Tumor ablation due to inhomogeneous – anisotropic diffusion in generic 3-dimensional topologies

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Abstract

We derive a full 3-dimensional (3-D) model of inhomogeneous – anisotropic diffusion in a tumor region coupled to a binary population model. The diffusion tensors are acquired using Diffusion Tensor Magnetic Resonance Imaging (DTI) from a patient diagnosed with glioblastoma multiform (GBM). Then we numerically simulate the full model with Finite Element Method (FEM) and produce drug concentration heat maps, apoptosis regions, and dose-response curves. Finally, predictions are made about optimal injection locations and volumes, which are presented in a form that can be employed by doctors and oncologists.

Keywords: Cancer, finite element method, diffusion tensor imaging, tumor ablation.
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1 Introduction

Among the various types of tumors, brain tumors are associated with very high mortality. The five-year survival rate for people with a malignant brain or central nervous system tumor is approximately 34% for men and 36% for women in the United States and brain tumors account for 85% to 90% of all primary central nervous system tumors [1].

One of the major obstacles to improve current treatments is the presence of some physical barriers such as the blood-brain barrier and the bloodbrain tumor barrier impeding drugs from reaching the tumor sites in the brain [2, 3, 4]. The blood-brain barrier (BBB), existing between the brains microvessels and tissue, prevents many macromolecules from entering interstitial space in the brain; thus separating the central nervous system and systemic circulation of the body. It is reported in [5] that BBB prevents entry of approximately 98% of the small molecules and nearly 100% of large molecules, such as recombinant proteins or gene-based medicines into brain tumors from the vascular compartment. Similarly, the bloodbrain tumor barrier (BBTB) is located between brain tumor tissues and the brain’s blood vessels formed by highly specialized endothelial cells, limiting the delivery of most anti-cancer drugs to tumor tissue. To overcome the challenges associated with these barriers, several
methods have been developed such as intrarterial administration, barrier disruption, drug packaging, and inhibiting drug efflux from tumors [6]. Regardless, oral and intravascular administration allows only a small fraction of therapeutic agents to reach the tumor region in the brain because the drug concentration decreases precipitously due to the sink effect of the extracellular space along the route of drug transport to the tumor region. Thus, necessitating the administration of a high dose to achieve sufficient drug concentrations to kill the tumor cells. Unfortunately, physiological toxicity limits the amount of therapeutic agent allowed in a particular therapy.

Significant effort has gone into developing therapies with high efficacy to toxicity ratios through the use of lower drug concentrations via direct administration in targeted regions. One such method is discussed in de Boer et al. [5]. Drug injection therapies allow for uncomplicated individualized treatment for solid accessible tumors [5, 7, 8, 9, 10]. Further, these types of therapies provide us with an opportunity to optimize drug efficacy by changing the fluidic properties of the injection as shown by Morhard et al. [9]. While testing a variety of therapeutic agents on animals is time intensive and costly, numerical simulations may prove to be a cheap and effective solution.

In order to conduct numerical experiments on the effects of drugs on cancerous tumors, we need transport – population coupled models. This may seem counter-intuitive to the goal of developing fast methods to determine efficacy and toxicity due to how computationally intensive sophisticated coupled models can be. Recent review articles and books show evidence of this in the wealth of transport models [11, 12], and separately in the variety of population models [13]; yet there is a dearth of coupled transport – population models. Further, while there are many sophisticated transport models for drugs penetrating into the tumor from the blood stream (e.g. [14, 15, 16]), there are few mathematical investigations of drugs injected into the tumor.

In [17], Rahman et al. present a simple drug diffusion – binary population model. It is assumed that a drug is being injected directly into the center of a homogeneous – isotropic spherical tumor, and hence the diffusion is radial with constant diffusivity. Furthermore, it is assumed that a cell is either dead if the concentration of the drug is greater than a threshold and alive if the concentration is less than this threshold; i.e., the drug acts as a trigger for cell death. From this model dose-response curves (response as a function of dose) are produced in order to relate it to relevant empirical data, such as Harvard Medical School’s LINCS data set. Since the data set does not include replication studies, artificial replication dose-response curves were produced, and the dose-response curves from the mechanistic model were shown, in many cases, to lie within 95% piecewise-linear confidence bands.

While the model of Rahman et al. [17] performed well against artificial replication data, the simplicity is burdened by the baggage of assumptions. Transport of drugs in the brain is a complex process due to the highly inhomogeneous and anisotropic structure of brain tissue, local pressure differences, and chemical interactions of the drug with the surrounding tissue. However, a model that does not obviate negligible contributions falls prey to computational constraints. Even with parallelization on a supercomputing cluster, would it be useful to an oncologist that is working directly with a patient?

In this investigation, we keep the simple binary population model, and explore the complexities of drug transport from a single injection into deformed globular tumors (topological 3-spheres). It is well known that diffusion dominates, but we assume it can be inhomogeneous
and anisotropic. This allows for fast in vivo simulations of direct injection therapies, which we use to produce dose-response curves, apoptosis regions, and optimal injection locations. This investigation endeavors to present results to aid practitioners in optimizing treatment strategies.

The remainder of the paper is organized as follows: We begin our discussions by deriving the inhomogeneous - anisotropic diffusion and binary population models in Sec. 2. Then in Sec. 3, we develop the computational foundation of the investigation in two steps. First, Sec. 3.1 sets up the finite element scheme. We use Galerkin Finite Element Method for the spatial discretization and a Crank-Nicolson scheme for the temporal integration. Then the diffusion tensors are constructed from patient MRI data in Sec. 3.2. Section 4 presents the numerical simulations and oncological predictions of our study. We first examine the drug diffusion in the tumor and observe the high inhomogeneity and anisotropy in the concentration heat maps. Then the apoptosis is simulated by invoking the binary population model. This allows us to create dose-response curves. Importantly, the model predicts optimal injection sites, evidenced by the dose-response curves, different from what intuition might suggest. Finally, the investigation is concluded in Sec. 5 with a discussion on viable oncological applications and future modeling directions.

2 Drug diffusion and binary population models

In this section we derive the inhomogenous – anisotropic diffusion model and the binary tumor population model. First we write a general diffusion model. It has been shown through Magnetic Resonance Imaging (MRI) in the brain that tumors often grow in an inhomogeneous – anisotropic diffusion-like manner [18, 19, 20, 21]. Using Diffusion Tensor Imaging (DTI) techniques [22], the effective diffusivity of water in tissue can be estimated. Since there is a large contrast between cancerous and healthy tissues, DTI can be used to map the geometry of a tumor and estimate the diffusivity of water in a tumor [23, 24, 25].

Consider a drug with molarity \(u\) diffusing from an injection into a porous tumor, with an effective diffusivity tensor \(D\). Next for the sake of brevity, let \(x = (x_1, x_2, x_3)\) be the position vector. Finally, we model the leak at the boundary of the region of interest as “Newton’s law of cooling” [26]. This gives us the generic model in Cartesian coordinates

\[
\frac{\partial u(x; t)}{\partial t} = \nabla \cdot (D(x) \nabla u(x; t)), \quad x \in \Omega; \tag{1a}
\]

\[
D(x) \nabla u(x; t) \cdot n = -\gamma u(x; t), \quad x \in \partial\Omega; \tag{1b}
\]

\[
u(x; t = 0) = \bar{u}(x), \tag{1c}
\]

where \(\bar{u}(x)\) is some generic initial concentration profile of the drug soon after injection and \(\gamma\) is the constant leak coefficient. Since all the cells at the boundary are assumed to be non-cancerous, the rate of leakage is equivalent to the rate of diffusion at the boundary.

We now impose a specific initial condition. In [17] a bump function (compact Gaussian) decaying to zero just within the domain was used. During inhomogeneous – anisotropic diffusion, the drug does not diffuse evenly, and hence a bump function that extends to the endpoints would not capture the irregularities expected in such a problem. Nevertheless, there are many numerical advantageous to using a bump function. We may either introduce
a sharper bump or try to capture the diffusive irregularities in the initial condition. In general, for an injection at point $x_c$, we have

$$\bar{u}(r) = \frac{U_0}{V_b} \begin{cases} \exp \left(1 - \frac{R_b^2 - r^2}{R_b^2 - R_b^2 - r^2} \right), & r < R_b \\ 0, & r \geq R_b \end{cases}$$

(2)

where, $r = \|x - x_c\|$, $R_b$ is the radius of the bump, $U_0$ is the injected concentration, and $V_b$ is the volume of the bump function in spherical coordinates; that is,

$$V_b = \int_0^\pi \int_0^{2\pi} \int_0^{R_b} \exp \left(1 - \frac{R_b^2}{R_b^2 - r^2} \right) r^2 \sin \phi dr d\theta d\phi$$

2.1 Binary population model

As done in [17], we use a binary population model: the tumor cell is dead after some exposure time $\tau$ (which is much larger than the diffusive time scale), if at any time during the diffusion process the drug concentration is above some given threshold value $u_T(\tau)$, otherwise it is alive. To simplify computation, the model assumes natural cell death rate is equivalent to the cell population growth rate, and effectively negate each other. We expect the threshold to decrease with time because it takes more toxins to kill a cell quickly than it does to kill it slowly. Further, since empirical studies often plot response data against log time, we expect $u_T$ to be a negative exponential with time $\tau$,

$$u_T(\tau) = a - be^{-c\tau},$$

(3)

where the parameters $a$, $b$, and $c$ are back calculated from a representative sample of the Harvard Medical School LINCS drug data set. From the representative sample we calculate what $u_T(\tau = 24 \text{ hrs})$, $u_T(\tau = 48 \text{ hrs})$, $u_T(\tau = 72 \text{ hrs})$ must be in order to produce the empirically observed response. Then we have three equations with three unknowns, which is solved explicitly in [17]. In this paper, we use the following threshold values.

$$u_T(24) = 0.230153 \ \mu M, \quad u_T(48) = 0.0700055 \ \mu M, \quad u_T(72) = 0.0499662 \ \mu M$$

3 Numerical procedure

In this section, we first describe the numerical procedure to approximate the solution of the system (1) in Sec. 2. Galerkin finite element method (GFEM) is used for the spatial discretization and a Crank-Nicolson scheme for the temporal integration. For a practical introduction finite element method, reader can refer to [27].

For the inhomogeneous – anisotropic diffusivity we incorporate diffusion tensors from diffusion tensor magnetic resonance imaging (DTI) data. The magnetic field gradients in different directions from the MRI is used to map out directions of faster and slower diffusion that is normalized to the diffusivity of water molecules. While in medical imaging the diffusion tensor is predominantly used to identify anomalies, and often averaged out in
preferential directions for that reason, we use it in the diffusivity of the transport model. Since the only errors are from the DTI data and GFEM, we can produce accurate qualitative simulations of in vivo scenarios.

There are a few studies in the literature integrating FEM with DT-imaging in a modeling framework. Kraft et al. incorporated DTI with FEM to investigate the mechanics of neurotrauma [28]. In [29], Ramasamy et al. proposed a subject-specific finite element model for the residual limb to assess the effect of a particular socket on deep tissue injury. They utilized DTI to reveal the anatomy of muscle fiber and mapped the information onto a finite element mesh. A nonlinear hyperelastic, transversely isotropic skeletal muscle constitutive law containing a deep tissue injury model were then solved with FEM. Clatz et al. [30] used FEM to simulate the invasion of GBM in the brain parenchyma and its mass effect on the invaded tissue. They described a coupling strategy between reaction-diffusion and linear elastic mechanical constitutive equations where diffusion tensor information was provided by DTI. In [31], a convection-enhanced drug delivery (CED), where the anti-cancer agent is directly administered into the brain tissue, was introduced. Governing equations concerning the transport of the therapeutic agent and tissue deformation was solved with the Finite Volume Method, where the information about the structures of the tissue is acquired through DTI.

3.1 Finite element discretization

Consider the Sobolev space \( H^1(\Omega) = \{ v \in L^2(\Omega) : \partial_x v \in L^2(\Omega) \ , \ i = 1, 2, 3 \} \), where \( \Omega \) is the domain of the PDE from Sec. 2. If \( u \) is sufficiently smooth, by multiplying (1a) with a test function \( v \in H^1(\Omega) \) and integrating over \( \Omega \) using Green’s formula, we obtain the variational formulation of (1a); that is, find \( u \) such that for every \( t \in I = [0, T] \),

\[
\int_{\Omega} \frac{\partial u}{\partial t} v dx = - \int_{\Omega} D\nabla u \cdot \nabla v dx - \int_{\partial\Omega} \gamma uv ds, \quad \forall v \in H^1(\Omega), \quad t \in I. \tag{4}
\]

Let

\[
\Omega_h = \{ K_1, K_2, ..., K_n \} \tag{5}
\]

be a geometrically conforming hexagonal triangulation of \( \Omega \). As a test space, we use the space of scalar valued piece-wise quadratic polynomials; i.e.,

\[
V_h = \{ p \in C^0(\bar{\Omega}) : p|_K \in Q_2(K), \quad \forall K \in \Omega_h \} \subset H^1(\Omega).
\]

Replacing \( H^1(\Omega) \) with \( V_h \), the finite element formulation of (4) reads: find \( u_h \) such that for every \( t \in I \),

\[
\int_{\Omega} \frac{\partial u_h}{\partial t} v_h dx = - \int_{\Omega} D\nabla u_h \cdot \nabla v_h dx - \int_{\partial\Omega} \gamma u_h v_h ds, \quad \forall v_h \in V_h, \quad t \in I. \tag{6}
\]

Let \( \{ \psi_i \}_{i=1}^n \) be a basis of the space \( V_h \) consisting of the orthogonal nodal basis functions satisfying \( \psi_i(N_j) = \delta_{ij} \) for every nodal point \( N_j \). For every \( u_h \in V_h \), there exist time dependent coefficients \( \xi_j(t) \) such that

\[
u_h(x, t) = \sum_{j=1}^n \xi_j(t)\psi_j(x). \tag{7}\]
From this construction, $\xi_j(t)$’s are the nodal values of $u_h$ for every time $t$. If we substitute (7) in (6), we obtain the following system of ordinary differential equations (ODEs)

$$M\dot{\xi}(t) = -(A + R)\xi(t),$$

where $\xi(t) = [\xi_1(t), \xi_2(t), ..., \xi_n(t)]^T$ and

$$M_{ij} = \int_\Omega \psi_j \psi_i, \quad A_{ij} = \int_\Omega D \nabla \psi_j \cdot \nabla \psi_i, \quad R_{ij} = \int_{\partial \Omega} \gamma \psi_j \psi_i.$$  

Note that the diffusion tensor $D$ is defined element-wise. Let $0 = t_0 < t_1 < ... < t_N = T$ be a partition of the interval $[0, T]$ with the constant time step $\Delta t = t_{n+1} - t_n$. Application of the Crank-Nicolson scheme for (8) yields

$$M \frac{\xi_{k+1} - \xi_k}{\Delta t} = -(A + R) \frac{\xi_k + \xi_{k+1}}{2},$$

where $\xi_0$ is chosen as the nodal values of $\bar{u}(x)$ defined in (1c) of Sec. 2. For the remainder of the manuscript we take the step size $\Delta t = 0.02$ with $N = 60$ equal time intervals and the leak coefficient is set to $\gamma = 0.002$. For the implementation of the problem (10), we use the open source finite element C++ library FeMUS [32].

### 3.2 Incorporating the diffusion tensor

Diffusion patterns of water molecules in biological tissue can be visualized by means of diffusion tensor magnetic resonance imaging (DTI). The diffusivity in the medium is quantified at each image voxel (a volumetric pixel) with a diffusion tensor that relates diffusive flux to a concentration gradient in each Cartesian direction. The three diagonal elements $D_{xx}$, $D_{yy}$, and $D_{zz}$ represent diffusion coefficients measured along each of the principal $x$-, $y$-, and $z$- axes. The six off-diagonal entries quantify the correlation of Brownian motion between corresponding principal directions. A generic diffusion tensor can be written as

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix},$$

where $D_{ij}$ has the unit of $mm^2/sec$.

The diffusivities from DTI are usually averaged out and illustrated by condensing the tensor information into a scalar quantity or plotted as a color encoded texture map. The former consists of scalar measurements to quantify the magnitude or the shape of the diffusion. In terms of magnitude, mean diffusivity (MD), which is the mean of the eigenvalues of the diffusion tensor, is one of the most common scalar measurements. On the other hand, fractional anisotropy (FA), which is the normalized variance of the eigenvalues, is the most commonly used anisotropy measure. In addition to various scalar measurements, one can also consider the direction of the major eigenvector (the eigenvector associated with the largest eigenvalue) and create a color map for the corresponding directions. The most commonly used color scheme in terms of anatomical planes is as follows; blue is superior-inferior, red
is left-right, and green is anterior-posterior [22]. For an extensive overview of the diffusion tensor imaging, the reader may refer to [33].

To capture the anisotropies of the diffusion in our numerical simulations we use a dataset that includes a diffusion tensor magnetic resonance image of a 35-year old male diagnosed with glioblastoma multiform (GBM). The dataset can be found in the tutorial [34]. From the diffusivity data, in Fig. 1, we derive and display the major eigenvector direction (indicated by the colors prescribed in the preceding paragraph), fractional anisotropy, and mean diffusivity. In the figure the GBM region can be observed around the right frontal lobe.

![Figure 1: Axial view of the brain DTI with illustrations from 3DSlicer of (a) the major eigenvalue direction, (b) fractional anisotropy, and (c) mean diffusivity. In all images the tumor region can be seen around the right frontal lobe.](image)

The coordinate dimensions of the sample volume is $256 \times 256 \times 51$ with voxel size $1 \times 1 \times 2.6$ mm. In the pre-processing of the DTI volume, we utilized the open source software 3DSlicer [35], which allows advanced medical image analysis and processing. It provides a graphical user interface with various modules as well as a Python console, which gives access to data arrays of image models for further analysis.

The diffusion tensor is symmetric and positive definite ( SPD) but in practice the positive definiteness can be corrupted due to measurement noise. Thus we first re-sample the DTI volume to correct the tensors that are not positive semi-definite. We are particularly interested in diffusion in the tumor tissue. Hence, we extract a region of $64 \times 64 \times 24$ voxel-wise enclosing the entire tumor region from the re-sampled volume and scale it into a cube $\Omega$ of sides 5 centered at the origin,

$$\Omega = \{(x, y, z) : -2.5 \leq x, y, z \leq 2.5\}. \quad (12)$$
We take $\Omega$ as the computational domain of the problem described in (1). After the re-scaling, the tumor region fits completely inside the rectangular subdomain of $\Omega$,

$$ T = \{(x, y, z) : -0.6 \leq x \leq 1.7, -1.5 \leq y \leq 1.5, -1.1 \leq z \leq 2.2\} \subset \Omega. \quad (13) $$

It is convenient to rescale the tensor $D$ over the region $T$ defined in (13). Let

$$ D_i = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \quad (14) $$

be the diffusion tensor defined for the hexagonal element $K_i$ in (5). Note that we define $D$ element-wise so it is essentially piece-wise discontinuous across the problem domain. Let $D_i^a = (D_{xx} + D_{yy} + D_{zz})/3$ be the element-wise apparent diffusion coefficient (ADC). We will use Algorithm 1 to scale the diffusion tensors in $\Omega$ and also identify the tumor elements in $T$.

**Algorithm 1**

| $N$ = number of elements |
| $D$ = diffusion tensor |
| $T$ = region enclosing the tumor bulk |
| AvgTr $=$ $0$, $Counter = 0$ |
| **for** $i = 1 : N$ **do** |
| **if** $K_i \in T$ **then** |
| $TrE = D_i^a$ |
| **if** $TrE > 0.002$ **then** |
| AvgTr = AvgTr + TrE |
| Counter = Counter + 1 |
| **end if** |
| **end if** |
| **end for** |
| $Scale = AvgTr/Counter$ |
| **for** $i = 1 : N$ **do** |
| $D_i = D_i/Scale$ |
| **end for** |

We set a tumor boundary threshold value of 0.002 by visual inspection. If our element-wise ADC $D_i^a > 0.002$ in the region $T$ for the raw data, we label it as cancerous element. With the algorithm above, the mean of ADCs across the assumed tumor elements is scaled to unity.

A major prediction made in this investigation is the fraction of the tumor volume killed against preassigned thresholds, $u_T(24)$, $u_T(48)$ and $u_T(72)$, from Sec. 2.1. This task essentially requires the elementwise identification of the tumor cells in $\Omega$. The only quantitative information about the sample data are the diffusion tensors at each voxel provided by DTI. No method is known to precisely differentiate the tumor and healthy cells by means of diffusion tensor information. However, we employ the fact that water diffuses significantly faster in GBM tissue than the surrounding healthy tissue [36].

We first assume that there is no tumor cell outside the region $T$. So, after the re-scaling of the diffusion tensor with Algorithm 1, we will mark any element $K_i$ in $T$ as cancerous if $D_i^a > 0.6$. This is the value where we observe a relatively sharp transition between the
normal and cancerous regions. To calculate the apoptosis fraction, first consider the unit step function

$$H(s) = \begin{cases} 1, & s > 0, \\ 0, & s \leq 0; \end{cases}$$

and the sub-region \(T_C \subset T\) defined as

$$T_C = \{x \in T : D^o(x) > 0.6\}$$

We compute the fraction of cells, \(\Upsilon\), that were once exposed to a concentration higher than \(u_T\) at the simulation time \(t = t_n\) as follows,

$$\Upsilon(\tau, t_n) = \frac{\int_{T_C} H(\max_{t \in [0,t_n]} [u(x, t) - u_T(\tau)])dV}{\int_{T_C} dV}$$

where \(\tau = 24, 48\) or 72 hours. Then to get the apoptosis fraction, \(\mathfrak{N}\), we prescribe \(t_n = T\) in (17),

$$\mathfrak{N}(\tau) = \Upsilon(\tau, T).$$

Note that the resulting fractions above are relative to the sub-region \(T_C\) since we assume all tumor cells lie in \(T\).

Different cross sections of the computational domain \(\Omega\) indicating the element-wise ADCs can be seen in Fig. 2. We construct \(\Omega\) to be consistent with the anatomical coordinate system described in [37]. Positive directions of the \(x\), \(y\), and \(z\) axes are chosen to be anterior, left, and superior, respectively. By this way, \(xy\), \(xz\), and \(xz\) coordinate planes correspond to transverse, frontal, and sagittal planes, respectively. In Fig. 2, for example, the horizontal plane with respect to the monitor corresponds to the transverse plane.

DTI is a non-invasive technique based on the measurement of the diffusion of water molecules. Therefore, the diffusion tensor \(D\) may be quantitatively different across the tissue of interest when another substance, such as a therapeutic agent, is used. Seemingly, there is no experimental study proposing a numerical relationship between the diffusion tensor of water and other fluids in brain tissue. Therefore, we will assume that although water and corresponding drug molecules have different fluidic properties, they display qualitatively similar behavior in the same medium. With this assumption, we will treat the diffusion tensors that we extracted from the dataset, described above, as the diffusion tensors of the agent used in the simulated treatment. For information on treatments of this type, the reader can refer to [30, 31].

4 Results and predictions

In this section we present the \textit{in vivo} direct injection treatment simulations resulting from the numerical solutions of our model (1). Based on the location of \(T\), we set the initial condition (15) (illustrated in Fig. 3) as follows

$$u(x; t = 0) = \frac{U_0}{V_b} \begin{cases} \exp \left(1 - \frac{1}{1-r^2}\right), & \text{for } r < 1, \\ 0, & \text{for } r \geq 1; \end{cases}$$
where \( V_b = 1.1990 \) and \( r = \sqrt{(x - 0.5)^2 + y^2 + z^2} \). By Algorithm 1, we scale the patient’s water diffusivity tensor to \( D/0.00271734 \), which effectively reduces the temporal time step for computation, and afterwards set the leak coefficient to be \( \gamma = 0.002 \, \text{m/s} \), which mimics the rate of diffusion for the scaled tensor. Further, a very high initial concentration of \( U_0 = 1.5 \, \mu\text{M} \) is taken for illustrative purposes.

In Sec 2.1, we assumed that if the concentration at the element \( K_i \) is above a certain threshold, \( u_T(\tau) \), at any simulation time, \( t \), then \( K_i \) will die out after the corresponding exposure times, \( \tau \). With this assumption, we can create a heat map indicating the regions which is predicted to die after the related exposure times, \( \tau = 24, 48, \) and 72 hours. It should be noted that although the precise tumor region is \( T_C \), we will display the apoptotic region within \( T \) for illustration purposes. Also note that the drugs eventually leak out beyond the region \( T_C \), and contribute to toxicity. Since the response of the healthy cells to the drug is a highly complex phenomenon, in the figures we will assume that any tissue element experiencing concentration above the thresholds in Sec. 2.1 will be killed irrespective of the location.

In Fig. 4, we present the apoptotic region induced by the initial bump function within the tumor region \( T \) (Fig. 4a) and the entire computational domain \( \Omega \) (Fig. Fig. 4b); that is, the region of cells expected to die within an exposure time \( \tau \) simply due to the initial condition before any diffusive spreading has occurred. In the figure, the outermost red region represents the location of the cells where the drug concentration is below any threshold value. The innermost dark blue region shows the locations where the concentration is above the threshold value \( u_T(24) \), and the heat map illustrates regions where the concentration of the bump function is above the respective threshold values.

As the drug diffuses across the computational domain, \( \Omega \), more cells are exposed to
Figure 3: Initial concentration profile $u(x; t = 0)$ centered at the location $x_c = (0.5, 0, 0)$ with an initial injection molarity of $U_0 = 1.5 \mu$M.

Figure 4: Apoptotic region induced by the initial bump function centered at $x_c = (0.5, 0, 0)$, with a very high drug concentration of $U_0 = 1.5 \mu$M for illustration purposes, within (a) the tumor region $\mathbb{T}$ and (b) the computational domain $\Omega$. The innermost blue region shows the locations where the tumor cells will die out within 24 hours. The outermost orange cells are predicted to die out within 72 hours of exposure. Finally, the deep red cells towards the outside of the regions do not die after up to 72 hours of exposure.
the drug over the course of the simulation. Figure 5 shows the planar projections of the concentration profiles as a heat map at increasing simulation times. Red represents a higher concentration of drugs and deep blue represents a concentration of zero. To improve the visibility of simulations, we scale the data to visible data range. The inhomogeneous - anisotropic nature of the diffusion can be clearly observed from the concentration profiles in Fig. 5.

Figure 5: Concentration profiles for an initial injection of $U_0 = 1.5 \ \mu M$ centered at $x_c = (0.5, 0, 0)$ at $t = 0.2, 0.5, 0.8, 1$, [(a) - (d)] respectively. The heat map is scaled to the visible range for each figure; i.e., the intensities are with respect to the concentration distribution in each figure independently of the other figures. Each figure is displayed with the intersection of three representative slices and two separate views of the frontal, $yz$-plane, and transverse $xy$-plane. The inhomogeneous - anisotropic nature of the diffusion can be observed in the planar slices accompanying the 3-D figures.

Now, we can compute the concentration levels at particular simulations times and compare them to the threshold values. For a particular simulation time, $t_n$, the volume fraction of the tumor where the concentration is above the threshold, $u_T(\tau)$, for the first time is calculated and summed with that of all previous times $t_i$ where $i < n$, using (17). When this is done for the final time, $t_n = T$, which is chosen to be large enough that all of the drug mixture leaks away after this time, then we have our apoptosis fraction, $\mathbb{N}(\tau)$ in (18). We report the exact fractions, $\mathbb{N}(\tau, t_n)$, from (17) in Table 1. Note that the fourth column is the final values that indicate the percentage of the tumor cells killed, $\mathbb{N}(\tau)$.

The effects of the inhomogeneous - anisotropic diffusion on apoptosis can be observed in Fig. 6. For example, the drug efficacy is significantly higher on the transverse plane compared to the sagital and frontal planes. This can be seen in Fig. 6h where the apoptotic region covers almost the entire transverse plane, while nontrivial portions of the frontal plane remains unscathed. Moreover, even though relatively high apoptosis fractions are achieved
Figure 6: Cells with a drug concentration higher than the given threshold, $\Psi(\tau, t_n)$, at simulation times $t_n = 0.2, 0.5, 0.8, 1$ after an initial injection of $U_0 = 1.5 \, \mu M$ centered at $x_c = (0.5, 0, 0)$. The column on the left, (a), (c), (e), (g), shows the entire computational domain, $\Omega$, and the column on the right, (b), (d), (f), (h), shows the tumor region, $\mathcal{T}$. Each figure is displayed with the intersection of three representative slices and two separate views of the frontal, $yz$-plane, and transverse $xy$-plane. It is observed that the number of cells exposed to a sufficient amount of drugs is higher on transverse, compared to the sagital, $xz$-plane, and the frontal plane. The inner most blue region shows the locations where $u(x, t) > u_T(\tau = 24\text{hours})$ for any $t = t_n$. The outermost orange cells correspond to $\tau = 72$ hours. Finally, the deep red cells towards the outside of the regions has concentrations $u(x, t) < u_T(\tau)$ for all $t$ and $\tau$. 
Table 1: Convergence of apoptosis fraction approximation for $U_0 = 1.5 \, \mu\text{M}$

| $t_n$ | $t_n = 0.2$ | $t_n = 0.5$ | $t_n = 0.8$ | $t_n = 1$ | $t_n = 1.2$ |
|-------|-------------|-------------|-------------|------------|-------------|
| $\Box (24, t_n)$ | 0.498408 | 0.528229 | 0.528229 | 0.528229 | 0.528229 |
| $\Box (48, t_n)$ | 0.698709 | 0.814072 | 0.864979 | 0.873871 | 0.877210 |
| $\Box (72, t_n)$ | 0.750721 | 0.878613 | 0.909647 | 0.915700 | 0.921299 |

in the tumor region, $\mathbb{T}$, it is observed in Fig. 7 that significant amounts of the drug leak out of $\mathbb{T}$. So our results indicate that considerable portions of the healthy cells are subject to toxicity. We can visually inspect the leakage of the drug by superimposing the representative slices of the computational domain $\Omega$ and the sub-region $\mathbb{T}$ (Fig. 7).

![Figure 7: A visual demonstration of toxicity.](image)

Figure 7: A visual demonstration of toxicity. The effect of the threshold is extended beyond the tumor region, $\mathbb{T}$, (the dark blue rectangular mesh), and the heat map is calculated in the $yz$, $xz$, and $xy$-planes from (17) at simulation times $t_n = 0, 0.2, 0.5, 1$, [(a) - (d)] respectively. It is observed that most of the drug mixture eventually diffuses outside of the tumor region. Thus, significant portions of healthy cells may potentially be subjected to toxicity. The inner most blue region shows the locations where $u(x, t) > u_T(\tau = 24\text{hours})$ for any $t = t_n$. The outermost orange cells correspond to $\tau = 72$ hours. Finally, the deep red cells towards the outside of the regions has concentrations $u(x, t) < u_T(\tau)$ for all $t$ and $\tau$.

It is observed in Table 1 that the current configuration of the problem leads to partial ablation in the tumor region since 92% of the region dies after 72 hours. In fact, as shown in the dose-response curves in Fig. 8, the apoptosis fraction seemingly asymptotes as we increase the amount of initial injection because the interaction of the drug with several obstacles, local inhomogeneities, and leakage, do not allow sufficient concentrations to diffuse to every part of
the tumor region. Thus, we can conclude that our mechanistic model is capable of reflecting the diffusion patterns mostly governed by location-wise structural differences.

Considering the internal injection scenario, several ways can be proposed to improve the efficacy of the drug without changing its fluidic properties. An obvious way may be to use a higher initial concentration, $U_0$. In fact, we can create dose-response curves for a broader view of the effects of various initial concentrations $U_0$ on the final apoptosis fractions. Figure 8 demonstrates the final percentages of the tumor that is killed for 31 different initial injections varying from $U_0 = 0.01 \, \mu M$ to $U_0 = 5 \, \mu M$. Dose-response curves reveal that even though the initial injection is excessively elevated, it is not possible to reach a complete tumor ablation. Indeed it is observed that apoptosis fractions barely improve after approximately $U_0 = 2 \, \mu M$ for $\tau = 48$ and 72 hours exposure times. We reported in Fig. 7 that even $U_0 = 1.5 \, \mu M$ causes the presence of significant concentrations of drugs outside of the tumor region $\mathbb{T}$. Thus we can conclude that the use of initial drug concentrations outside of a certain range is prohibitive and can severely contribute to toxicity.

![Figure 8: Dose-response curves (24, 48, and 72 hours from bottom to top) produced from 31 different initial injections varying from over the interval $[0.01, 5]$. It can be seen that the apoptosis fraction starts to asymptote beyond $U_0 = 2$ for 48 and 72 hours exposure options.](image)

Another important parameter effecting the apoptosis fraction is the location of injection. Our initial choice as the center of the bump function is $(0.5, 0, 0)$, which we pick by visual inspection to be near the center of the tumor. We found that changing the injection location greatly effects the diffusion pattern, and hence the final apoptosis fraction. In this sense, an important prediction in this investigation is that a seemingly poor location in $\mathbb{T}$ in terms of the distance from the center of the tumor bulk can yield higher apoptosis frac-
tions than some locations that are close to the tumor center. To illustrate this phenomenon, in Fig. 9, we choose four different injections points \( P_1(0.5, -0.3, -0.5) \), \( P_2(-0.3, 0, -0.6) \), \( P_3(-0.3, -0.3, -0.6) \), and \( P_4(0, 1, 0) \), and create dose response curves for each location. Our results demonstrate that finding the optimal injection location to maximize apoptosis fractions is quite an unpredictable process and cannot be achieved with a basic visual inspection. For example, we pick \( P_4 \) to be the “poor” location considering its position relative to the center of the tumor, and expected to get lower apoptosis fractions compared to the other locations, but Fig. 9 shows a different outcome. Although \( P_1, P_2, \) and \( P_3 \) yield relatively similar patterns, \( P_4 \) produces a better results for 48 and 72 exposure times after \( U_0 = 0.8 \). However, efficacy is remarkably low for \( P_1 \) comparing to others if one opts to measure the apoptosis after 24 hours. We should also note that similar to the initial findings, none of these configurations lead to full ablation in the tumor region.

Figure 9: Dose-response curves with 4 different injection points: \( P_1(0.5, -0.3, -0.5) \), \( P_2(-0.3, 0, -0.6) \), \( P_3(-0.3, -0.3, -0.6) \), and \( P_4(0, 1, 0) \). (a) 24 hour dose-response curves. (b) 48 hour dose-response curves. (c) 72 hour dose-response curves. Although \( P_4 \) is picked as an intuitively “poor” location in terms of distance to the center of the tumor bulk, it yields better efficacy for 48 and 72 hour exposure times after \( U_0 = 1 \mu M \) and \( U_0 = 0.7 \mu M \), respectively.

We can further investigate this idea in a slightly different context. Let us manually choose 20 different injection points around the tumor region and calculate the apoptosis fractions by fixing the initial injection to \( U_0 = 1.5 \mu M \). We then label corresponding locations with these fractions and display them inside the tumor region \( T \) in Fig. 10. In the figure, blue points represent lower efficacy (69%) and red points represent higher efficacy (90%) for an exposure of 72 hours. It is observed that the injection location has a significant influence on the efficacy of the drug. For example, in Fig. 10, \( P_4(0, 1, 0) \) (the right most red point) from Fig. 9 is represented and had a much higher efficacy than several points taken around the center. In a realistic treatment case, one can increase the number of points used in the simulations to obtain broader information about the optimal injection sites. However, if the same figure is created with a sufficient number of injection points around (and even outside) the tumor region, we can create a more fine-grained apoptosis heat map. In this way, we can obtain a volumetric partition of the tissue of interest with respect to mean apoptosis fractions. Such a work-flow can allow practitioners to determine the optimal infusion locations. Once the corresponding partition is identified, we can utilize the simulation to find an ideal injection amount which can strike a balance between toxicity and efficacy.

In 3D simulations, computation time is undoubtedly of great importance and essentially
Figure 10: Location based apoptosis fractions with $U_0 = 1.5 \, \mu$M based on 20 injection points. The numbers attached to the points are the predicted apoptosis fractions at these locations. (b) is a magnified version of (a).
determines if the proposed model is feasible in practical applications. In finite element models, the type and number of elements in the computational domain is the primary factor effecting the computation time. In this paper, we constructed the domain with 98,403 bi-quadratic hexagonal elements. Our computing environment is 9th Generation Intel(R) Core(TM) i7-9750H (12MB Cache, up to 4.5GHz, 6 cores) with 32GB DDR4-2666MHz RAM. We run the simulations with an MPI-based parallel environment on four cores and observed that computation time is approximately 15 minutes for one simulation with an initial injection of $U_0 = 1.5 \, \mu M$ and an output of apoptosis fractions for a given threshold, $u_T(\tau)$, the results of which are reported in Table 1 and 5.2 hours to create the dose-response curve using 31 initial injection values in Fig. 8. We should carefully note that the number of elements in this framework should be completely determined by the dimension of the diffusion tensor volume extracted from the original data. Thus, to be able to describe the corresponding quantities in finer detail, diffusion tensor images with higher resolutions are needed, but in this case we need a more powerful environment to obtain the results in a reasonable computing time.

In future studies, a more realistic computational domain may be created. For simplicity, we worked with a cubic domain in this study. However, it may possible to locate and cut out the tumor region more accurately and create a volumetric mesh based on this segmented region. A rough description of the tumor region extracted from the original data can be seen in red in Fig. 11. We display the tumor along with a discretized representation of the brain. We can then feed this mesh structure into the existing model. This approach has the potential to generate a more realistic model, but it can be quite challenging. For example, we would need to properly address how to interpolate the diffusion tensors across the boundary of this new domain if boundary conditions are to be imposed only on the surface of the tumor volume.

5 Conclusion and future work

Brain tissue poses a unique transport challenge due to the highly inhomogeneous - anisotropic nature of the medium. Since drug exposure directly impacts cell death, the geometry and topography of the tumor will have a significant effect on efficacy. Further, the tumor will also grow in an inhomogeneous - anisotropic manner [18, 19, 20, 21], and hence its structure can be quite unpredictable. Diffusion Tensor Magnetic Resonance Imaging (DTI) provides structure level information on an individual basis [22]. While there have been articles on employing DTI to study drug transport in the brain [5], thus far none have simulated the efficacy of a drug as a consequence of drug transport. With a drug transport - tumor population coupled model, there is potential in producing computer aided treatment strategies.

In this paper, we derived an inhomogeneous - anisotropic drug diffusion model of molarity $u(x,t)$, with the drug mixture injected into a porous tumor region in Sec. 2. Then in Sec. 2.1, we developed the binary population model, where natural tumor cell death is equivalent to the rate of tumor population growth and cell death due to the drug occurs when $u(x,t) > u_T(\tau)$ for a concentration threshold $u_T$ and exposure time $\tau$, similar to that of [17]. The model is solved numerically, in Sec. 3 through our finite element method. Since information on the diffusion tensor is imperative to the numerical solution, the model
employs DTI data (Sec. 3.2) of a 35-year old male diagnosed with glioblastoma multiform (GBM). This DTI data was pre-processed with an open source medical image processing software 3DSlicer [35] and fed into our finite element framework. In Sec. 4 we present the results from the simulation in a form that can be used by oncologists and doctors, and make predictions that may be easily overlooked in practice. We investigated apoptosis fractions in the tumor region through the binary population model in Sec. 2.1 This allowed us to plot dose-response curves and test various injection locations. Importantly, the various locations show that the intuitive choice may not always be the best. This opens the door to develop tools to aid oncologists and doctors in deciding on an optimal treatment strategy.

The response of cancer cells to a therapeutic agent is undoubtedly a highly complex phenomenon. However, some aspects of it can be addressed with the help of a mathematical model. In this sense, our aim in this study was to build a partial differential equation framework based on patient-specific data that can be used to predict the efficacy of drug diffusion in the brain tissue occupied by tumor cells. Moreover, this framework may be used to create diffusion models which take into account more complex considerations. For example, a problem encountered in some cancer therapies is drug resistance, which can be defined as the ability of cancer cells to survive and grow despite various anti-cancer treatments [38]. Further, oxygen concentration also has an effect on drug efficacy [39, 40, 41, 42]. In this paper, we assumed that the tumor cells exposed to a drug concentration above certain threshold values will be ablated after the corresponding exposure times. However, if reliable empirical knowledge is present about drug resistance and oxygen concentration, a
time dependent or location-based threshold model may be integrated into this framework. In this regard, using finite element method in the model provides a great flexibility since it allows us to attach scalar quantities in the desired locations.

In addition, while the binary population model has computational advances due to its simplicity, a more accurate model would be a stochastic dynamical system that is dependent on the concentration threshold. One concern may be the complexity of coupling, but fortunately transport happens on a much faster timescale than apoptosis. We would solve the partial differential equations for the transport, and then tackle the population dynamics to produce the apoptosis fractions. However, as with any model, adding more complexity is counterproductive unless it is accompanied by reliable data. This gives us a singular opportunity to develop both biological and physical experiments to accurately estimate parameters and test the models.

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