Oxygen Diffusion Module For A Hybrid Computational Model of Breast Cancer

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by
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Abstract

Oxygen is a vital nutrient necessary for tumor cells to survive and proliferate. Oxygen is diffused from our blood vessels into the tissue, where it is consumed by our cells. This process can be modeled by partial differential equations with sinks and sources. This project focuses on adding an oxygen diffusion module to an existing 3D agent-based model developed in Professor Norton's lab. The mathematical model will include designing PDEs to simulate movement of oxygen molecules, writing functions to numerically evaluate said PDEs through Crank-Nicolson finite difference method, and finally, designing an error analysis function. After the mathematical model is complete, it will be programmed into the existing ABM, which means combining continuous and agent-based models into one hybrid model. The addition of an oxygen module will make the cancer model more realistic and will allow more accurate results in future in silico experiments.

Contents

Dedication

Text for dedication

Acknowledgments

Text of acknowledgments.

1
Introduction

Cancer is described by uncontrollable expansion of cells in our bodies, which grants it several hallmark abilities. This makes tumors difficult to treat, with frequent remissions and recurrences. Triple Negative Breast Cancer (TNBC) is a particularly difficult tumor to treat, as it lacks three most commonly targeted receptors. Professor Kerri-Ann Norton's computational biology lab has developed a 3-dimensional agent-based model of TNBC. The most recent research purpose of Norton's lab was to simulate effects of a newly developed immunotherapy on the tumor, and observe the parameters and conditions that affect the effectiveness of this treatment. This project aims to improve the model by adding an oxygen diffusion module.

Diffusion refers to the movement of material from high to low concentrations. A classic example of this process is movement of heat through a rod. This project looks at the diffusion of oxygen from our blood vessels into tissue. Once the oxygen is diffused into the tissue, it is then absorbed by our cells as a form of nutrition necessary to support cell life and reproduction. Like any other cells, tumorous cells also rely on oxygen to sustain their lives and expansion. The term Hypoxia refers to cells being too far from vasculature to obtain oxygen. The TNBC model this project builds on incorporates hypoxia and alters tumor behavior accordingly. For example, hypoxic cells have slower proliferation and migration rates than cells that have access of oxygen and nutrition. Therefore, having an accurate and realistic representation of the movement of oxygen molecules through our tissue and to the tumorous cells is crucial for having in our model yield realistic results.

Adding an oxygen diffusion module requires several steps. First, the design of accurate partial differential equations to model diffusion with sources (vasculature) and sinks (tumor cells absorbing oxygen). Second, a numerical evaluation method will be necessary to estimate the value (amount) of oxygen at a given location. This method will have to apply to three spacial and one time dimension, as the existing method is 3-dimensional. Third, the mathematical model, which is sometimes referred to a continuous model, will have to be integrated into the existing agent-based model. Finally, there will be a need for an error analysis function to bound the round-off and computational errors yielded by numerical approximations and computation scales. After the model is complete, it will be validated to prove its correctness. Then, we will re-run previous simulations to check for significant differences in results.

2
Mathematics Background

2.1 Partial Differential Equations (PDEs)

Partial differential equations, or PDEs, are equations that depict a relationship between an unknown function and its partial derivatives. These functions in PDEs, unlike in ordinary differential equations, depend on more than one variable; for example, time and space as opposed to just time or just space. Most physical phenomena can be modeled and described through PDEs. Some common examples include the heat equation, the wave equation, laws of motion, certain quantum mechanics phenomena, etc. In other words, most processes that describe the change of a quantity over time across space can be modeled by a PDE. The mathematical model described in this project will implement a type of diffusion equation. Therefore, we begin by exploring the derivation and evaluation of the classic diffusion equation.

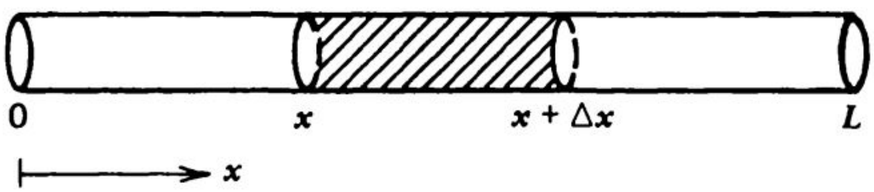
2.1.1 The Diffusion Equation With One Spatial Dimension

Diffusion refers to the process of matter moving from high to low concentrations of some medium. A classic example comes from a physics problem that looks at heat diffusing through a rod. We begin with a rod of fixed length L. Heat is traveling through this rod from one end to another. In order to be able to calculate the function U at a given time t at a given location x, we need to write and evaluate a partial differential equation. In this chapter, we set up the mathematical model and thus derive the classic diffusion equation.

Before the we set up the PDE, we have to specify our *initial* and *boundary* conditions. Initial conditions refer to the temperature throughout the rod at time $t = 0$. In other words, what is the initial temperature of the rod? If $U(x,t)$ denotes temperature at time t and location x, some examples of initial conditions can include $U(x,0) = 0$, $U(x,0) = sin(x)$, etc. Boundary conditions refer to the temperature of the rod on the boundary. Namely, when $x = 0$ and when $x = L$. For example, we could have

$$\begin{cases} U(0,t) = 0 \\ U(L,t) = T, \end{cases}$$

for some temperature T, and for $0 < t < \infty$.



Thin Conducting Rod

Next, we derive the heat equation commonly known as $U_t = U_{xx} + F(x,t)$, where $U_t = \frac{\partial U}{\partial t}$, $U_{xx} = \frac{\partial^2 U}{\partial x^2}$, and $F(x,t)$ is the source/sink function.To keep things simple, we will ignore constant coefficients that would come up in physical occurrences. For this part, we think about how heat moves through the rod over time - in other words, what factors affect U_t. It makes sense for us to conclude that the change in temperature at a given location is affected by two things: first, the flow of heat through that location. Second, any outside sources or sinks affecting the rod at that location, for example, a swing of a baseball bat that could provide external source of heat. So, we have

$$\text{change in } U \text{ in time} = \text{Flow of heat at } x,t + \text{external heat from sources or sinks at } x,t.$$

Let $Q(x,t)$ be the heat flow (or flux) function through the rod. In other words, the function that represents how heat flows from one location to the other. We define heat to flow from left to right. That means that when heat flux is negative, we have bigger temperature on the right boundary compared to the left boundary. So, when flux is negative, we have positive change to the temperature at that location. Therefore, we need to multiply the heat flow by a negative sign in our equation. Then, to show how the heat flow changes at a given location, we take the space derivative to see that

$$U_t = -Q_x + F(x,t).$$

Next, we derive Q in terms of U. A good way to demonstrate the process is to slice our rod into tiny cylindrical pieces starting at x and ending at $x + \Delta x$, where Δx is arbitrarily small. Then, we see that the flow of heat through this cylindrical slice of rod is the difference in the temperatures at the two ends of the slice averaged through the length of the slice. So, to find the flux of heat through this slice, we have $Q_x = \frac{U(x,t)-U(x+\Delta x,t)}{\Delta x}$. However, since we are interested at the instantaneous flux of heat at x as opposed to through the slice, we take the limit as Δx goes to 0. This gives us

$$Q_x = \lim_{\Delta x \to} \frac{U(x,t) - U(x+\Delta x,t)}{\Delta x} = -U_x.$$

Substituting the above equation in our current diffusion equation, we get

$$U_t = -(-U_x)_x + F(x,t) = U_{xx} + F(x,t).$$

This concludes our derivation of the heat equation with one spatial dimension.

2.1.2 Diffusion Equation For Higher Spatial Dimensions

Let us generalize the diffusion equation for higher dimensions. For this part, we follow the same general structure as in the previous chapter. However, we now focus on a 3-dimensional volume instead of a one dimensional rod. This volume can have arbitrary shape and size.

Now, let us once again think about what components affect the total change of temperature in time. As we saw with the rod example, two factors contribute to the total change in temperature. First, heat can be flowing into or from the object. But, since we now have an object with volume, heat would flow through the boundary. Second, we can have additional source or sink of heat inside the volume (for example, the object can receive an external hit, which can generate additional heat energy). So, we have a rough equation that looks like

Total change in Temperature $=$ Heat flowing through the boundary + External source or sink

First, let us think about how to calculate heat flux through the boundary. Here, we refer to Fourier's Law of Heat Conduction.

Theorem 2.1.1 (Fourier's Law of Heat Conduction)**.** *The rate of heat transfer through a material is proportional to the negative gradient in the temperature and to the area, at right angles to that gradient, through which the heat flows.*

Putting Fourier's Law in differential form, (ignoring constants), we get $\vec{Q}(X,t) = -\vec{\nabla}U(X,t)$, where X is the spatial position vector and Q represents heat flux. However, recall that we define heat to flow from left to right. Therefore, in our final equation, we need to use the negative of heat flux, because the body gains heat if Q is negative. Additionally, we need to take the dot product of Q with the normal vector $\vec{n}$ pointing perpendicular to the surface. This way, we get the direction of the heat flux to or from the object. Then, if V is the volume of the object, and S is its surface, we need to look at the change total heat energy of the object as well as the total flux through the entire surface and the total additional heat energy from sinks/sources across the volume. This calls for volume and surface integrals. Therefore, we end up with

$$\frac{\partial \iiint_V U(X,t)\,dV}{\partial t} = -\iint_S \vec{Q}(X,t)\cdot\vec{n}\,dS + \iiint_V F(X,t)\,dV$$

In order to make matters easier, we need to find a way to convert the surface integral into a volume integral. For that, we refer to Gauss's Theorem of Divergence.

Theorem 2.1.2 (Gauss's Theorem of Divergence)**.** *Suppose V is a subset of $\mathbb{R}^n$ (in the case of $n = 3, V$ represents a volume in three-dimensional space) which is compact and has a piecewise smooth boundary S (also indicated with $\partial V = S$). If F is a continuously differentiable vector field defined on a neighborhood of V, then*

$$\iiint_V (\nabla\cdot F)\,dV = \iint_S (F\cdot\vec{n})\,dS,$$

The left side is a volume integral over the volume V, the right side is the surface integral over the boundary of the volume V. The closed manifold ∂V is oriented by outward-pointing normals, and n is the outward pointing unit normal at each point on the boundary ∂V. d *may be used as a shorthand for* dS.) *In terms of the intuitive description above, the left-hand side of the equation represents the total of the sources in the volume V, and the right-hand side represents the total flow across the boundary S.*

Using this theorem, we can rewrite $\iint_S \vec{Q}(X,t)\cdot\vec{n}\,dS$ as $\iiint_V (\vec{\nabla}\cdot(Q(X,t)\,dV$. Then, our final equation ends up being

$$\frac{\partial \iiint_V U(X,t)\,dV}{\partial t} = -\iiint_V (\vec{\nabla}\cdot(Q(X,t)\,dV + \iiint_V F(X,t)\,dV$$

Next, we use Fourier's Law to write

$$\frac{\partial \iiint_V U(X,t)\,dV}{\partial t} = \iiint_V (\vec{\nabla}\cdot\vec{\nabla}U(X,t)\,dV + \iiint_V F(X,t)\,dV$$

We rearrange terms to get

$$\iiint_V U(X,t)_t - \vec{\nabla}^2 U(X,t) - F(X,t)\,dV = 0.$$

However, recall that this equation is true for arbitrary volume V. Therefore, the only way for this volume integral to always equal 0 is if the expression inside the integral itself equals 0. Therefore, we get

$$U(X,t)_t - \vec{\nabla}^2 U(X,t) - F(X,t) = 0$$

, therefore,

$$U(X,t)_t = \vec{\nabla}^2 U(X,t) + F(X,t).$$

This equation is known as higher dimensional heat diffusion equation. We will use this later on in our mathematical model of oxygen diffusion, where oxygen diffuses from blood vessels into three dimensional tissue. In the next chapter, we look at ways to numerically evaluate diffusion-type equations.

2.2 The Finite Difference Method

Text.

2.2.1 Crank-Nicolson Method

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3
Computer Science Background

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3.0.1 Agent-Based Versus Continuous Models

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3.0.2 Error Analysis

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4
Setup of Mathematical Model

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5
Computational Methods

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6
Validating the Model

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7
Results

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8
Discussion and Conclusions

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Appendix A
Title of First Chapter of Appendices

A.1 Title of First Section of Appendices

Text.

Bibliography

[1] first name last name, *title*, publisher, city, year.

[2] ———, *title*, journal name **volume number** (year), starting page–ending page.

[3] ———, *title*, `webaddress`.

[4] ———, *title*. arXiv address.