Numerical solution for model of tumour growth and metastasis

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Abstract

In this project I use the system of coupled partial differential equations modeling the growth of tumours developed in [2] to (i) study and understand the physical interpretation of the states and parameters, (ii) derive weak forms of the system of partial differential equations, (iii) compute a numerical solution for the states using FEniCS, (iv) model the growth of tumors in one-dimensional space in time, and (v) interpret the numerical solution.

1 INTRODUCTION

The development of mathematical models to describe the dynamics of tumor growth has made the analysis of the disease easier and less expensive. There are many ordinary differential equations that describe the dynamics of tumor growth [11, 12, 6, 13]. A major modeling deficit of such models, however, is that they fail to capture the spatial dependence of tumor growth. As stated in [4], it is not merely the cell count of tumors that makes them deadly, but rather how the tumor spatially occupies surrounding organs and tissues. Thus various partial differential equation models of tumor growth have been developed [1, 9, 10] to capture spatial evolution. In this paper I will consider the mathematical model developed in [2] by Anderson, Chaplain, Newman, Steele, and Thompson.

1.1 DESCRIPTION OF MODEL

1.2 Vocabulary

The following biological terms will be used freely in the following descriptions.

avascular: *A biological term describing the lack of blood vessels.*
angiogenesis: *A chemically induced formation of capillaries. In tumour growth these capillaries penetrate the tumour and connect it to the circulatory system.*
metastasis: *A biological term describing the spread of tumours from their original site to other organs in the body.*
intravasation: *The action of tumour cells entering the circulatory system.*
extravasation: *The action of tumour cells exiting the circulatory system.*
extracellular matrix (ECM): *The tissue surrounding the tumour cells.*
matrix degradative enzymes (MDE): *Enzymes which degrade the ECM.*
haptotaxis: *A chemically induced directed movement of tumour cells.*

1.3 States and Parameters

$\mathbf{J}_{hapto}$: *The haptotactic flux.*
$\mathbf{J}_{random}$: *The flux describing the random motility of tumour cells.*
n : *The state of the system describing tumour cell density.*
f : *The state of the system describing the ECM concentration.*
m : *The state of the system describing the MDE concentration.*

d_n : *Non-dimensionalised tumour random motility coefficient.*
γ : *Non-dimensionalised cancer cell proliferation rate.*
η : *Non-dimensionalised degradation rate.*
d_m : *Non-dimensionalised MDE diffusion coefficient.*
α : *Non-dimensionalised MDE production rate.*
β : *Non-dimensionalised natural MDE decay rate.*

1.4 Description of system

A solid tumour begins with a single mutated cell which divides and develops into a nodule of tumour cells. The division continues and an *avascular* tumour develops. Due to the avascular nature of the tumour it can only receive nutrients and remove waste my means of diffusion. Thus as the size of the tumour increases the center is unable to be nourished and the growth rate decreases. The tumour can continue to develop if it induces *angiogenesis*. Once angiogenesis occurs the new capillaries deliver nutrients to the tumour and it can continue to grow without bound. Additionally, once connected to the circlulatory system the tumour can *metastasize*.

An important step in metastasis is the degradation of the *extracellular matrix* (ECM). *Matrix degradative enzymes* (MDEs) contribute to the degradation of ECM as well as to other stages of tumour growth and metastasis. Additionally, MDEs induce *haptotaxis*. In our mathematical model, we describe the contribution of this chemical response as the haptotactic flux, with a positive haptotactic coefficient. Tumour cells also move due to random motion, whose contribution to cell motility is described by a random flux with a positive random motility coefficient. The model assumes that MDEs immediately degrade ECM with positive degradation rate. MDEs are activated by tumour cells at a positive rate, diffuse throughout the tissue with a positive diffusion coefficient, and naturally decay with a positive rate.

The process above is described in the following non-dimensionalised system of partial differential equations, as derived in [2].

1.5 Non-dimensionalized model

$$\frac{\partial n}{\partial t} = d_n \nabla^2 n - \gamma \nabla \cdot (n \nabla f) \tag{1}$$

$$\frac{\partial f}{\partial t} = -\eta m f \tag{2}$$

$$\frac{\partial m}{\partial t} = d_m \nabla^2 m + \alpha n - \beta m \tag{3}$$

The following zero-flux boundary conditions are imposed for outward unit normal $\hat{\mathbf{n}}$, where the domain in one dimension is the interval [0,1],

$$\hat{\mathbf{n}} \cdot (-d_n \nabla n + n\gamma \nabla f) = 0 \tag{4}$$

$$\hat{\mathbf{n}} \cdot (-d_m \nabla m) = 0 \tag{5}$$

The initial conditions of the system are

$$n(x,0) = \begin{cases} e^{-x^2/0.01} & x \in [0, 0.25] \\ 0 & x \in (0.25, 1] \end{cases} \quad f(x,0) = 1 - 0.5n(x,0), \quad m(x,0) = 0.5n(x,0).$$

1.6 Nominal parameter values and ranges

Parameter	Lower Bound	Nominal Value	Upper Bound
d_n	0.0009	0.001	0.0011
γ	0.0045	0.005	0.0055
η	9	10	11
d_m	0.0009	0.001	0.0011
α	0.09	0.1	0.11
β	-0.01	0	0.01

Table 1: Nominal values and ranges of non-dimensionalized parameters in mathematical model. For the purposes of this project, ranges have been assumed to be 10% below and above the nominal value.

2 DERIVATION OF WEAK FORM

In order to implement the following numerical methods to solve the system (1)-(3), we must write the partial differential equations in their weak form. We first set each equation equal to zero

$$\frac{\partial n}{\partial t} - d_n \nabla^2 n + \gamma \nabla \cdot (n \nabla f) = 0 \tag{6}$$

$$\frac{\partial f}{\partial t} + \eta m f = 0 \tag{7}$$

$$\frac{\partial m}{\partial t} - d_m \nabla^2 m - \alpha n + \beta m = 0 \tag{8}$$

We then multiply each term by test function v_1, v_2, v_3, respectively, and integrate over the domain, Ω.

$$\int_\Omega (\frac{\partial n}{\partial t} - d_n \nabla^2 n + \gamma \nabla \cdot (n \nabla f)) v_1 = \int_\Omega 0 v_1 \tag{9}$$

$$\int_\Omega (\frac{\partial f}{\partial t} + \eta m f) v_2 = \int_\Omega 0 v_2 \tag{10}$$

$$\int_\Omega (\frac{\partial m}{\partial t} - d_m \nabla^2 m - \alpha n + \beta m) v_3 = \int_\Omega 0 v_3 \tag{11}$$

For notational sake, let

$$\mathbf{F_1} = -d_n \nabla^2 n + \gamma \nabla \cdot (n \nabla f) = \nabla \cdot (-d_n \nabla n + n \gamma \nabla f),$$

and

$$\mathbf{F_2} = -d_m \nabla^2 m = \nabla \cdot (-d_m \nabla m).$$

Equations (6)-(8) become,

$$\int_\Omega \frac{\partial n}{\partial t} v_1 + \int_\Omega \nabla \cdot \mathbf{F_1} v_1 = 0 \tag{12}$$

$$\int_\Omega \frac{\partial f}{\partial t} v_2 + \int_\Omega \eta m f v_2 = 0 \tag{13}$$

$$\int_\Omega \frac{\partial m}{\partial t} v_3 + \int_\Omega \nabla \cdot \mathbf{F_2} v_3 - \int_\Omega \alpha n v_3 + \int_\Omega \beta m v_3 = 0 \tag{14}$$

Simplification using the Divergence Theorem, integration by parts, and implementation of boundary conditions specified in (4) and (5) yields,

$$\int_\Omega \frac{\partial n}{\partial t} v_1 + \int_\Omega \nabla v_1 \cdot \mathbf{F_1} = 0 \tag{15}$$

$$\int_\Omega \frac{\partial f}{\partial t} v_2 + \int_\Omega \eta m f v_2 = 0 \tag{16}$$

$$\int_\Omega \frac{\partial m}{\partial t} v_3 + \int_\Omega \nabla v_3 \cdot \mathbf{F_2} + \int_\Omega (-\alpha n + \beta m) v_3 = 0 \tag{17}$$

A full derivation of this weak form can be found in the appendix.

3 NUMERICAL SOLUTION

3.1 A discussion of methods

The authors of [2] compute numerical solutions to the tumour growth system using the Numerical Analysis Group (NAG) routine `D03PCF`. This routine computes numerical solutions for systems of linear or nonlinear parabolic partial differential equations. The routine uses a method of lines to discretize the system into a system of ordinary differential equations using a central difference scheme. This discretized system of ODEs is then solved using a backward differentiation scheme [8].

The `D03PCF` scheme integrates the parabolic system of PDEs of the specific form given in [8],

$$\sum_{j=1}^{numPDEs} P_{i,j} \frac{\partial U_j}{\partial t} + Q_i = x^{-m} \frac{\partial}{\partial x}(x^m R_i), \;\; i = 1, 2, ...numPDEs,$$

with boundary conditions,

$$\phi_i(x,t) R_i(x,t,U,\frac{\partial U}{\partial x}) = \psi_i(x,t,U,\frac{\partial U}{\partial x})$$

In this notation, $numPDE$ is the number of state equations in the system, U is the state vector, $P_{i,j}, Q_i, R_i$ depend on x, t, U, and $\frac{\partial U}{\partial x}$. For the tumour growth system of nonlinear parabolic PDEs, these functions are defined as follows.

$$P_{i,j} = \begin{cases} 0 & i \neq j \\ 1 & i = j \end{cases} \quad Q_i = \begin{cases} 0 & i = 1 \\ \eta m f & i = 2 \\ -\alpha n + \beta m & i = 3 \end{cases} \quad R_i = \begin{cases} d_n \nabla n - \gamma n \nabla f & i = 1 \\ 0 & i = 2 \\ d_m \nabla m & i = 3 \end{cases}.$$

The boundary conditions are satisfied by

$$\phi_i = \begin{cases} 1 & i = 1 \\ 0 & i = 2 \\ 1 & i = 3 \end{cases} \quad \psi_i = \begin{cases} 0 & \forall i \end{cases}.$$

Implementing these functions as defined above in the NAG `D03PCF` routine will yield a one-dimensional solution to the tumour growth system in time.

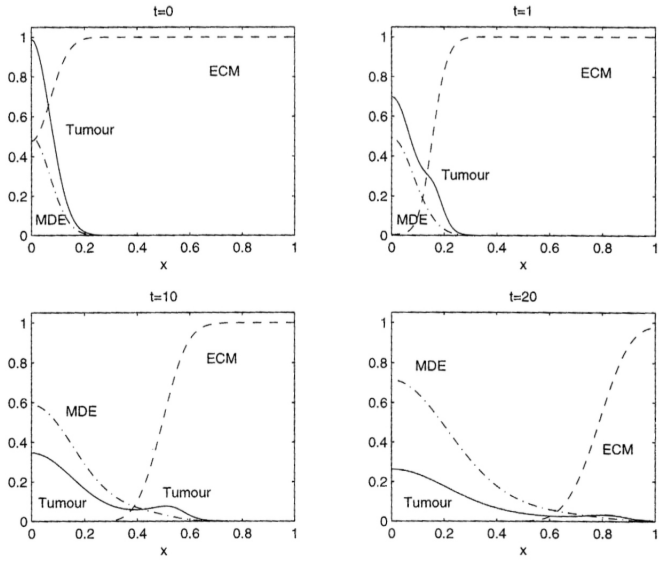

Figure 1: Numerical solution from [2] to system of parabolic partial differential equations describing the growth and metastasis of tumours in time. The solutions have been computed using the NAG D03PCF routine using non-dimensional parameter values defined in Table 1.

NOTE: After learning about the `D03PCF` *routine and successfully installing NAG* (`nag4py`), *and after defining and implementing the previous function definitions, I kept getting fishy error messages. Following many tests, examples, and scouring of online help forums, I learned that I do not have the license necessary to run NAG, and to obtain one I would need to send an email request. The process for requesting a trial license number is extremely involved and I have not yet done this. Considering that I trust my definitions to be the same as those of the authors of [2], I expect the numerical results to be the same.*

In [3], Chaplain details another numerical method for integrating a similar system of parabolic PDEs originally developed in [5]. The authors refer to this scheme as a Custom Finite Volume Code (CFVC), which also employs the method of lines. Unlike the NAG routine, however, the CFVC uses a higher-order upwind-based finite volume discretization of space instead of a central difference discretization. The system of ODEs is integrated using the linearly implicit Runge-Kutta method, ROWMAP [14]. This method is used due to the stiff nature of the system and because there is no explicit subroutine to evaluate the Jacobian. The linear systems are then solved using Arnoldi processes.

3.2 Implementation of system in FEniCS

FEniCS [7] is a finite element based python package for computing numerical solutions for partial differential equations. Implementation in FEniCS requires writing the system in the weak form derived above.

The implementation of this PDE is in the attached `tumor_growth.py` document. The steps necessary to implement the system are clearly noted and thus will not be reproduced here. It is important to note that the solver used is a Newton Solver that implements an LU factorization to solve the nonlinear problem. Additionally, because this system has explicit dependence on time, we discretize the terms $\frac{\partial n}{\partial t}$, $\frac{\partial f}{\partial t}$, and $\frac{\partial m}{\partial t}$ as $\frac{n-n_{n-1}}{\delta t}$. We then time step through and solve the solutions at each time step. This implementation

was inspired by an example in [7] and while I believe it has been implemented correctly, my unfamiliarity with the package prevents me from stating so with full confidence. All implementation choices made and described in `tumor_growth.py` have been inspired by examples in [7] and various online forums. However, no matter what example I found, all systems differed in one or more important ways from the tumour growth system explored here. Thus I have done my best piecing together, understanding, and interpreting a variety of resources.

NOTE: After fiddling around with different solvers and different ways by which to implement boundary conditions, I finally got my solver to converge. However, I am unable to plot the solutions. This may be because I don't fully understand the data structures used within the FEniCS package. Alternatively it may be because, despite the absence of error messages and the presence of convergence, I didn't implement this problem correctly.

4 FUTURE WORK

I do not feel satisfied by my FEniCS implementation and still seek to find a numerical solution for the tumour growth system presented here. I intend to use this model to explore global parameter sensitivity analysis for my research. For future work with this system I will adapt and implement the numerical method discussed in [5] wherein a custom finite volume method has been developed to compute numerical solutions for a very similar system for tumour growth. I will then conduct numerical experiments to test the convergence and stability of the methods. Once I have implemented a satisfiable numerical method for this system, I will be able to use the model and its solution in my research.

Now that I have the FEniCS package installed, I plan to further study it. Too large of a chunk of the time I spent on this project was used trying to wrangle and install various packages. I aim to continue to study and learn how to use this package and feel confident implementing it to compute solutions for other (easier) partial differential equations. The tutorial and explanations offered in [7] are thorough and clear as far as I can tell, and I plan to dedicate more time to fully understanding the package.

5 APPENDIX

5.1 Derivation of weak form

We first set each equation equal to zero

$$\frac{\partial n}{\partial t} - d_n \nabla^2 n + \gamma \nabla \cdot (n \nabla f) = 0$$

$$\frac{\partial f}{\partial t} + \eta m f = 0$$

$$\frac{\partial m}{\partial t} - d_m \nabla^2 m - \alpha n + \beta m = 0$$

We then multiply each term by test function v_1, v_2, v_3, respectively, and integrate over the domain, Ω.

$$\int_\Omega (\frac{\partial n}{\partial t} - d_n\nabla^2 n + \gamma\nabla\cdot(n\nabla f))v_1 = \int_\Omega 0v_1$$
$$\int_\Omega (\frac{\partial f}{\partial t} + \eta m f)v_2 = \int_\Omega 0v_2$$
$$\int_\Omega (\frac{\partial m}{\partial t} - d_m\nabla^2 m - \alpha n + \beta m)v_3 = \int_\Omega 0v_3$$

For notational sake, let

$$\mathbf{F_1} = -d_n\nabla^2 n + \gamma\nabla\cdot(n\nabla f) = \nabla\cdot(-d_n\nabla n + n\gamma\nabla f),$$

and

$$\mathbf{F_2} = -d_m\nabla^2 m = \nabla\cdot(-d_m\nabla m).$$

Equations (6)-(8) become,

$$\int_\Omega \frac{\partial n}{\partial t}v_1 + \int_\Omega \nabla\cdot\mathbf{F_1}v_1 = 0$$
$$\int_\Omega \frac{\partial f}{\partial t}v_2 + \int_\Omega \eta m f v_2 = 0$$
$$\int_\Omega \frac{\partial m}{\partial t}v_3 + \int_\Omega \nabla\cdot\mathbf{F_2}v_3 - \int_\Omega \alpha n v_3 + \int_\Omega \beta m v_3 = 0$$

By the product rule,

$$\int_\Omega \nabla\cdot\mathbf{F}v = \int_\Omega \nabla v\cdot\mathbf{F} + \int_\Omega v(\nabla\cdot\mathbf{F}).$$

Integration by parts on the last term in this expression gives,

$$\int_\Omega v(\nabla\cdot\mathbf{F}) = v\int_\Omega \nabla\cdot\mathbf{F} - \int_\Omega \left(\int_\Omega \nabla\cdot\mathbf{F}\right) dv.$$

By the Divergence Theorem,

$$\int_\Omega \nabla\cdot\mathbf{F} = \int_{\partial\Omega} \mathbf{F}\cdot\hat{\mathbf{n}}$$

where $\hat{\mathbf{n}}$ is the unit normal on $\partial\Omega$. Consider $\mathbf{F_1} := -d_n\nabla n + n\gamma\nabla f$ and $\mathbf{F_2} := -d_m\nabla m$. Then for both $\mathbf{F_1}$ and $\mathbf{F_2}$, we impose the zero-flux boundary conditions (4) and (5) and

$$\int_{\partial\Omega} \mathbf{F}\cdot\hat{\mathbf{n}} = 0.$$

Thus,

$$\int_\Omega \nabla\cdot\mathbf{F}v = \int_\Omega \nabla v\cdot\mathbf{F}.$$

We use this result to simplify and the final weak form yields,

$$\int_\Omega \frac{\partial n}{\partial t}v_1 + \int_\Omega \nabla v_1\cdot\mathbf{F_1} = 0$$
$$\int_\Omega \frac{\partial f}{\partial t}v_2 + \int_\Omega \eta m f v_2 = 0$$
$$\int_\Omega \frac{\partial m}{\partial t}v_3 + \int_\Omega \nabla v_3\cdot\mathbf{F_2} + \int_\Omega (-\alpha n + \beta m)v_3 = 0$$

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