilon_r^{n,k} \phi_i dx,$$

$$\int_0^L c_h^{n,k+1} \phi_i \, dx$$

$$= (\Delta t) \int_0^L \frac{\lambda_1 \upsilon_h^{n,k+1} \eta_h^{n,k}}{1 + \nu_1 \upsilon_h^{n,k+1}} \phi_i dx \, + \int_0^L c_h^{n-1} \phi_i \, dx,$$

$$\int_0^L f_h^{n,k+1} \phi_i \, dx$$

$$= \Delta t \int_0^L \left(\beta(f_h^{n,k}) \, (f_{M_h} - f_h^{n,k}) \eta_h^{n,k} - \frac{\lambda_4 (c_a)_h^{n,k+1} f_h^{n,k}}{1 + \nu_4 f_h^{n,k}} \right) \phi_i dx + \int_0^L f_h^{n-1} \phi_i \, dx,$$

$$\int_0^L a_h^{n,k+1} \phi_i \, dx$$

$$= -\Delta t \int_0^L \frac{\lambda_3 a_h^{n,k} \eta_h^{n,k}}{1 + \nu_3 a_h^{n,k}} \phi_i \, dx$$

$$\int_0^L (\imath_a)_h^{n,k+1} \phi_i \, dx$$

$$= \Delta t \int_0^L \frac{\lambda_3 a_h^{n,k+1} \eta_h^{n,k+1}}{1 + \nu_3 a_h^{n,k+1}} \phi_i \, dx$$

$$\int_0^L \eta_h^{n,k+1} \phi_i \, dx + D_1 \Delta t \int_0^L (\eta_h^{n,k+1})_x (\phi_i)_x \, dx$$

$$= \int_0^L \left(\frac{\eta_h^{n,k}}{(\tau_1)_h^{n,k+1}} (\tau_1)_h^{n,k+1})_x \right) (\phi_i)_x \, dx + \int_0^L \eta_h^{n-1} \phi_i \, dx,$$

$$\int_0^L \sigma_h^{n,k+1} \phi_i \, dx + D_2 \Delta t \int_0^L (\sigma_h^{n,k+1})_x (\phi_i)_x \, dx$$

$$= \int_0^L \left(\frac{(\sigma_h^n)^k}{(\tau_2)_h^{n,k+1}} (\tau_2)_h^{n,k+1})_x \right) (\phi_i)_x \, dx + \int_0^L \sigma_h^{n-1} \phi_i \, dx,$$

$$\int_0^L m_h^{n,k+1} \phi_i \, dx + D_3 \Delta t \int_0^L (m_h^{n,k+1})_x (\phi_i)_x \, dx$$

$$= \int_0^L \left(\frac{m_h^{n,k}}{(\tau_3)_h^{n,k+1}} (\tau_3)_h^{n,k+1})_x \right) (\phi_i)_x \, dx + \int_0^L m_h^{n-1} \phi_i \, dx,$$

For $k = 0$, the initial values are set to the values of the previous timestep. As the system iterates, the resulting approximations are used in place of the previous ones. The iteration continues until a presubscribed convergence criterion is satisfied or the iteration fails (in which case the timestep is reduced). The system is then solved using a banded Cholesky solver, with the integration approximated by a three-point Gauss quadrature rule.

5 Implementation

For all computations presented here the domain $[0, L]$ is developed into $p-1$ elements and continuous piecewise quadradic basis functions are used. The nodes of the elements are not uniformly spaced as in the computations presented in [3]. A nonuniform mesh is chosen here so that the behavior of the variables may be more efficiently captured. This results in a finer mesh within the area of greatest change, thereby allowing a higher degree of accuracy. Since fewer points are required for a comparable approximation near the boundaries, a coarser mesh is used in these fairly static regions. With a uniform mesh, more points would be required to attain similar results; thus a non-uniform mesh requires fewer calculations, meaning less calculation time. As mentioned above, a dynamic timestep is also used for similar reasons.

At each timestep, the equations are solved in as uncoupled manner. That is, first they are solved for $u_h^{n,k+1}$, then used to solve for $v_h^{n,k+1}$, etc. This reduces the solving to a small linear system for each variable. For example, for 100 elements, there is a 101×101 banded matrix. Moreover, the coefficient matrix is a symmetric positive definite matrix which can be factored once using a banded Cholesky factorization and then stored. Hence at each iteration each of the varlables is determined by only performing the backsolver ($O(p^2)$) operation. The remaining variables η, σ, and m have a coefficient matrix which depends on time and hence must be assembled at each timestep; this matrix is also banded, symmetric, and positive definite so that a Cholesky solver can be used.

The convergence criterion used for the iteration at each timestep is based on the residual vector for the entire system. Once an iteration has completed, a residual vector is computed and compared against the current solution. If the L^2 norm of these vectors is within a certain tolerance, the system has converged sufficiently and calculations are begun on the next timestep. If the solutions do not converge they are discarded and the process is stopped. In order to obtain convergence the timestep size is then reduced, after which the calculations are resumed at the beginning of the new timestep.

A typical run used an initial timestep of $\frac{1}{2}(\Delta x)^2$ hours. The number of timesteps varied; for shorter runs, about 400 timesteps were used. For medium runs, between 24,000 and 48,000 timesteps were used, and for the longer runs roughly 96,000 timesteps were needed. On average, the number of iterations required for convergence on each timestep was between four and six.

Originally this project was modelled using MATLAB on a G3 Macintosh. However, this proved to be unreasonably slow, and so the project code was ported to Fortran and run on a DEC Alphastation. The results of the Fortran code were then saved to a MATLAB script file, which was then transferred to the Macintosh. From there, the data were graphed using MATLAB. This allowed the visulaization of the impact of various parameters on the system.

6 Numerical Results

The first aspect of the model that this project focused on was to make a modification to the equations proposed by Levine, et al. [3]. Within Dr. Levine's project, the equation $c_a = \frac{c}{1+\nu_e i_a}$ was used to represent the concentration of active protease when angiostatin acts as an inhibitor generator. When angiostatin acts as the inhibitor itself, the equation changes to $c_a = \frac{c}{1+\nu_e a}$. The results of the angiostatin as inhibitor generator are shown in Fig. (refoldca). These equations represent the deactivation of protease by an inhibitor. However, they do not take into account the fact that while protease is reacting with one molecule of fibronectin, it is unable to react with another molecule of fibronectin [4]. In order to more accurately represent this, the equations are modified to the following:

$$
\begin{aligned}
c_a &= \frac{c}{1 + \nu_e \imath_a + \nu_4 f} \\
c_a &= \frac{c}{1 + \nu_e a + \nu_4 f}
\end{aligned}
$$

for angiostatin acting as an inhibitor generator and as an inhibitor, respectively. The results of this modification in the case of angiostatin being the inhibitor generator are shown in Fig. (refnewca). Fig. (refnewvsoldrepair) shows a comparison of the fibronectin for the old and new c_a equations at various timesteps. Fig. (refnewvsolddecay) shows a comparison of the two cases for small times. It is possible to see that the fibronectin begins to be degraded later and repaired sooner with the new value of c_a than with the old one. This is to be expected as less protease is now available to begin interacting with the fibronectin at any given time.

With the use of the new equation for c_a, the project looks at the differences that occur when angiostatin acts as an inhibitor generator versus when it acts as an inhibitor. It also studies impact of different values for the rate of increase of angiostatin and its equilibrium constant. In figures (refig2.5) through (refig250t), angiostatin is considered as an inhibitor generator with an equilibrium constant $\nu_e = 1000$. In (refig2.5), the rate of increase of angiostatin, a_r, is 2.5, while it is set to 25 in (refig25) and 250 in (refig250t). It can be seen that a few of the graphs change noticeably, while the others remain fairly stable. As the rate at which angiostatin is supplied increases, the fibronectin begins to repair itself noticably sooner. The endothelial cell concentration is also of note; as the rate of supply increases, the cell concentration comes to a peak sooner and more steeply. The same can also be seen in figures (refig250) to (refig25000). These figures consider the values $a_r(x,t) = 250, 2500, 25000$ respectively for the equilibrium constant $\nu_e = 1.0$. Again, the fibronectin begins to repair itself sooner as the rate of supply of angiostatin increases. However, in this case it is not very noticeable until $a_r(x,t) = 25000$.

Angiostatin is then considered as an inhibitor. Figures (refi2.5) and (refi25) again correspond to $a_r = 2.5$ and $a_r = 25$ respectively, with an equlibrium constant $\nu_e = 1000$. Similarly, figures (refig2500) and (refig25000) represent the results when $a_r = 2500$ and $a_r = 25000$ respectively, with $\nu_e = 1.0$. It is important to note that when $a_r = 250$ and $nu_e = 1.0$ while angiostatin is acting as an inhibitor, the results fail to converge with this algorithm. It is possible to see that a similar trend is developed with the lower rates of increase in the sense that the fibronectin again repairs itself sooner with higher rates of supply of angiostatic factor. On the other hand, when the value of $a_r(x,t)$ exceeds 2500, little to no difference is apparent.

It interesting to note that there does not appear to be much difference between the corresponding figures of angiostatin acting as an inhibitor and as an inhibitor generator. However, it should be pointed out that there is a noticable difference in the healing of the fibronectin between figures (refi2500) and (refig2500). Also, when comparing figures (refi25000) and (refig25000) it can be seen that there is a discrepency between the graphs of endothelial cells.

The grid size this project used (81 points) is a good demonstration of compromise between precision and calculation time. Figure (refnx) shows a significant magnification of the tip of the endothelial cell graph taken at an arbitrary timestep. It can be seen that the largest jump occurs between 61 and 71 nodes. The increase in precision between 81 and 101 nodes is drastically smaller even though the number of nodes is increased by twice as much.

The following constants table was used:

Table 1: Data set for numerical simulations

$\eta(x,t)$ (Endothelial cell movement)	$D_1 = 3.6 \times 10^{-5}$	$\alpha_1 = 0.001$	$\alpha_2 = 1.0$	$\gamma_1 = 1.2$
η (EC movement continued)		$\beta_1 = 1.0$	$\beta_2 = 0.001$	$\gamma_2 = 1.2$
$\sigma(x,t)$ (PC movement)	$D_2 = 3.6 \times 10^{-5}$	$\alpha_3 = 1.5^{-3}$	$\alpha_4 = 1.0$	$\gamma_3 = 2.0$
$m(x,t)$ (MC movement)	$D_3 = 3.6 \times 10^{-5}$	$\beta_3 = 0.5$	$\beta_4 = 1.0$	$\gamma_4 = 2.0$
u (Chemotactic factor kinetics)	$\lambda_2 = 75.0$	$\nu_2 = 0.01$		
v (Angiogenic factor kinetics)	$\lambda_1 = 73.0$	$\nu_1 = 0.007$	$v_r(x,t) = 0.0$	
c (Proteolytic enzyme kinetics)	$\lambda_1 = 73.0$	$\nu_1 = 0,007$	$\mu = 0.0$	
f (Fibronectin rate law)	$\beta = 0.22$	$\lambda_4 = 19.0$	$\nu_4 = 1.205$	$f_m = 0.01$
a, $\imath_a$ (Angiostatin as inhibior generator)	$\lambda_3 = 100.0$	$\nu_3 = 0.002$	$\nu_e = 1.0 \times 10^3$	
a_r (Angiostatin as inhibitor generator)	$a_r(x,t) = 0.0$	$a_r(x,t) = 25.0$		
a_r (Angiostatin as inhibitor)		$a_r(x,t) = 250.0$	$\nu_e = 1.00$	
u_r (Chemotactic factor forcing term)		$u_0 = 15$	$\theta = 0.0$	$m = 40$

7 Conclusion and Future Research

In conclusion, this project has demonstrated that the revision from [4] to incorporate the new equation for c_a does in fact result in a more accurate model. The figures show that changing the equilibrium constant ν_e has a greater impact than increasing the rate of supply of angiostatic factor. This may be more practical as well, due to physiological limitations. Also, this project has demonstrated that refining the grid size beyond 81 nodes does not result in a significant increase in accuracy.

Areas of further research interest include:

- Refining the algorithm to be more stable

- Grid refinement to a more efficient arrangement of points
- Parameter studies
- Expantion to two and three dimensions

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