LATTICE BOLTZMANN METHOD FOR INTEGRATING THE BLOCH EQUATION IN
MUSCLE FIBERS AND MICROVESSELS

BY

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THESIS

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ABSTRACT

Reduction in lean body mass and increase in fat mass lead to decline in strength and physical function and are therefore largely associated with aging and obesity. Recent research has demonstrated that Magnetic Resonance Imaging (MRI) can measure the local properties of directional water diffusion and lipid concentration in the human muscle. Strong correlations have also been found between overall fitness and MRI measurements related to the transport of water inside the muscle fibers. In addition to water diffusion within the muscle, MR imaging has been used to obtain measurements of the cerebral blood flow. Blood flow in microvascular vessels plays a vital role in the functional exchange of nutrients essential for healthy development, and toxic waste to be removed from the body, between the blood and tissue. Study of the properties of microvascular flow is important in order to effectively understand the change in metabolic support of brain neurons and glial cells with aging or disease.

The two objectives of this research project is to interpret MRI measurements related to the diffusion of water inside the muscle fibers, and to utilize the physics underlying how encoding by MRI characterizes the blood flow within the cerebral microvasculature. This is achieved by simulating the way MRI encodes information and applying these simulations to understand the transport of metabolites within the muscle fiber. The primary focus of this thesis is the development of a Lattice Boltzmann model of a single muscle fiber that can be parallelized in the future to include an ordered or disordered array of myofibrils and lipid domains inside the muscle fiber, and numerically simulate the multiphase transport of water, certain metabolites and calcium ions. The combination of Lattice Boltzmann modeling with data obtained from non-invasive MR imaging techniques provides an insight into muscle physiology and metabolism by exploring the connection between local directional diffusion and the distribution of lipids inside the muscle, which was previously only available from invasive techniques requiring muscle biopsy, or was ostensibly impossible. Using a similar approach as the muscle diffusion modeling, the cerebral microvascular blood flow was studied by inputting simple flow inputs on the model with properties characteristic of the cerebral microvessels, thereby providing an innovative technique to extract intrinsic microvascular parameters in the normal aging brain.
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CHAPTER 1: INTRODUCTION

1.1 Muscle Quality in Aging and Obesity

The loss of muscle mass with age known as sarcopenia is one of the main determinants of frailty in old age [1]. Additionally, obesity which is defined by a body mass index (BMI) greater than or equal to 30 kg/m², is increasing at a rapid rate across all ages among the United States population [2]. The total number as well as the percentage of older persons that are obese have increased substantially with obesity being a more common occurrence in women than in men [2, 3]. This is supported by population statistics indicating that nearly 70% of women over 60 years of age are overweight or obese [2]. The results of obesity include reductions in mobility, decline of physical condition [4] and increased nursing home admissions [5]. Moreover, the relative importance of “fitness” compared to “fatness” is of high clinical importance from a public health perspective. The healthcare specialist needs to choose appropriate interventions to alleviate disability related to the body composition in elderly women. The most important factor responsible for the physical function in obese frail elderly individuals has been determined to be muscle quality which is quantified as leg strength normalized by leg mineral free lean mass [6, 7]. The scientific challenge is to relate the muscle quality to the intrinsic properties of the muscle. These are of importance in metabolism and force generation which are the primary functions of the muscle.

According to exercise physiology, fit muscle metabolizes lipids efficiently in order to avoid the depletion of carbohydrate depots [8]. It has been demonstrated in recent research that lipids associated with the muscle, specifically intramyocellular triglycerides, are permanently relocated to the interior of the muscle fiber in obese individuals [9, 10]. These lipids can alter the compartmentalization of the muscle cell due to muscle loss and fat infiltration during aging [11], thereby affecting metabolism and cell contraction. Therefore, intramyocellular lipids may play a much more important role than it is currently recognized with regard to muscle quality as weight
loss and exercise regimens are imposed on the elderly. Furthermore, the localization of glycogen in the muscle fiber has been recently shown to affect muscle performance.

The role of lipids in muscle quality has been explored by a team led by the PI in a systematic study that involved the measurement of the water diffusion tensor using Diffusion Tensor Imaging (DTI) and the distribution of intramyocellular and extramyocellular lipids in thigh muscles by Magnetic Resonance Spectroscopy (MRS). The measurements were correlated with muscle strength measurements of elderly women differing in adiposity and habitual physical activity, after exercise training and weight loss. The study showed that exercise impacts muscle quality more than body fatness or weight loss in the elderly. Moreover, changes in normalized muscle strength were correlated with local changes in the principal components of the diffusion tensor as well as with spatial distribution of lipids associated with the muscle in addition to their quantity.

1.2 Magnetic Resonance Imaging and Development of Muscle Diffusion Model

In recent times, in vivo techniques such as ultrasound and Magnetic Resonance Imaging (MRI) have been applied to the pursuit of investigating metabolism in striated muscle. Proton MRI encodes the position and state of water molecules in Fourier space in a temporally convolved manner [12]. Consequently, interpreting the MRI signal requires the solution of an inverse problem from Fourier space to real space. When MRI is used to encode diffusion, the inversion problem is based on the diffusion equation. This research project aims to frame the scientific challenge in the context of Magnetic Resonance Imaging (MRI) methodology by developing a model for multiscale transport of water-soluble metabolites and then coupling it with the MRI signal.

The ultimate goal is to start from the largest functional unit of contractile filament of the muscle, and build a microstructural model for a single muscle fiber that can accommodate internal barriers to diffusion, such as semipermeable membranes and lipid inclusions. Following the successful development of the model for muscle fiber diffusion, the DTI and MRS signals will be connected with the characteristic parameters such as the shape, proportion and size of the
water filled interstitial space. This will result in the formation of an inverse problem which can be solved to reconstruct these parameters from the signal. Further, subject specific model parameters of the composite model will be estimated using the DTI and MRS measurements from the human study. This work addresses only the problem of two dimensional water diffusion in a single homogenous myocyte bound by a semi-permeable membrane and surrounded by a periodic arrangement of identical myocytes.

The successful completion of the work described will result in the development of a flexible framework for interpreting experimental DTI and MRS data through a physiology based model of intramyocellular water and other small molecules. This will allow the assignment of metabolic fluxes in a representative muscle fiber towards a future integration with a fiber-level bioenergetics model for the muscle.

1.3 Importance of Microvascular Blood Flow across the Life Span

The functional exchange of nutrients and metabolic byproducts between blood and tissue occurs in the microvascular vessels, extending from the arterioles through the capillaries and into the venules. The significance of the flow properties and structural organization of the microvasculature has started to be recognized only in recent times. For instance, MRI measurements of cerebral blood volume were seen to provide an imaging correlate of neurogenesis [13], as well as of aging in the healthy brain [14]. Additionally, it has been found that the capillaries that feed into the cerebral tissues have structure including density and orientation that corresponds to the local neural organization. A systematic reconstruction of microvascular beds in portions of the cerebral cortex [15, 16] has shown that the capillaries form arborescences that are fed and drained by arterioles and venules, which run perpendicular to the sulcal surface in cerebral cortex as represented in Figure 1.1(a). More importantly, the cerebral microvasculature has been shown to change with aging or disease [17]. The tools that are developed in the current research for the study of cerebral microvasculature will provide a non-invasive, in-vivo imaging assessment of microvascular structure that will enable monitoring of changes which lead to declines in tissue viability with age and pathology.
With age the cerebral vasculature undergoes significant reorganization as shown in a lot of literature that demonstrate a decline in blood flow, luminal diameter, and vascular reserve which are linked to neurophysiological and neuropsychological changes [18-20] and generally to cerebral underperfusion [21]. Various parameters of the capillaries in the dorsal lateral geniculate nucleus in the brain were examined and significant decreases in capillary volume fraction and diameter were indicated in older rats [22]. Studies have shown similar changes for humans along with modifications to the structure of the vascular network. The appearance of “coiling and looping” in arteries and venules in elderly adult brains, as shown in Figure 1.1(b) [21, 23], results in differences in flow through the tissue. The functional implications of these changes to the microvascular flow could lead to decreases in reactivity of neural tissue, loss of cognitive performance with age, or damage to the tissue due to ischemic, thermal, or chemical stresses.

Little is directly known about the role that changes in the microstructure of cerebral vasculature plays in age-related declines of tissue. Although MRI has been used to probe age-related changes in cerebral hemodynamics [24], no techniques have been developed that probe the microstructural reorganization of the vasculature that may precede any functional changes which respond to homeostatic mechanisms. However, several MRI techniques, when coupled with

![Figure 1.1. Demonstration of Microstructural Organization of the Vasculature in the Cortex: (a) Figure from [15], demonstrating organization of cortical capillaries relative to cortical surface (surface is at bottom of image, scale bar is 1 mm), (b) Coiling and looping in arteries and venules in elderly cerebral microvasculature compared to young adults. Figure from [21], which is adapted from [23].](image-url)
computer simulations of microvasculature networks of blood flow, will provide a non-invasive means to monitor such changes in healthy volunteers.

1.4 Motivation for Computational Imaging of the Aging Cerebral Microvasculature

The main objective of the microvasculature flow research is to develop a computational imaging approach to assess, non-invasively, the microstructure of cerebral vasculature in aging subjects. The methodology consists of interpreting images by using the physics underlying the imaging process and employing high performance computing to extract intrinsic microvascular parameters in the normal aging brain. Currently, there are no other techniques that are available to provide this critical information about microcirculation in the brain tissue of healthy subjects in vivo. When developed and validated, this technique will usher in a continuum of research examining the variation of the metabolic support of brain neurons and glial cells in aging or disease.

In order to achieve the above mentioned objective, a model needs to be developed to characterize the flow within the cerebral microvasculature. This thesis addresses the development of a computational method using the Lattice Boltzmann Method to analyze two dimensional flow in a single microvessel embedded in the brain parenchyma. This is the first step towards building more sophisticated models of microvascular beds.
CHAPTER 2: THEORY

2.1 The Bloch-Torrey Equation [25, 26]

The molecular diffusion of water within the tissue of interest is quantitatively studied using Magnetic Resonance Imaging (MRI). The hydrogen protons present in water molecules have a net electric charge and rotate about their own axis due to a nonzero spin. The spinning of a charged object creates a magnetic field around it which is physically represented as the vector quantity \( \mu \), and is called the magnetic moment. The vector sum of all the microscopic magnetic moments in the object is referred to as the macroscopic magnetization vector, \( \mathbf{M} \) [25]. If \( \mu_n \) represents the magnetic moment of the \( n \)th nuclear spin, then,

\[
\mathbf{M} = \sum_{n=1}^{N_s} \mu_n 
\]

(2.1)

where, \( N_s \) is the total number of spins in the object being imaged. The Bloch equation quantitatively describes the time dependent behavior of the macroscopic magnetization vector \( \mathbf{M} \) in the presence of an applied magnetic field, \( \mathbf{B}_{\text{ext}} = \mathbf{B}_0 + \mathbf{g}(\mathbf{r}, t) \). The general form of the Bloch equation is represented in Equation (2.2) [25].

\[
\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_{\text{ext}} - \frac{\mathbf{M}}{T_2} - \frac{(M_z - M_z^0)k}{T_1} 
\]

(2.2)

where, \( M_z^0 = \frac{\gamma^2 \hbar^2 B_0 N_s}{4KT_s} \) is the thermal equilibrium value for the magnetization vector, \( \mathbf{M} \) in the presence of \( \mathbf{B}_0 \) only,

\( \mathbf{B}_0 \) is the static or effective magnetic field in the longitudinal \( z \)-direction that a nucleus “sees” in the absence of the external magnetic field \( \mathbf{B}_1(t) \) which is applied perpendicular to it,
\( \gamma \) is the gyromagnetic ratio which for protons is 267.5 MHz/T,

\[ h = \frac{\hbar}{2\pi} \]

in which \( \hbar = 6.6 \times 10^{-34} \) J-s is Planck’s constant,

\( K = 1.38 \times 10^{-23} \) J/K is Boltzmann’s constant,

\( T_s \) is the absolute temperature of the spin system,

\( \mathbf{B}_{\text{ext}} = \mathbf{B}_0 + \mathbf{g}(\mathbf{r}, t) \) is the effective external magnetic field with \( \mathbf{g}(\mathbf{r}, t) \) as the effective gradient dependent on space and time,

\( \mathbf{M}_\perp = M_z \hat{i} + M_j \hat{j} \) is the transverse magnetization,

\( M_z \) is the longitudinal magnetization,

\( T_1 \) is the time taken for the longitudinal component of the magnetic moment (z-direction by convention) to regain 53% of its thermal equilibrium value during free relaxation,

and, \( T_2 \) is the time taken for the transverse magnetization to lose 37% of its excited state magnetization during free relaxation (local spin-spin relaxation).

The time constants, \( T_1 \) and \( T_2 \), characterize the relaxation process of a spin system after it has been disturbed from its thermal equilibrium state. While \( T_1 \) is caused by the magnetic field and the protons gradually align back during the free relaxation period, \( T_2 \) is an intrinsic property caused by the spin-spin interactions in the transverse directions between the protons [25].

The diffusion process is numerically modeled based on Fick’s second law of diffusion given by,

\[
\frac{\partial \phi}{\partial t} = \nabla \cdot (D \nabla \phi) \tag{2.3}
\]

where, \( \phi \) is a scalar variable that represents the concentration of the species (or magnetization in the case of the Bloch-Torrey equation), \( t \) is time in seconds, \( D \) is the diffusion coefficient matrix and \( \nabla = \left[ \frac{\partial}{\partial x}, \frac{\partial}{\partial y} \right] \) is the gradient operator in two dimensions. The standard
convection (advection) – diffusion equation which incorporates the advection process is given by,

$$\frac{\partial \phi}{\partial t} + \mathbf{V} \cdot \nabla \phi = \nabla \cdot (D \nabla \phi) + S \quad (2.4)$$

where, \( \mathbf{V} \) is the velocity and \( S \) is the source term. In the absence of a source term and assuming an isotropic domain with constant diffusion coefficient \( D \), the above equation becomes,

$$\frac{\partial \phi}{dt} + \mathbf{V} \cdot \nabla \phi = D \nabla^2 \phi \quad (2.5)$$

When the Bloch equation given in Equation (2.2) is modified to include advection and diffusion in Equation (2.5), it becomes the Bloch-Torrey equation [26]. The species undergoing diffusion is the macroscopic magnetization vector. The general form of the Bloch-Torrey equation is represented below,

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_{ext} - \frac{M_x \mathbf{i} + M_y \mathbf{j}}{T_2} - \frac{(M_z - M^0_z) \mathbf{k}}{T_1} + \nabla \cdot (D \nabla \mathbf{M}_{\perp}) + \mathbf{V} \cdot \nabla \mathbf{M}_{\perp} \quad (2.6)$$

The Bloch-Torrey equation in (2.6) is simplified as shown below in the rotational frame of reference in which \( \mathbf{B}_{ext} = \mathbf{g}(\mathbf{r}, t) = B_z \mathbf{k} \). Equation (2.7) states the Bloch-Torrey equation explicitly in three dimensions in the rotational frame of reference.

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}_{ext} - \frac{M_x \mathbf{i} + M_y \mathbf{j}}{T_2} - \frac{(M_z - M^0_z) \mathbf{k}}{T_1} + \nabla \cdot (D \nabla \mathbf{M}_{\perp}) + \mathbf{V} \cdot \nabla \mathbf{M}_{\perp}$$

$$\frac{d\mathbf{M}}{dt} = \gamma \begin{vmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ M_x & M_y & M_z \\ 0 & 0 & B_z \end{vmatrix} - \frac{M_x \mathbf{i} + M_y \mathbf{j}}{T_2} - \frac{(M_z - M^0_z) \mathbf{k}}{T_1} + \nabla \cdot \left( D \left( \frac{\partial^2 \mathbf{M}_{\perp}}{\partial x^2} + \frac{\partial^2 \mathbf{M}_{\perp}}{\partial y^2} \right) + \left( V_x \frac{\partial \mathbf{M}_{\perp}}{\partial x} + V_y \frac{\partial \mathbf{M}_{\perp}}{\partial y} \right) \right)$$

$$\frac{d\mathbf{M}}{dt} = \gamma \begin{vmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ M_x & M_y & M_z \\ 0 & 0 & B_z \end{vmatrix} - \frac{M_x \mathbf{i} + M_y \mathbf{j}}{T_2} - \frac{(M_z - M^0_z) \mathbf{k}}{T_1} + \nabla \cdot \left( D \left( \frac{\partial^2 \mathbf{M}_{\perp}}{\partial x^2} + \frac{\partial^2 \mathbf{M}_{\perp}}{\partial y^2} \right) + \left( V_x \frac{\partial \mathbf{M}_{\perp}}{\partial x} + V_y \frac{\partial \mathbf{M}_{\perp}}{\partial y} \right) \right)$$
\[
\begin{align*}
\frac{dM_x}{dt} &= \gamma B_z M_x - \frac{M_x}{T_2} + D \left( \frac{\partial^2 M_x}{\partial x^2} + \frac{\partial^2 M_x}{\partial y^2} \right) + V_x \frac{\partial M_x}{\partial x} + V_y \frac{\partial M_x}{\partial y} \\
\frac{dM_y}{dt} &= -\gamma B_z M_y - \frac{M_y}{T_2} + D \left( \frac{\partial^2 M_y}{\partial x^2} + \frac{\partial^2 M_y}{\partial y^2} \right) + V_x \frac{\partial M_y}{\partial x} + V_y \frac{\partial M_y}{\partial y} \\
\frac{dM_z}{dt} &= -\frac{(M_z - M_z^0)}{T_1}
\end{align*}
\] (2.7)

The external magnetic field, \( B_{ex} = B_z \hat{k} \) is applied as a Diffusion Weighted Gradient Echo sequence which is described in the following section.

### 2.2 Diffusion Weighted Gradient Echo

The Diffusion Weighted Gradient Echo (DWGE) pulse sequence is used in MRI to obtain a signal measurement that captures the molecular diffusion of water. The DWGE sequence comprises of timed radio frequency (RF) pulses with intermittent magnetic field gradients applied over a certain time duration. The pulse sequence is illustrated in Figure 2.1.

![Diffusion Weighted Gradient Echo Pulse Sequence](image)

*Figure 2.1. Diffusion Weighted Gradient Echo Pulse Sequence.*

Three parameters are used to describe the diffusion gradient pair – the diffusion gradient amplitude \( G \), the gradient duration \( \delta \), and the time duration \( \Delta \) between the start of the two gradients. \( t_0 \) is the time at which the RF pulse ends and the \(+G\) pulse starts, \( t_0 \) is the time at which...
the $+G$ pulse ends, $t_{\Delta}$ is the time at which the $-G$ pulse starts, and $t_E$ is the echo time and the time at which the signal is acquired.

During the duration of the pulse sequence, the magnetic moment vectors are de-phased and then re-phased while the protons undergo free diffusion. The movement of the water molecules affect the signal captured at time $t_E$. A parameter called the diffusion decay factor or “$b$-factor” which characterizes the timing, amplitude and shape of the gradient is defined in Equation (2.8). In the DWGE sequence, $b$ values are varied by changing either the gradient amplitude, $G$ or the time durations, $\delta$ and $\Delta$.

$$b = \gamma^2 G^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right)$$  \hspace{1cm} (2.8)

where, $\left( \Delta - \frac{\delta}{3} \right)$ is the effective diffusion time.

A series of diffusion weighted images with $b = b_0 = 0$ and finite $b$ values are obtained in order to determine the apparent diffusion coefficient, $D_{\text{eff}}$. The local apparent diffusion coefficient is extracted from fitting the formula,

$$\frac{S(b,t_E)}{S_0} = e^{-bD_{\text{eff}} t_E}$$  \hspace{1cm} (2.9)

where, $S(b,t_E)$ is the signal acquired with different $b$ values at time, $t_E$, and, $S_0$ is the signal acquired at $b_0$.

For a particular $b$ value, the signal at any time $t$ during the sequence is calculated as,

$$\frac{S(t)}{S(0)} = \sqrt{\left[ M_x(t) \right]^2 + \left[ M_y(t) \right]^2}$$

$$\text{Area of the Domain}$$  \hspace{1cm} (2.10)

where, $M_x(t)$ and $M_y(t)$ are the total magnetization along the two directions of the transverse plane at time, $t$ and $S(0)$ is the signal at time, $t = 0$. In the rotational frame of
reference, the external magnetic field, \( \mathbf{B}_{\text{ext}} = B_{\parallel} \mathbf{k} \) is applied one dimensionally in the transverse plane according to the conventional Cartesian coordinate system. Consequently, an apparent diffusion coefficient can be determined along each direction by fitting the signal decay curve in Equation (2.9). \( B_{\parallel} \) is therefore a function of space and time expressed as,

\[
B_{\parallel} = \begin{cases} 
G \cdot x & 0 \leq t \leq t_{\delta} \\
0 & t_{\delta} \leq t \leq t_{\Delta} \\
G \cdot x & t_{\Delta} \leq t \leq t_{E} 
\end{cases}
\quad \text{(2.11)}
\]

where, \( G \) is the gradient amplitude,

and, \( x \) is the one dimensional displacement in the transverse plane.

The two dimensional Bloch-Torrey equation in Equation (2.7) based on the Diffusion Weighted Gradient Echo pulse sequence is modeled using two numerical methods – the Lattice Boltzmann Method (LBM) in FORTRAN and the Finite Element Method (FEM) in COMSOL for different geometries. The geometries were chosen such that the model closely represents a two dimensional cross-section of the myocyte. Further, simpler geometries were created to analyze the effectiveness of the numerical models in simulating diffusion in the intracellular and extracellular regions of a myocyte. Lastly, the diffusion and velocity effects of blood flow in the brain was studied.

### 2.3 The Lattice Boltzmann Method

The Lattice Boltzmann Method is used to model the diffusion process since it is a numerical scheme that has the capability to model the complex physics and boundary conditions involved with directional diffusion, while providing the option of a parallel computing environment for more intensive modeling. The Lattice Boltzmann Method (LBM) is a mesoscopic numerical method of applying the Boltzmann Transport Equation to simulate fluid flow on a discrete grid [27]. For the purpose of this diffusion model, the Bhatnagar-Gross-Krook (BGK) approximation of the Boltzmann Equation is used with an appropriate single relaxation time (SRT). The Bloch-Torrey equation in Equation (2.7) is modeled using the Lattice Boltzmann Method in three major steps:
• Diffusion
• Free Precession
• Relaxation

Only the transverse magnetization is simulated as the molecular diffusion process is characterized by the diffusion of spins in the transverse plane.

2.3.1 Diffusion

The convection–diffusion part of the Bloch-Torrey equation is modeled using a two dimensional LBM model with five discrete velocities (D2Q5) as shown in Figure 2.2. The discrete velocity set in the D2Q5 model is,

\[
e_i = \begin{cases} 
(0,0) & (i = 0) \\
(\pm1,0),(0,\pm1) & (i = 1,2,3,4)
\end{cases}
\]  

(2.12)

The equilibrium distribution function, \( g^{eq}_i \) for the D2Q5 model can now be described which is given in Equation (2.14). The discretized velocities carry distinct weighting factors, \( \omega_i \) that denote their contribution to the motion of the particle at a particular lattice node as shown below,

\[
\omega_i = \begin{cases} 
\varepsilon_D, & (i = 0) \\
\varepsilon_D/2, & (i = 1,2,3,4)
\end{cases}
\]  

(2.13)

\[
g^{eq}_i(x,t) = \left( \omega_i + \frac{\delta t v_j}{\delta x \varepsilon_D} e_j \omega_i \right) \phi(x,t)
\]  

(2.14)

where, \( \omega_i \) is the weighting factor for the velocities in the five lattice directions,

\( \delta t \) is the diffusion time step,

\( \delta x \) is the lattice grid size,
and, \( v_j \) is the velocity in each dimensional direction (i.e. \( x \) and \( y \) directions in the transverse plane).

The weighting factors, \( \omega_i \) are chosen such that the center particle carries the most weight, \( \varepsilon_D \) while the velocities in the horizontal and vertical directions have a weighting factor of \( \frac{\varepsilon_D}{2} \).

The constant \( \varepsilon_D = 1/3 \) for the D2Q5 model. The subscript ‘\( j \)’ in the above equation denotes the dimensional direction on the transverse plane in consideration. For a 2D model, \( j = 1, 2 \).

Once, the LBM simulation has been initialized, the next step in the numerical method is discretization of the particle motion in time and space using the Lattice BGK Equation given in Equation (2.15). This is done in order to update the cells over time and space by means of an iterative process.

\[
g_i(x + e_i \cdot \delta t, t + \delta t) - g_i(x, t) = -\frac{1}{\tau} \left[ g_i(x, t) - g_i^{eq}(x, t) \right]
\]

(2.15)

where, \( g_i \) is the particle distribution function and \( \tau \) is the relaxation time.

The above Lattice-BGK Equation is solved in two steps, during each iteration loop, as collision and streaming steps. The collision step accounts for the many particle collisions that can occur within the lattice at each time step if more than one particle arrives at the same lattice point. The collision step particle motion is described in terms of particle density function using the Collision Step Lattice BGK Equation in Equation (2.16).

\[
g_i^{out}(x, t) = g_i^{in}(x, t) - \frac{1}{\tau} \left[ g_i^{in}(x, t) - g_i^{eq}(x, t) \right]
\]

(2.16)

where, \( g_i^{in} \) is the initial particle distribution function at each time step,

\( g_i^{eq} \) is the equilibrium particle distribution function determined using Equation (2.15),

\( \tau \) is the single relaxation time period,
and, \( g_{i}^{\text{out}} \) is the particle distribution function at the end of the collision step.

The relaxation time parameter, \( \tau \) is related to the diffusion coefficient, \( D \) as follows,

\[
\tau = \frac{1}{2} + \frac{\delta t}{\varepsilon_{0}(\delta x)^{2}} D
\]  

(2.17)

where, \( \delta t \) is the time step,

and, \( \delta x \) is the lattice grid size.

The particle distribution function calculated at the end of the collision step, \( g_{i}^{\text{out}} \) is used as the input in the streaming step to calculate the distribution function for the next iteration over time and space. The streaming step accounts for the flow of the particles to their neighboring cells according to their distinct velocity directions, following the interaction with neighboring particles, at each iteration loop over time and space. The streaming step Lattice BGK Equation is defined in Equation (2.18).

\[
g_{i}^{\text{in}}(x + e_{i} \cdot \delta t, t + \delta t) = g_{i}^{\text{out}}(x, t)
\]  

(2.18)

where, \( g_{i}^{\text{out}} \) is the particle distribution function at the start of the streaming step and the end of the collision step of the current iteration,

and, \( g_{i}^{\text{in}} \) is the particle distribution function at the end of the streaming step which is also the initial data point for the collision step of the next iteration.

The lattice vector at position zero, however, has no change in its particle distribution function at the end of the streaming step as the particle at this position was defined to be at rest. The collision and streaming steps together complete a single iteration of solving the Lattice-BGK Equation over time and space. At the end of each LBM iteration, the magnetization macroscopic variable, \( M \) (\( M \) represents both \( M_x \) and \( M_y \) with each being computed using the described LBM algorithm for diffusion) obtained at the end of the diffusion step is updated by summation of the distribution functions as given in Equation (2.19).
\[ M = \sum_{i} g_{i} \]  

Having defined the numerical Lattice-BGK model over the domain, it is important to define the boundary conditions for the model. The behavior of the particles at the boundaries should be treated in a special manner as the diffusion at the walls of the domain and at the semipermeable membrane between the internal and external regions of a myocyte or a blood vessel is not the same as the rest of the domain. The boundary conditions used in the models for the various geometries described later in Chapter 3 are discussed in detail below. These conditions may be applied as required to the other geometries for the different boundaries.

A. **Dirichlet Boundary Condition**

The Dirichlet boundary condition comprises of a prescribed value for the dependent variable given by,

\[ \phi = \Phi_{d} \]  

The Dirichlet boundary condition is enforced in LBM at the streaming step according to the scheme developed by Li, Mei and Klausner [28] as shown in Equation (2.21). The notation and variables used in this equation are described in detail in Section 1.1. where the same Dirichlet boundary condition is used in deriving the membrane boundary condition.

\[ g_{-}(x_{j}, t + \delta t) = 2(\Delta - 1) \hat{g}_{+}(x_{j}, t) - \left( \frac{2(\Delta - 1)^{2}}{2\Delta + 1} \right) \hat{g}_{+}(x_{j}, t) + 2 \left( \frac{2\Delta - 1}{2\Delta + 1} \right) \hat{g}_{-}(x_{j}, t) + \left( \frac{3 - 2\Delta}{2\Delta + 1} \right) \varepsilon_{d} \Phi_{d} \]  (2.21)

B. **Periodic Boundary Condition**

A periodic boundary condition is enforced on opposite boundaries to replicate the physics on either side of the domain. Implementing periodic boundary conditions enables the simulation of a tissue by modelling a single cell. For the purpose of referencing, in each pair of opposite boundaries, one is defined as the source boundary and the other as the destination boundary. In LBM, if the node from which the post collision value travels \((x_{dst} - e_{\delta x})\) is outside the domain,
then the periodic boundary condition is imposed at $x_{dist}$ and $x_{src} = x_{dist} + N\delta x$, where, $N$ is the number of grid points and $N\delta x$ is the total length or width of the domain. The value of the equilibrium distribution function at the wall where periodic boundary condition is imposed is given by Equation (2.22).

$$g_i^{in}(x_{dist}, t + \delta t) = g_i^{out}(x_{src}, t)$$  \hspace{1cm} (2.22)

where, $x_{dist}$ represents the location of the destination boundary,
and, $x_{src}$ represents the location of the source boundary.

C. Membrane Boundary Condition

\((g) \, \text{post-collision species}\)

\[ g_d(x_j, t + \delta t) : \text{Effective population from inside the membrane i.e. } x_j \rightarrow x_e \]
\[ g_d(x_j, t + \delta t) : \text{Effective population from outside the membrane i.e. } x_e \rightarrow x_j \]

Figure 2.3. Schematic Depiction of the Lattice Link Intersected by the Membrane.

The boundary condition at the membrane incorporates a combination of Neumann and Dirichlet boundary conditions, and satisfies the permeable membrane diffusive flux physics. The lattice link cut by the membrane is depicted in Figure 2.3 [28].
The arbitrary distance from the lattice point on the intracellular region of the membrane to the point at which the membrane cuts the lattice link is denoted by Δ as shown in the above figure. Since the lattice grid size is unity, the distance from the lattice point on the extracellular region of the membrane to the membrane is given by Δex = 1 − Δ. The membrane boundary condition is enforced at the end of the collision step. For the purpose of the membrane boundary condition, the post collision species is denoted as ĝ, and the post streaming step is denoted as g. Furthermore, the direction of the particle distribution towards the membrane is denoted by the subscript a, and the direction of the particle distribution away from the membrane is denoted by the subscript ā. Lastly, Φn denotes the flux normal to the membrane.

The Neumann and Dirichlet boundary conditions used to derive the membrane boundary condition are based on the scheme developed by Li, Mei and Klausner [28]. These are stated as,

i. **Neumann Boundary Condition:**

\[
g_a(x_j, t + \delta t) = c_{n1} \hat{g}_a(x_j, t) + c_{n2} \hat{g}_a(x_{j'}, t) + c_{n3} \hat{g}_a(x_j, t) + c_{n4} (\delta t / \delta x) \Phi_{na}
\]

where, \(c_{n1}, c_{n2}, c_{n3}\), and \(c_{n4}\) are coefficients related to Δ, and \(\Phi_{na} = \Phi_n\)

\[
\begin{align*}
c_{n1} &= 1 \\
c_{n2} &= -\frac{2\Delta - 1}{2\Delta + 1} \\
c_{n3} &= \frac{2\Delta - 1}{2\Delta + 1} \\
c_{n4} &= \frac{2}{2\Delta + 1}
\end{align*}
\]

(2.24)

ii. **Dirichlet Boundary Condition:**

\[
g_a(x_j, t + \delta t) = c_{d1} \hat{g}_a(x_j, t) + c_{d2} \hat{g}_a(x_{j'}, t) + c_{d3} \hat{g}_a(x_j, t) + c_{d4} c_D \Phi_d
\]

where, \(c_{d1}, c_{d3}\), and \(c_{d4}\) are coefficients related to Δ

(2.25)
\[
\begin{align*}
\begin{cases}
    c_{d1} &= 2(\Delta - 1) \\
    c_{d2} &= -\left(\frac{(2\Delta - 1)^2}{2\Delta + 1}\right) \\
    c_{d3} &= 2\left(\frac{2\Delta - 1}{2\Delta + 1}\right) \\
    c_{d4} &= \frac{3 - 2\Delta}{2\Delta + 1}
\end{cases}
\end{align*}
\]  
(2.26)

iii. **Membrane Boundary Condition:**

The Neumann and Dirichlet boundary conditions can be determined for the effective population of the species going from the interior of the membrane to the exterior and vice versa denoted by \( g_a(x_e, t + \delta t) \) and \( g_a(x_f, t + \delta t) \) respectively. Since there are two unknowns, two equations are required to solve the problem and obtain the effective populations going across the membrane in both directions. First, the Neumann boundary condition for the two effective populations is determined based on Equation (2.23) as follows,

\[
g_a(x_f, t + \delta t) = c_{d1}g_a(x_f, t) + c_{d2}g_a(x_{ff}, t) + c_{d3}g_a(x_f, t) + c_{d4} \frac{\delta t}{\partial x} \Phi_{n_a,int}
\]  
(2.27)

\[
g_a(x_e, t + \delta t) = c_{d1}g_a(x_e, t) + c_{d2}g_a(x_{ee}, t) + c_{d3}g_a(x_e, t) + c_{d4} \frac{\delta t}{\partial x} \Phi_{n_a,ext}
\]  
(2.28)

The superscripts ‘in’ and ‘ex’ on the coefficients denote the coefficients on the interior and exterior sides of the membrane respectively. \( \Phi_{n_a,int} \) and \( \Phi_{n_a,ext} \) are the fluxes normal to the membrane pointing towards the interior and exterior sides of the membrane respectively. Using the coefficients from Equation (2.24) and the relationship \( \Delta^{ex} = 1 - \Delta \), the coefficients in Equations (2.27) and (2.28) are given below in Equations (2.29) and (2.30).
\[
\begin{cases}
    c_{n1}^{in} = 1 \\
    c_{n2}^{in} = \frac{-2\Delta - 1}{2\Delta + 1} \\
    c_{n3}^{in} = \frac{2\Delta - 1}{2\Delta + 1} \\
    c_{n4}^{in} = \frac{2}{2\Delta + 1}
\end{cases}
\tag{2.29}
\]

\[
\begin{cases}
    c_{n1}^{ext} = 1 \\
    c_{n2}^{ext} = \frac{-1 - 2\Delta}{3 - 2\Delta} \\
    c_{n3}^{ext} = \frac{1 - 2\Delta}{3 - 2\Delta} \\
    c_{n4}^{ext} = \frac{2}{3 - 2\Delta}
\end{cases}
\tag{2.30}
\]

Substituting the coefficients from Equations (2.29) and (2.30) in Equations (2.27) and (2.28), and rearranging Equations (2.27) and (2.28) to obtain the fluxes $\Phi_{n_a, \text{int}}$ and $\Phi_{n_a, \text{ext}}$, we get,

\[
\Phi_{n_a, \text{int}} = \left( \frac{\delta t}{\delta x} \right) \left( \frac{2\Delta + 1}{2} \right) \left\{ g_a(x_f, t + \delta t) - \hat{g}_a(x_f, t) - \left( \frac{2\Delta - 1}{2\Delta + 1} \right) \left[ \hat{g}_a(x_f, t) - \hat{g}_a(x_g, t) \right] \right\} \tag{2.31}
\]

\[
\Phi_{n_a, \text{ext}} = \left( \frac{\delta t}{\delta x} \right) \left( \frac{3 - 2\Delta}{2} \right) \left\{ g_a(x_e, t + \delta t) - \hat{g}_a(x_e, t) - \left( \frac{1 - 2\Delta}{3 - 2\Delta} \right) \left[ \hat{g}_a(x_e, t) - \hat{g}_a(x_{e'}, t) \right] \right\} \tag{2.32}
\]

If the sign convention is adopted such that the normal flux to the membrane is positive towards the interior, then,

\[
\Phi_{n_a, \text{ext}} = -\Phi_{n_a, \text{int}} \tag{2.33}
\]

Equating the flux equations in Equations (2.31) and (2.32) based on the condition in Equation (2.33), the first equation of the system of equations to solve is determined as,
\[
\frac{2\Delta+1}{2} \left\{ g_a \left( x_f, t + \delta t \right) - \hat{g}_a \left( x_f, t \right) - \left( \frac{2\Delta-1}{2\Delta+1} \right) \left[ \hat{g}_a \left( x_f, t \right) - \hat{g}_a \left( x_f, t \right) \right] \right\} \\
= \frac{3-2\Delta}{2} \left\{ -g_a \left( x_f, t + \delta t \right) + \hat{g}_a \left( x_f, t \right) + \left( \frac{1-2\Delta}{3-2\Delta} \right) \left[ \hat{g}_a \left( x_f, t \right) - \hat{g}_a \left( x_f, t \right) \right] \right\}
\]

(2.34)

Next, the Dirichlet boundary condition for the two effective populations is determined based on Equations (2.25) and (2.26) as follows,

\[
g_a \left( x_f, t + \delta t \right) = 2(\Delta-1) \hat{g}_a \left( x_f, t \right) - \left( \frac{2\Delta-1}{2\Delta+1} \right) \hat{g}_a \left( x_f, t \right) + \left( \frac{3-2\Delta}{2\Delta+1} \right) \epsilon_D \Phi_{a,int} 
\]

(2.35)

\[
g_a \left( x_e, t + \delta t \right) = -2\Delta \hat{g}_a \left( x_e, t \right) - \left( \frac{1-2\Delta}{3-2\Delta} \right) \hat{g}_a \left( x_e, t \right) + \left( \frac{2\Delta+1}{3-2\Delta} \right) \epsilon_D \Phi_{a,ext} 
\]

(2.36)

The above equations can be rearranged to give the internal and external fluxes at the membrane,

\[
\Phi_{a,int} = \frac{1}{\epsilon_D} \left( \frac{2\Delta+1}{3-2\Delta} \right) \left\{ g_a \left( x_f, t + \delta t \right) - 2(\Delta-1) \hat{g}_a \left( x_f, t \right) \right\}
\]

(2.37)

\[
\Phi_{a,ext} = \frac{1}{\epsilon_D} \left( \frac{3-2\Delta}{2\Delta+1} \right) \left\{ g_a \left( x_e, t + \delta t \right) + 2\Delta \hat{g}_a \left( x_e, t \right) \right\}
\]

(2.38)

The effective flux at the membrane can be determined by relating the internal and external fluxes at the membrane, \( \Phi_{d,int} \) and \( \Phi_{d,ext} \) with the permeability of the membrane, \( K \). This permeability condition at the membrane is given by Equation (2.39) and the logic behind this condition is shown in the schematic in Figure 2.4.
Substituting Equations (2.37) and (2.38) in Equation (2.39) gives the second equation of the system of equations required to solve for the effective populations across the membrane.

\[
K \left( \Phi_{\text{d,ext}} - \Phi_{\text{d,inn}} \right) = \Phi_{\text{inn}}
\]  

(2.39)

\[
\frac{K}{\varepsilon_D} \left( \frac{3-2\Delta}{2\Delta+1} \right) \left[ g_a(x_e,t+\delta t) + 2\Delta \hat{g}_a(x_e,t) + \left( \frac{(1-2\Delta)^2}{3-2\Delta} \right) \hat{g}_a(x_e,t) - 2 \left( \frac{1-2\Delta}{3-2\Delta} \right) \hat{g}_a(x_e,t) \right] 
- \frac{K}{\varepsilon_D} \left( \frac{2\Delta+1}{3-2\Delta} \right) \left[ g_a(x_f,t+\delta t) - 2(\Delta-1) \hat{g}_a(x_f,t) + \left( \frac{(2\Delta-1)^2}{2\Delta+1} \right) \hat{g}_a(x_f,t) - 2 \left( \frac{2\Delta-1}{2\Delta+1} \right) \hat{g}_a(x_f,t) \right] 
= \frac{\delta x}{\delta t} \left[ g_a(x_f,t+\delta t) - \hat{g}_a(x_f,t) \right] 
\]  

(2.40)

g_a(x_f,t+\delta t) \text{ and } \hat{g}_a(x_e,t+\delta t) \text{ can now be determined by solving Equations (2.34) and (2.40) as a system of linear equations. In the simplified case of } \Delta = 0.5 \text{ and using } \varepsilon_D = 1/3 \text{ for a D2Q5 LBM model, Equations (2.34) and (2.40) become,}

\[
g_a(x_f,t+\delta t) - \hat{g}_a(x_f,t) + g_a(x_e,t+\delta t) - \hat{g}_a(x_e,t) = 0
\]  

(2.41)

\[
3K \left\{ -g_a(x_f,t+\delta t) - \hat{g}_a(x_f,t) + g_a(x_e,t+\delta t) + \hat{g}_a(x_e,t) \right\} 
= \frac{\delta x}{\delta t} \left[ g_a(x_f,t+\delta t) - \hat{g}_a(x_f,t) \right]
\]  

(2.42)

For the special case of infinite permeability, \( K \to \infty \) and \( \Delta = 0.5 \), Equation (2.42) reduces to,

\[
-g_a(x_f,t+\delta t) - \hat{g}_a(x_f,t) + g_a(x_e,t+\delta t) + \hat{g}_a(x_e,t) = 0
\]  

(2.43)

Coupling Equation (2.43) with Equation (2.41) gives,

\[
g_a(x_f,t+\delta t) = \hat{g}_a(x_e,t)
\]  

(2.44)

\[
g_a(x_e,t+\delta t) = \hat{g}_a(x_f,t)
\]  

(2.45)
Equations (2.44) and (2.45) imply that after the collision step of the LBM algorithm, the particle distribution function \( \hat{g}_a \) crosses the membrane unaltered during the streaming step if the permeability, \( K \to \infty \) and \( \Delta = 0.5 \).

For finite permeability \( K \) values and \( \Delta = 0.5 \), Equations (2.41) and (2.42) can be manipulated by applying \( \frac{1}{2} \left[ \text{Equation(44)} - \frac{1}{3K} \text{Equation(45)} \right] \) to give the following,

\[
\frac{1}{2} \left[ g_a(x_f, t + \delta t) - \hat{g}_a(x_f, t) + g_a(x_e, t + \delta t) - \hat{g}_a(x_e, t) \right] = \frac{1}{2} \left[ 0 - \frac{1}{3K} \frac{\delta x}{\partial t} \left\{ g_a(x_f, t + \delta t) - \hat{g}_a(x_f, t) \right\} \right]
\]

\[
\Rightarrow g_a(x_f, t + \delta t) - \hat{g}_a(x_e, t) = \frac{\delta x}{6K \partial t} \left\{ g_a(x_f, t + \delta t) - \hat{g}_a(x_f, t) \right\}
\]

\[
\Rightarrow \left( 1 + \frac{1}{6K \partial t} \right) g_a(x_f, t + \delta t) = \hat{g}_a(x_e, t) + \frac{\delta x}{6K \partial t} \hat{g}_a(x_f, t)
\]

(2.46)

Let’s define a parameter, \( P = \frac{1}{6K \partial t} \). Then Equation (2.46) becomes,

\[
(1 + P) g_a(x_f, t + \delta t) = \hat{g}_a(x_e, t) + P \hat{g}_a(x_f, t)
\]

\[
\Rightarrow g_a(x_f, t + \delta t) = \frac{1}{1 + P} \hat{g}_a(x_e, t) + \frac{P}{1 + P} \hat{g}_a(x_f, t)
\]

(2.47)

Substituting Equation (2.47) back in Equation (2.41) gives,

\[
g_a(x_e, t + \delta t) = \frac{P}{1 + P} \hat{g}_a(x_e, t) + \frac{1}{1 + P} \hat{g}_a(x_f, t)
\]

(2.48)

Equations (2.47) and (2.48) therefore quantitatively describe the particle distribution functions across the membrane, \( g_a(x_f, t + \delta t) \) and \( g_a(x_e, t + \delta t) \) at the end of the streaming step.
for finite permeability $K$ values and the assumption, $\Delta = 0.5$. For the more complex case of varying $\Delta$ at each lattice link, the particle distribution functions, $g_a(x, t + \Delta t)$ and $g_a(x_\epsilon, t + \Delta t)$ are determined by directly solving Equations (2.34) and (2.40).

2.3.2 Free Precession

After the external force is removed, the magnetized spin system that had been perturbed from its thermal equilibrium by the RF pulse will return to its equilibrium state. This process is characterized by the precession of the bulk magnetization, $\mathbf{M}$ about the static magnetic field, $\mathbf{B}_0$ called free precession, followed by the longitudinal and transverse relaxation. The relaxation step is discussed in more detail in the following section. The equations used to simulate free precession in LBM are given below,

$$\Delta \varphi = \gamma G \left( I - \frac{N}{2} \right) \Delta x \Delta t$$

$$M_x^{n+1/2}[\mathbf{r}] = M_x^n[\mathbf{r}] \cos(\Delta \varphi) - M_y^n[\mathbf{r}] \sin(\Delta \varphi)$$

$$M_y^{n+1/2}[\mathbf{r}] = M_x^n[\mathbf{r}] \cos(\Delta \varphi) + M_y^n[\mathbf{r}] \sin(\Delta \varphi)$$

(2.49)

where, $\Delta \varphi$ is the accumulated phase during each time step for the $i^{th}$ spin isochromat,

$N$ is the spin isochromat numbers along the gradient direction,

$\Delta x$ is the spatial step size for discretization which is the same as the lattice grid size, $\delta x$,

$\Delta t$ is the time step size for discretization which is larger than the diffusion time step, $\delta t$,

$n$ is the time step at the end of diffusion

and, $\mathbf{r}$ is the location of the lattice grid point in the computational domain.

In order to maintain generality, the gradient center is placed at the middle of the sample, such that $N$ becomes the length of the lattice domain along the gradient direction, and $I$ is the location of each lattice node on the lattice domain along the gradient direction.
2.3.3 Relaxation

The spins relax continuously during the entire gradient pulse. Since the modeling of the molecular diffusion process is confined in the transverse plane, the transverse relaxation is simulated using LBM as follows,

\[ M_x^{n+1} = M_x^{n+1/2} e^{-\frac{\Delta t}{T_1[r]}} \]
\[ M_y^{n+1} = M_y^{n+1/2} e^{-\frac{\Delta t}{T_1[r]}} \]  (2.50)

The free precession and relaxation processes occur simultaneously and are therefore simulated within one time step between \( n \) and \( n+1 \).

2.4 The Finite Element Method

An analytical solution for the complex geometries studied is difficult to obtain. Consequently, the numerical solution determined using LBM is validated by a Finite Element Method (FEM) algorithm in COMSOL. A two dimensional model is created in COMSOL using the “Coefficient Form PDE” physics. The equation based model is represented as follows in Equation (2.51).

\[ e_a \frac{\partial^2 \mathbf{u}}{\partial t^2} + d_a \frac{\partial \mathbf{u}}{\partial t} + \nabla \cdot (-c \nabla \mathbf{u} - \mathbf{a} \mathbf{u} + \gamma_s) + \beta \cdot \nabla \mathbf{u} + a \mathbf{u} = f \]  (2.51)

where, \( e_a \) is the mass coefficient,
\( d_a \) is a damping coefficient or a mass coefficient,
\( c \) is the diffusion coefficient,
\( \mathbf{a} \) is the conservative flux convection coefficient,
\( \beta \) is the convection coefficient,
\( a \) is the absorption coefficient,
\( \gamma_s \) is the conservative flux source term,
\( f \) is the source term,
and, \( \mathbf{u} = u_x \mathbf{i} + u_y \mathbf{j} \) is the dependent variable.

The above equation is reduced to the Bloch-Torrey equation in Equation (1.7) by setting the mass coefficient \( e_a \), conservative flux convection coefficient \( a \), conservative flux source term \( \gamma \), and source term \( f \) to zero. For an isotropic domain, \( c = \begin{bmatrix} D & 0 \\ 0 & D \end{bmatrix} \) with \( D \) as the diffusion coefficient input. The absorption coefficient, \( a = \begin{bmatrix} \frac{1}{T_2} & -\gamma B_z(x,t) \\ \gamma B_z(x,t) & \frac{1}{T_2} \end{bmatrix} \) with \( T_2 \) as the local spin-spin relaxation time, \( \gamma \) as the gyromagnetic ratio for a proton and \( B_z \) as the external magnetic field as a function of space and time according to Equation (2.11). The convection coefficient, \( \beta = \begin{bmatrix} V_x & 0 \\ 0 & V_y \end{bmatrix} \) with velocity, \( \mathbf{V} = V_x \mathbf{i} + V_y \mathbf{j} \).

A time-dependent study is carried out for the same number of time steps as the LBM algorithm. While the time step, \( \delta t \) is chosen exactly the same as LBM, the grid size is variable. The grid size is automatically determined based on the geometry with a finer grid closer to the boundaries and membrane. An error analysis for different grid sizes is performed before choosing the mesh with least error.

Unlike LBM, the geometry is divided into three domains – the extracellular region, the membrane, and the intracellular region. Within each domain, the Bloch-Torrey equation in Equation (2.7) is modeled to study the molecular diffusion of water within the tissue of interest. In each domain, different diffusion coefficients and relaxation time parameters corresponding to the properties of the domain are used, while maintaining continuity boundary conditions at the boundaries between the domains. For the case of advection-diffusion or diffusion alone, Equation (2.5) or Equation (2.3) is modeled using the Coefficient Form PDE in Equation (2.51) by setting the absorption coefficient, \( a = 0 \).
Lastly, the boundaries of the model should be defined separately by a set of equations as the diffusion at the walls of the domain and across a semipermeable membrane which is present in a myocyte or a blood vessel is not the same as the rest of the domain. The boundary conditions used in the COMSOL finite element models for the various geometries are discussed in detail below based on the geometry with simple vertical membrane ($\theta = 0^\circ$). Similar to the case of LBM, the boundary conditions for the other geometries are imposed as required.

A. **Dirichlet Boundary Condition**

The Dirichlet boundary condition in Equation (2.20) is modeled in COMSOL by entering a value or expression for the dependent variables on the boundary.

\[
\mathbf{u} = \begin{bmatrix} u_x \\ u_y \end{bmatrix} = \begin{bmatrix} \Phi_x \\ \Phi_y \end{bmatrix}
\]  

(2.52)

B. **Periodic Boundary Condition**

The periodic boundary condition is enforced on pairs of opposite boundaries in COMSOL based on Equation (2.53). Just like in LBM, for the purpose of referencing, in each pair of opposite boundaries, one is defined as the source boundary and the other as the destination boundary.

\[
-\mathbf{n}_{dst} \cdot (-D\nabla \mathbf{u})_{dst} = \mathbf{n}_{src} \cdot (-D\nabla \mathbf{u})_{src}
\]  

(2.53)

where, $\mathbf{n}_{dst}$ is the normal vector to the destination boundary surface,

$(D\nabla \mathbf{u})_{dst}$ is the diffusion flux on the destination boundary surface,

$\mathbf{n}_{src}$ is the normal vector to the source boundary surface,

and, $(D\nabla \mathbf{u})_{src}$ is the diffusion flux on the source boundary surface.

Furthermore, the periodicity is assumed to be continuous along the direction in which the periodic boundary condition is applied. The continuity conditions shown in Equation (2.54) is imposed in order to obtain a symmetric replication of the domain.
\[ u(x_{dst}) = u(x_{src}) \] (2.54)

where, \( x_{dst} \) represents the location of the destination boundary, and \( x_{src} \) represents the location of the source boundary.

C. Membrane Boundary Condition [29]

As described earlier, the membrane boundary condition in the COMSOL FEM algorithm is imposed by defining a domain with a diffusion coefficient and spin-spin relaxation time pertaining to the properties of the membrane. A schematic of the setup is shown in Figure 2.5. The diffusion coefficient for the membrane domain, \( D_{mem} \) is chosen based on the permeability of the membrane \( K \) and the membrane thickness \( \Delta x_{mem} \). The relationship between the three parameters is defined by Fick’s first law of diffusion,

\[ J = -D_{mem} \frac{\Delta \phi}{\Delta x_{mem}} = -K \Delta \phi \] (2.55)

where, \( J \) is the diffusive flux, and, \( \phi \) is a scalar variable that represents the concentration of the species.

Therefore, the diffusion coefficient for the membrane domain, \( D_{mem} \) is derived from the above equation as,

\[ D_{mem} = K \Delta x_{mem} \] (2.56)
The Bloch-Torrey equation is then simulated in the membrane domain with the diffusion coefficient, $D_{\text{mem}}$ just like the other domains of the geometry.

### 2.5 Stability and Accuracy of the Lattice Boltzmann Method

In the Lattice Boltzmann Method, the macroscale diffusion coefficient, $D$ is related to the local relaxation time parameter, $\tau$ as follows,

$$D = \frac{1}{3} \left( \tau - \frac{1}{2} \right) \frac{\delta x^2}{\delta t} \quad (2.57)$$

where, $\delta x$ is the lattice grid size in $\mu m$, and, $\delta t$ is the lattice time step in $ms$.

In the LBM model, the dimensions of the geometry are scaled to lattice units using the grid size, $\delta x$. If the length of the domain is $L$, then the length of the computational domain, $L'$ in lattice units is,

$$L' = \frac{L}{\delta x} \quad (2.58)$$

The grid size and time step are chosen such that the LBM collision relaxation parameter, $\tau$ determined using Equation (2.17) satisfies the stability criterion $\tau \geq 0.5$. An analysis of the grid size and its effect on the simulation was carried out for both LBM and FEM algorithms for particular cases in Chapter 4. It was found that the length of the computational domain, $L'$ played an important role in determining the stability of the vessel flow model. This was due to the effect of the Péclet number – a dimensionless number that is defined as the ratio of the advective transport rate to the diffusive transport rate given by,

$$Pe = \frac{LU}{D} \quad (2.59)$$

where, $Pe$ is the Peclet number,

$L$ is the characteristic length of the domain of interest,
$U$ is the velocity of the flow in the domain of interest,

and, $D$ is the diffusion coefficient for the flow in the domain of interest.

Since the Péclet number plays an important role in the numerical stability of the vessel flow model, it is important to study the effects of the grid size and domain length on the Péclet number, and its consequent effect on the results. In the vessel flow model, it was concluded that high Péclet numbers cause instability in the model due to the high velocity of the flow that is imposed together with long diffusion length, $L$. A detailed study of these numerical effects was not performed and is required in the future to determine the computational limitations of the LBM and FEM simulations.
CHAPTER 3: GEOMETRIC MODELS

3.1 Elliptical Myocyte Model

Figure 3.1. (a) Karampinos’ Muscle Fiber Model: The model consists of infinitely long cylindrical muscle fibers surrounded by the water permeable sarcolemma membrane and embedded in the extracellular endomysium. (b) Cross-section of a Single Myofiber in a Periodic Model of the Muscle: The perimeter of the elliptical myocyte consists of a membrane with finite water permeability.

According to the composite medium model [30], the muscle fibers are infinite cylinders with an elliptical cross section as shown in Figure 3.1.

The major and minor axes of the elliptical cross-section of the muscle fiber are defined as $a_{\text{ellipse}}$ and $b_{\text{ellipse}}$ respectively. The length and width of the external endomysium domain of the myocyte model are defined as $L_{\text{dom}}$ and $W_{\text{dom}}$ respectively. The ellipticity of the elliptical cross-section which is the geometric ratio of the minor and major axes ($b_{\text{ellipse}}/a_{\text{ellipse}}$) is estimated to be in the range 0.40 – 0.80 [31], based on studies on the skeletal muscle of mammals. It is assumed that the endomysium does not contribute to diffusion anisotropy since the muscle fibers in the endomysium are arranged along the same direction in the relaxed muscle. Therefore, the myocyte model can be simplified into a two compartment system including the intracellular region of the muscle fiber and the extracellular region consisting of endomysium separated by
the sarcolemma membrane. The semipermeable sarcolemma membrane is represented in red in the above Figure 3.1(b). The myocyte model is assumed to be periodic two dimensionally. This results in the application of periodic boundary conditions to the two sets of opposite boundaries of the external domain. These boundaries are represented in blue in Figure 3.1(b). The wall and membrane boundaries are specially treated in the numerical model, a detailed description of which is presented in Chapter 2.

3.2 Disc Myocyte Model

The transverse cross-section of the muscle fiber is also modeled as a disc in order to study the behavior of the diffusion weighted signal in a symmetric domain when gradients are applied along the two perpendicular transverse directions. A schematic of the muscle fiber cross-section is shown in Figure 3.2. The dimensions of the disc muscle fiber in the square external domain is determined by maintaining the same surface area, volume and inclusion fraction as the myocyte model with elliptical cross section. Let $c_{\text{ellipse}}$ and $c_{\text{disc}}$ be the longitudinal lengths of the muscle fibers with elliptical and disc shaped transverse cross-sections respectively.

Since the volumes of the myocyte models with elliptical and disc shaped cross-sections are the same,

\[
\frac{\pi}{2} a_{\text{ellipse}} b_{\text{ellipse}} c_{\text{ellipse}} = \pi r^2 c_{\text{disc}}
\]

\[
\frac{c_{\text{disc}}}{c_{\text{ellipse}}} = \frac{a_{\text{ellipse}} b_{\text{ellipse}}}{4r^2} \tag{3.1}
\]

Since the surface areas of the myocyte models with elliptical and disc shaped cross-sections are equal,

\[
\pi \sqrt{\frac{a_{\text{ellipse}}^2 + b_{\text{ellipse}}^2}{2}} c_{\text{ellipse}} = 2\pi r c_{\text{disc}}
\]

![Figure 3.2. Transverse Disc Shaped Cross-Section of the Muscle Fiber.](image)
\[
\frac{c_{\text{disc}}}{c_{\text{ellipse}}} = \frac{1}{2r} \sqrt{\frac{a_{\text{ellipse}}^2 + b_{\text{ellipse}}^2}{2}} \tag{3.2}
\]

Setting Equations (3.1) and (3.2) equal to each other, the radius of the disc, \( r \), is obtained as follows,

\[
\frac{a_{\text{ellipse}}b_{\text{ellipse}}}{4r^2} = \frac{1}{2r} \sqrt{\frac{a_{\text{ellipse}}^2 + b_{\text{ellipse}}^2}{2}}
\]

\[
\frac{a_{\text{ellipse}}b_{\text{ellipse}}}{2r} = \sqrt{\frac{a_{\text{ellipse}}^2 + b_{\text{ellipse}}^2}{2}}
\]

\[
\Rightarrow r = \frac{a_{\text{ellipse}}b_{\text{ellipse}}}{2} \sqrt{\frac{2}{a_{\text{ellipse}}^2 + b_{\text{ellipse}}^2}} \tag{3.3}
\]

The inclusion fraction of the muscle fiber is defined as the ratio of the area of the muscle fiber cross-section to the area of the external domain cross-section. If the inclusion fraction of the muscle fiber with disc shaped cross-section in a square external domain shown in Figure 3.2, is the same as the inclusion fraction of the muscle fiber with elliptical cross-section in the rectangular external domain shown in Figure 3.1(b), then the side \( S_{\text{dom}} \) of the square external domain is given by,

\[
\frac{\text{Area of Elliptical Muscle Fiber}}{\text{Area of External Rectangular Domain}} = \frac{\text{Area of Disc Shaped Muscle Fiber}}{\text{Area of External Square Domain}}
\]

\[
\frac{\pi a_{\text{ellipse}}b_{\text{ellipse}}}{4L_{\text{dom}} W_{\text{dom}}} = \frac{\pi r^2}{S_{\text{dom}}^2}
\]

\[
\Rightarrow S_{\text{dom}} = 2r \sqrt{\frac{L_{\text{dom}} W_{\text{dom}}}{a_{\text{ellipse}}b_{\text{ellipse}}}} \tag{3.4}
\]

Similar to the previous elliptical myocyte model, the disc myocyte model is also a two compartment model with the intracellular and extracellular region separated by the water
permeable sarcolemma membrane illustrated in red in Figure 3.2. The model is assumed to be periodic in two dimensions and consequently periodic boundary conditions are applied to the two sets of opposite boundaries of the external domain illustrated in blue in Figure 3.2.

3.3  Simple Vertical Membrane Model

In order to analyze the effectiveness of the numerical algorithms in simulating the diffusion process, the numerical stability of the LBM and FEM models is tested by simulating a simple geometry. The geometry comprises of rectangular extracellular and intracellular domains separated by a permeable membrane as shown in Figure 3.3. The dimensions of the simple rectangular model with a vertical membrane are chosen on the same order of magnitude as that of the myocyte cell with an overall length $L$, and width $W$. The length of each domain, both extracellular and intracellular is $L/2$.

![Figure 3.3. Simple Vertical Membrane Model with Length, L and Width, W. Description of Boundary Conditions: i. Blue: Dirichlet boundary condition, $\phi(0, y) = \Phi_{d1}$, ii. Red: Dirichlet boundary condition, $\phi(L, y) = \Phi_{d2}$, iii. Green: Periodic boundary condition, iv. Purple: Membrane boundary condition (Note: Membrane is modeled as a separate domain in COMSOL as discussed in Chapter 2 under FEM model).](image)
Dirichlet boundary conditions for the concentration, \( \phi \) are imposed on the wall boundaries at \( x = 0 \) and \( x = L \) given by,

\[
\begin{align*}
\phi(0, y) &= \Phi_{d,1} \\
\phi(L, y) &= \Phi_{d,2}
\end{align*}
\] (3.5)

Periodic boundary conditions are imposed in the \( y \)-direction according to Equation (3.6).

\[
-n_{y=0} \cdot (-D \nabla \phi)_{y=0} = n_{y=W} \cdot (-D \nabla \phi)_{y=W}
\] (3.6)

where, \( n_{y=0} \) is the normal vector to the boundary wall at \( y = 0 \)

\( (D \nabla \phi)_{y=0} \) is the diffusive flux on the boundary wall at \( y = 0 \)

\( n_{y=W} \) is the normal vector to the boundary wall at \( y = W \),

and, \( (D \nabla \phi)_{y=W} \) is the diffusive flux on the boundary wall at \( y = W \).

Lastly, the membrane boundary conditions are applied across the membrane at \( x = L/2 \) in the \( x \)-direction according to the methods discussed in Chapter 2 for the Lattice Boltzmann and Finite Element algorithms. In LBM, the membrane boundary condition for the special case of finite permeability \( K \) and \( \Delta = 0.5 \) is implemented.

### 3.4 Wedged Membrane Model

In addition to the simple vertical membrane modeled discussed in the last section, a wedged membrane models with different wedge angles were created in order to analyze the numerical stability and effectiveness of the Lattice Boltzmann and Finite Element algorithms at corners where there is sharp gradient differences or more than one condition that needs to be satisfied. The geometry of this model is shown in Figure 3.4. The dimensions of the model such as the length \( L \), and width \( W \) remain the same as that of the simple vertical membrane model. The membrane wedge is formed at \( y = W/2 \) at an inclination angle of \( \theta \). Simulations are carried
out at angles, $\theta = 30^\circ, 45^\circ, 60^\circ$. The equations of the lines forming the membrane are given below in Equation (3.7).

$$x = \begin{cases} \frac{L}{2} - \left(\frac{1}{4}W - y\right)\tan\theta, & \left(0 < y < \frac{W}{2}\right) \\ \frac{L}{2} + \left(\frac{3}{4}W - y\right)\tan\theta, & \left(\frac{W}{2} < y < W\right) \end{cases}$$ (3.7)

![Diagram of Wedged Membrane Model](image)

Figure 3.4. Wedged Membrane Model with Length $L$, Width $W$, and Membrane Wedge Angle $\theta$. Description of Boundary Conditions: i. Dirichlet boundary condition, $\phi(0, y) = \Phi_{d1}$, ii. Red: Dirichlet boundary condition, $\phi(L, y) = \Phi_{d2}$, iii. Green: Periodic boundary condition, iv. Purple: Membrane boundary condition (Note: Membrane is modeled as a separate domain in COMSOL as discussed in Chapter 2 under FEM model).

Just like the simple vertical membrane model, Dirichlet boundary conditions are imposed on the walls at $x = 0$ and $x = L$ according to Equation (3.5). Periodic boundary conditions are imposed on the walls at $y = 0$ and $y = W$ according to Equation (3.6). Lastly, the membrane boundary conditions are implemented according to the methods discussed in Chapter 2 for both Lattice Boltzmann and Finite Element algorithms.
Unlike the simple vertical membrane model, variable $\Delta$ values are used to implement the membrane boundary condition in LBM according to Equations (2.34) and (2.40). Moreover, for the case of the wedged membrane model, the permeability condition must be applied in the $y$-direction as well as the $x$-direction in LBM. Therefore, $\Delta$ values must be determined in both directions at each lattice link that the membrane crosses.

Let $\Delta_x$ and $\Delta_y$ be the $\Delta$ values defined along the $x$ and $y$ directions respectively as shown in Figure 3.5. $\Delta_x$ and $\Delta_y$ values at each lattice link that the membrane crosses can be determined as follows:

### i. $x$-direction

If $(I, J)$ is a point on the lattice grid with each link of the lattice grid having a length of one unit, then at every point $(I, J)$ in the extracellular domain for which the point $(I+1, J)$ lies in the intracellular domain (i.e. crossing of membrane), the value of $\Delta_x$ is given by the following equation and is stored as a variable $\Delta_x(I,J)$ in the LBM algorithm.

$$
\Delta_x = \begin{cases} 
1 - \left[ \frac{X_{\text{max}}}{2} - \left( \frac{1}{4} Y_{\text{max}} - J \right) \tan \theta \right] - I, & \left( 0 \leq J < \frac{Y_{\text{max}}}{2} \right) \\
1 - \left[ \frac{X_{\text{max}}}{2} + \left( \frac{3}{4} Y_{\text{max}} - J \right) \tan \theta \right] - I, & \left( \frac{Y_{\text{max}}}{2} < J \leq Y_{\text{max}} \right)
\end{cases}
$$

(3.8)

where, $X_{\text{max}} = \frac{L}{\delta x}$ is the length of the domain in lattice units,

$$Y_{\text{max}} = \frac{W}{\delta x}$$

is the height of the domain in lattice units,

and, $\delta x$ is the grid size.

Figure 3.5. Variable $\Delta$ Values defined across the Membrane Lattice Link.
ii. y-direction

The equation of the wedged membrane is redefined in terms of the complimentary angle, \( \theta_c \) in Equation (3.9) so that the parameter \( \Delta_y \) can be determined with ease. The angle \( \theta_c \) is defined in Figure 3.4.

\[
y = \begin{cases} 
\frac{1}{4}W - \left( \frac{L}{2} - x \right) \tan \theta_c, & 0 < y < \frac{W}{2} \\
\frac{3}{4}W + \left( \frac{L}{2} - x \right) \tan \theta_c, & \frac{W}{2} < y < W 
\end{cases}
\]

(3.9)

If \((I,J)\) is a point on the lattice grid with each link of the lattice grid having a length of one unit, then at every point \((I,J)\) in the extracellular domain for which either the point \((I,J - 1)\) lies in the intracellular domain over the interval \(0 \leq J < \frac{Y_{\text{max}}}{2}\), or the point \((I,J + 1)\) lies in the intracellular domain over the interval \(\frac{Y_{\text{max}}}{2} < J \leq Y_{\text{max}}\), the value of \(\Delta_y\) is given by the following equation,

\[
\Delta_y = \begin{cases} 
1 - \left[ J - \left( \frac{1}{4}Y_{\text{max}} - \left( \frac{X_{\text{max}}}{2} - I \right) \tan \theta_c \right) \right], & 0 \leq J < \frac{Y_{\text{max}}}{2} \\
1 + \left[ J - \left( \frac{3}{4}Y_{\text{max}} + \left( \frac{X_{\text{max}}}{2} - I \right) \tan \theta_c \right) \right], & \frac{Y_{\text{max}}}{2} < J \leq Y_{\text{max}} 
\end{cases}
\]

(3.10)

where, \(X_{\text{max}} = \frac{L}{\delta x}\) is the length of the domain in lattice units,

\(Y_{\text{max}} = \frac{W}{\delta x}\) is the height of the domain in lattice units,

and, \(\delta x\) is the grid size.
3.5 Vessel Flow Model

Blood flow in the brain is modeled in both Lattice Boltzmann and Finite Element using the Bloch-Torrey equation with convection in order to study the diffusive and convective processes with changes in the applied external magnetic field. The two dimensional domain comprises of a simple horizontal blood vessel surrounded by the grey matter in the brain as shown in Figure 3.6. The extravascular domain that consists of grey matter is modeled as a rectangle with length $L$, and width $W$. The intravascular domain that consists of the vessel is modeled as running horizontally through the middle of the domain and assumed to occupy 5-10% of the total area of the domain.

Therefore, a sample width of the vessel that occupies 5% of the total area of the domain and passes through the center of the domain of grey matter in the model is given by,

$$\text{Area of Vessel} = 5\% \text{ Area of Domain}$$
\[ W_{\text{vessel}} L = 0.05 WL \]

\[ \Rightarrow W_{\text{vessel}} = 0.05 W \quad (3.11) \]

The model is assumed to be periodic in two dimensions and consequently periodic boundary conditions are applied to the two sets of opposite boundaries of the external domain illustrated in grey in Figure 3.6. The blood brain barrier is assumed to be almost impermeable and a permeability value of \( K = 0 \, \mu m/s \) is used for the purpose of validating the model.
CHAPTER 4: RESULTS & DISCUSSION

4.1 Elliptical Myocyte Model

The muscle fibers were modeled two dimensionally as elliptical myocytes within a rectangular extracellular domain. Due to the periodic boundary conditions imposed on the rectangular computational domain, the maximum inclusion or volume fraction that can be attained under these constraints is 0.70. The geometry parameters of the elliptical myocyte model are therefore chosen such that the inclusion fraction is nearly 0.70. Simulations were carried out using both LBM and FEM algorithms for different input parameters of diffusion coefficients and local spin-spin relaxation times over a range of $b$ values from $0 – 1000 \ s/mm^2$. The gradient duration used is $\delta = 16 \ ms$, and the time duration between the start of two gradients is, $\Delta = 40 \ ms$ which results in a total echo time of, $t_E = 56 \ ms$. Table 4.1 shows the six different simulation cases that were run in order to study various aspects of diffusion within the myocyte. $D_{in}$ and $D_{ex}$ represent the intracellular and extracellular diffusivities respectively, while, $T_{2,\text{in}}$ and $T_{2,\text{ex}}$ represent the intracellular and extracellular local spin-spin relaxation times.

First, the ellipticity of the muscle fibers was chosen as 0.70 based on previous work carried out by Karampinos et al. in 2009 [30]. Case 1 studies the complete 2D model of the myocyte with intracellular and extracellular diffusion coefficients and relaxation times that are characteristic of the domains. The membrane between the two domains is assumed to be fully permeable. Next, the geometry effects of ellipticity were studied in Case 2 by running simulations for the case of ellipticity 0.38 using the same input parameters and inclusion fraction as that of the 0.70 ellipticity model. In Case 3, the importance of the inclusion fraction of the elliptical cross-section in the rectangular computational domain is analyzed in the model with ellipticity 0.70. The diffusion and relaxation parameters are assumed to be the same in both domains in order to bring out the results of the change in geometry alone. The effect of the local spin-spin relaxation times in the two different ellipticity models was then validated while keeping the diffusion coefficient constant in both the intracellular and extracellular domains in Cases 4(a) and (b). In this case, the simulation was run only at $b = 0 \ s/mm^2$ as only the relaxation...
time effect is seen in the signal at this $b$ value. Lastly, the permeability effects on diffusion were simulated for the two ellipticity models – 0.70 and 0.38 in Cases 5(a) and (b).

### Table 4.1. Input Parameters for the Simulation of Diffusion in Ellipse Myocyte Model

<table>
<thead>
<tr>
<th>Case</th>
<th>Ellipticity</th>
<th>Inclusion Fraction</th>
<th>$D_{\text{in}}$ (μm²/ms)</th>
<th>$D_{\text{ex}}$ (μm²/ms)</th>
<th>$T_{2,\text{in}}$ (ms)</th>
<th>$T_{2,\text{ex}}$ (ms)</th>
<th>$K$ (μm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.70</td>
<td>0.70</td>
<td>1.6</td>
<td>2.0</td>
<td>30</td>
<td>110</td>
<td>$\infty$</td>
</tr>
<tr>
<td>2</td>
<td>0.38</td>
<td>0.70</td>
<td>1.6</td>
<td>2.0</td>
<td>30</td>
<td>110</td>
<td>$\infty$</td>
</tr>
<tr>
<td>3</td>
<td>0.70</td>
<td>0.174</td>
<td>2.0</td>
<td>2.0</td>
<td>110</td>
<td>110</td>
<td>$\infty$</td>
</tr>
<tr>
<td>4(a)</td>
<td>0.70</td>
<td>0.70</td>
<td>2.0</td>
<td>2.0</td>
<td>30</td>
<td>30</td>
<td>$\infty$</td>
</tr>
<tr>
<td>4(b)</td>
<td>0.70</td>
<td>0.70</td>
<td>2.0</td>
<td>2.0</td>
<td>110</td>
<td>110</td>
<td>$\infty$</td>
</tr>
<tr>
<td>5(a)</td>
<td>0.70</td>
<td>0.70</td>
<td>1.6</td>
<td>2.0</td>
<td>30</td>
<td>110</td>
<td>13</td>
</tr>
<tr>
<td>5(b)</td>
<td>0.38</td>
<td>0.70</td>
<td>1.6</td>
<td>2.0</td>
<td>30</td>
<td>110</td>
<td>13</td>
</tr>
</tbody>
</table>

#### 4.1.1 Case 1: Simulation of 2D Myocyte Model with Ellipticity 0.70, Diffusion and Relaxation Time Parameters Characteristic of Intracellular and Extracellular Domains, and Infinite Permeability

The dimensions of the elliptical myocyte model with ellipticity 0.70 are defined based on the parameter definitions in Figure 3.1(b). The lengths of the major and minor axes of the elliptical cross section of the muscle fiber are $a_{\text{ellipse}} = 94 \ \mu m$ and $b_{\text{ellipse}} = 66 \ \mu m$ respectively. The dimensions of the extracellular rectangular domain are $L_{\text{dom}} = 100 \ \mu m$ and $W_{\text{dom}} = 70 \ \mu m$.

The inclusion fraction for this geometry, $\text{Inclusion Fraction} = \frac{\text{Area of Ellipse}}{\text{Area of Rectangle}}$, is calculated to be 0.696 which is consistent with the maximum allowable inclusion fraction for two dimensional model with periodic domain given as 0.70.

The diffusion coefficients used for intracellular and extracellular domains of the muscle fiber are $D_{\text{in}} = 1.6 \ \mu m^2/ms$ and $D_{\text{ex}} = 2.0 \ \mu m^2/ms$ respectively based on values found in literature for mammals. Similarly, the local spin-spin relaxation times used are $T_{2,\text{in}} = 30 \ ms$ and $T_{2,\text{ex}} = 110 \ ms$ in the intracellular and extracellular regions of the myocyte. The myocyte membrane is assumed to be completely permeable. Figure 4.1 shows the signal ratio $ln(S/S_0)$ as a function of $b$.
value ranging from $0 – 1000 \text{ s/mm}^2$ for gradients applied along the $x$ and $y$ axes, and compares the results from simulations run using LBM and FEM.

From the above figure, it can be seen that the signal ratio drops as a function of $b$ value and exhibits a nearly biexponential behavior. There are two inflection points observed at around $b = 200 \text{ s/mm}^2$ and $b = 600 \text{ s/mm}^2$ when the gradient is applied along both the $x$ and $y$ axes. The apparent diffusion coefficient, $D_{\text{eff}}$ is theoretically extracted by fitting the following equation derived from Equation (2.9),

$$\ln \left( \frac{S(b, t_E)}{S_0} \right) = -D_{\text{eff}} b$$

(4.1)

where, $S(b, t_E)$ is the surface averaged signal acquired with different $b$ values at time, $t_E$, and, $S_0$ is the surface averaged signal acquired at $b_0$. 

Figure 4.1. $\ln (S/S_0)$ vs. $b$ value for Case 1 of the Elliptical Myocyte Model.
However, contrary to the monoexponential nature of the behavior predicted by theory, the results show that for diffusion within a myocyte assuming fully permeable membrane, the signal ratio obtained as a function of $b$ value deviates from this behavior. Consequently, the apparent diffusion coefficient, $D_{\text{eff}}$, cannot be determined from the monoexponential model in Equation (4.1). Moreover, it is observed that the signal behavior is not the same for the two directions along which the gradients are applied. This difference can be attributed to the asymmetry in the elliptical geometry of the myocyte which has a longer diffusion length along the $x$ axis in comparison to the $y$ direction.

The maximum relative error between the signal ratio results obtained using LBM and FEM is 0.0456 and 0.0269 for simulations run with gradients applied along the $x$ and $y$ axes respectively. The relative error between the signal ratios, $(S/S_0)_{\text{LBM}}$ and $(S/S_0)_{\text{FEM}}$ obtained using LBM and FEM respectively is calculated as follows,

$$\text{Relative Error} = \frac{\ln(S/S_0)_{\text{LBM}} - \ln(S/S_0)_{\text{FEM}}}{\ln(S/S_0)_{\text{FEM}}} \quad (4.2)$$

Moreover, the resultant signal which is the square root of the sum of the squares of the transverse magnetization, $M_x$ and $M_y$ at each point in the computation domain obtained using LBM and FEM can be compared. The relative error between them with respect to the FEM results can be calculated as given below,

$$\text{Relative Error} = \frac{S_{\text{LBM}} - S_{\text{FEM}}}{S_{\text{FEM}}} \quad (4.3)$$

The absolute error between the resultant signal obtained using LBM and FEM is given by,

$$\text{Absolute Error} = |S_{\text{LBM}} - S_{\text{FEM}}| \quad (4.4)$$

where, $S_{\text{LBM}}$ is the signal obtained from the LBM simulation, and, $S_{\text{FEM}}$ is the signal obtained from the FEM simulation in COMSOL.
The difference in results from the simulations run using the two numerical algorithms is compared based on the relative or absolute error discussed in Equations (4.3) and (4.4). Depending on the particular model under study and the simulation being analyzed, either the relative error or the absolute error is calculated.

![Signal Domain](a)
![Relative Error](b)

**Figure 4.2. Signal Domain for the Case of Ellipticity 0.70 at \( b = 200 \text{ s/mm}^2 \) with Gradient Applied along \( x \)-axis using (a) COMSOL and (b) LBM.**

The signal domain computed for the case of \( b = 200 \text{ s/mm}^2 \) when the gradient is applied along the \( x \) axis is shown in Figure 4.2. The relative error between the signals computed using the two different algorithms is shown in Figure 4.3. The maximum error and minimum error are calculated to be 0.0564 and \( 3.0244 \times 10^{-6} \) respectively. The maximum error is observed near the boundary of the ellipse, where there is a change in parameter value for diffusion coefficients and local spin-spin relaxation times. This error can be attributed to the difference in the type of mesh that is used in the two algorithms which is discussed in further detail below. The FEM algorithm in COMSOL uses a variable mesh with several elements close to the boundaries where there is

![Relative Error](c)

**Figure 4.3. Relative Error between COMSOL and LBM for the Case of Ellipticity 0.70 at \( b = 200 \text{ s/mm}^2 \) with Gradient Applied along \( x \)-axis.**
a change in properties while, the LBM algorithm uses a mesh with constant grid size resulting in less continuous changes in properties between the extracellular and intracellular regions of the myocyte.

An analysis of the grid size and its effect on the simulation was carried out for both LBM and FEM algorithms. This study was done only for the elliptical myocyte model with ellipticity 0.70, diffusion coefficients and local spin-spin relaxation parameters characteristic of the intracellular and extracellular domains, and infinite permeability membrane. Also, only the case with gradient applied along the x direction was studied. In LBM, the grid size and time step were chosen such that the LBM single relaxation factor, $\tau$ determined using Equation (2.17) satisfies the stability criterion $\tau \geq 0.5$. The results in Figure 4.1 were obtained using a grid size, $\delta x = 0.5 \mu m$ and time step, $\delta t = 0.01 \ ms$ in LBM. The relaxation factors in the intracellular and extracellular domains for these model parameters were $\tau_{in} = 0.692$ and $\tau_{ex} = 0.740$ respectively, both of which satisfy the stability criterion $\tau \geq 0.5$. The average computation time for the simulation using these model parameters was approximately 1.45 min. The change in the accuracy of the results with grid size and time step was studied by running the LBM simulation with grid size, $\delta x = 0.2 \mu m$ and time step, $\delta t = 0.0016 \ ms$ while maintaining the same relaxation factors in the two domains. With the finer grid size and time step, the maximum relative percentage error obtained for the signal ration when compared with FEM reduced to 3.655%. However, the average computation time for the simulation run using these parameters increased to 117 min. Therefore, $\delta x = 0.5 \mu m$ and $\delta t = 0.01 \ ms$ were used as the grid size and time step respectively for all other simulations that were performed in LBM based on the above analysis in which the accuracy of the results improved by only 0.909% while the average computational time increased dramatically by nearly 80%.

The mesh used for the FEM algorithm in COMSOL is an automatically generated free triangular mesh with variable grid size. The error due to mesh size was determined in order to use the ideal range of variable mesh size which provided minimum computational time without compromising on the numerical accuracy of the results. Simulations were carried out in COMSOL for different ranges of mesh size at $b = 254.1 \ s/mm^2$ and the signal, $S$ at $t_E = 56 \ ms$ is
determined at a point on the myocyte membrane. This location was chosen as large error is expected on the membrane boundary due to the nature of the permeability physics imposed in simulations, and consequently several elements are used near the membrane boundary by COMSOL to compute the numerical solution. Assuming that the mesh option with least maximum element size gives the most accurate result, the relative error due to the mesh was calculated as shown below for each mesh size.

\[ Mesh\ Relative\ Error = \frac{|S - S_{\delta x_{\text{max},0}}|}{S_{\delta x_{\text{max},0}}} \]  

(4.5)

where, \( S \) is the signal at different mesh sizes,
and, \( S_{\delta x_{\text{max},0}} \) is the signal obtained with least mesh size.

Table 4.2. Signal, \( S \) on the Membrane Boundary at \( b = 254.1 \text{ s/mm}^2 \) for Different Mesh Sizes

<table>
<thead>
<tr>
<th>Max. Element Size (( \mu m ))</th>
<th>Min. Element Size (( \mu m ))</th>
<th>( M_x )</th>
<th>( M_y )</th>
<th>Signal, ( S )</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>5</td>
<td>0.07071</td>
<td>-0.03164</td>
<td>0.07746</td>
</tr>
<tr>
<td>20</td>
<td>1.6</td>
<td>0.0679</td>
<td>-0.03378</td>
<td>0.07584</td>
</tr>
<tr>
<td>13</td>
<td>0.6</td>
<td>0.06826</td>
<td>-0.03313</td>
<td>0.07588</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>0.0711</td>
<td>-0.02789</td>
<td>0.07638</td>
</tr>
<tr>
<td>6.7</td>
<td>0.03</td>
<td>0.06723</td>
<td>-0.03102</td>
<td>0.07404</td>
</tr>
<tr>
<td>5.3</td>
<td>0.03</td>
<td>0.06712</td>
<td>-0.03156</td>
<td>0.07417</td>
</tr>
<tr>
<td>3.7</td>
<td>0.0125</td>
<td>0.06757</td>
<td>-0.03058</td>
<td>0.07417</td>
</tr>
<tr>
<td>2</td>
<td>0.0075</td>
<td>0.06777</td>
<td>-0.02887</td>
<td>0.07366</td>
</tr>
<tr>
<td>1</td>
<td>0.002</td>
<td>0.06642</td>
<td>-0.03126</td>
<td>0.07341</td>
</tr>
</tbody>
</table>

Table 4.2 provides the signal values on the membrane boundary obtained at \( b = 254.1 \text{ s/mm}^2 \) with decreasing mesh size, and Figure 4.4 illustrates the relative error described in Equation (4.5) as a function of the maximum element size in the mesh with variable element size. The plot indicates that the most feasible mesh used in COMSOL has \( \delta x_{\text{max}} = 3.7 \text{ \( \mu m \)} \) and \( \delta x_{\text{min}} = 0.0125 \text{ \( \mu m \)} \) as the error becomes stable and follows a linear trend below this grid size. The
physics based COMSOL variable mesh setting that corresponds to this mesh size is called “finer” and is used in all further simulations.

Since there is an overall agreement between the two different numerical methods used in solving the Bloch-Torrey equation within the myocyte, one or the other method can be used in further modeling of diffusion within the muscle fiber based on computational power and time. The LBM method is more computationally efficient and offers the advantage of future three dimensional parallelization of the model. Therefore, the goal and focus of this project is to develop a fully functional LBM model to simulate the different models and use the FEM based COMSOL software as a method of validation of the LBM model.

![Figure 4.4. Relative Error due to Mesh Size in COMSOL as a Function of Maximum Mesh Size.](image)
4.1.2 Case 2: Simulation of 2D Myocyte Model with Ellipticity 0.38, Diffusion and Relaxation Time Parameters Characteristic of Intracellular and Extracellular Domains, and Infinite Permeability

Just like the previous case, the dimensions of the elliptical myocyte model with ellipticity 0.38 are also defined based on the parameter definitions in Figure 3.1(b). The lengths of the major and minor axes of the elliptical cross section of the muscle fiber are $a_{\text{ellipse}} = 136 \, \mu m$ and $b_{\text{ellipse}} = 52 \, \mu m$ respectively. The dimensions of the extracellular rectangular domain are $L_{\text{dom}} = 142 \, \mu m$ and $W_{\text{dom}} = 56 \, \mu m$. The inclusion fraction for this domain is calculated to be 0.698 which is lower than the maximum allowable inclusion fraction for two dimensional model with periodic domain given as 0.70. The change in the signal obtained with change in geometry while maintaining the same inclusion fraction is studied in this case.

The diffusion coefficients and local spin-spin relaxation times used for intracellular and extracellular domains of the muscle fiber are the same as those used for the case of ellipticity $b_{\text{ellipse}} = 52 \, \mu m$ respectively. The dimensions of the extracellular rectangular domain are $L_{\text{dom}} = 142 \, \mu m$ and $W_{\text{dom}} = 56 \, \mu m$. The inclusion fraction for this domain is calculated to be 0.698 which is lower than the maximum allowable inclusion fraction for two dimensional model with periodic domain given as 0.70. The change in the signal obtained with change in geometry while maintaining the same inclusion fraction is studied in this case.

![Figure 4.5. ln (S/S₀) vs. b value for Case 2 of the Elliptical Myocyte Model.](image-url)
0.70 in Case 1. The myocyte membrane is assumed to be completely permeable. Figure 4.5 shows the signal ratio \( \ln(S/S_0) \) as a function of \( b \) value ranging from \( 0 - 1000 \text{ s/mm}^2 \) for gradients applied along the \( x \) and \( y \) axes, and compares the results from simulations run using LBM and FEM. It is observed that the signal ratio drops as a function of \( b \) value just like the previous case with ellipticity 0.70, and exhibits a nearly biexponential behavior. However, inflection points are observed at around \( b = 100 \text{ s/mm}^2, \ b = 400 \text{ s/mm}^2 \) and \( b = 600 \text{ s/mm}^2 \) when the gradient is applied along the \( x \) axis. There are no inflection points observed when the gradient is applied along the \( y \) axis. Again, the results do not fit the monoexponential nature of the model predicted by theory which means that the apparent diffusion coefficient, \( D_{\text{eff}} \) cannot be determined by fitting Equation (2.9). The dissimilar signal behavior for the two directions along which the gradients are applied can again be attributed to the asymmetry in the elliptical geometry of the myocyte which has a longer diffusion length along the \( x \) axis in comparison to the \( y \) direction. Furthermore, the minor axis of the elliptical cross-section with ellipticity 0.38 is shorter than the cross-section with ellipticity 0.70 by 14 \( \mu m \). This could have resulted in the lack of inflection points in the signal ratio curve for the gradient applied along the \( y \) axis. The maximum relative error between the signal ratio results obtained using LBM and FEM is 0.0410 and 0.0842 for simulations run with gradients applied along the \( x \) and \( y \) axes respectively.

The signal obtained across the entire computation domain by simulating the Bloch-Torrey equation at \( b = 200 \text{ s/mm}^2 \) applied along the \( x \) axis is plotted above in Figure 4.6. The
relative error between the signals computed using the two algorithms over the entire domain is shown in Figure 4.7. The maximum and minimum relative errors are 0.0778 and $3.0556 \times 10^{-7}$ respectively. The maximum error is observed near the north and south boundaries of the ellipse. Unlike the previous case with ellipticity 0.7, the errors are minimal at the east and west ellipse boundaries. This difference in error distribution shows that the geometry of the muscle fiber plays an important role in the diffusion process and the consequent Bloch-Torrey model. The ellipse with ellipticity 0.38 is more elongated and narrow along one axis than the other which results in more diffusion length along major axis. Further, from both ellipticity simulations, it can be seen that diffusion within the neighboring myocytes also affect the signal obtained in the myocyte of interest. This is evident from the high errors closer to the periodic boundaries which represent the presence of the neighboring myocytes. Therefore, the proximity of the neighboring myocytes plays an important role in the model. Changing the dimensions of the external rectangular domain can show how the diffusion process in the myocyte changes if the myocyte is assumed to be isolated from the neighboring myocytes.

### 4.1.3 Case 3: Simulation of 2D Myocyte Model with Ellipticity 0.70 and Inclusion Fraction 0.174

The effect of the change in inclusion fraction on the signal obtained from the Bloch-Torrey is studied in order to understand the effect of the diffusion process in the neighboring myocytes on the myocyte of interest. The inclusion fraction of the ellipse in the rectangular computation domain is reduced from 0.70 in the previous cases to 0.174 by increasing the area of the extracellular domain. This change in area simulates a two dimensional periodic array of myocytes that are placed at a larger distance from each other than the previous two cases. The
ellipticity chosen for the elliptical cross-section of the muscle fiber is 0.70 with the lengths of the major and minor axes as \( a_{\text{ellipse}} = 94 \, \mu m \) and \( b_{\text{ellipse}} = 66 \, \mu m \) respectively. The dimensions of the extracellular rectangular domain are increased to \( L_{\text{dom}} = 200 \, \mu m \) and \( W_{\text{dom}} = 140 \, \mu m \).

Since the purpose of this simulation is to study the inclusion fraction effects, the simulation was performed only using FEM in COMSOL due to the faster computation time and user friendly nature of the software for comparing the different inclusion fraction geometries. The same diffusion coefficients and local spin-spin relaxation times were used in both intracellular and extracellular domains so that the apparent diffusion coefficient remains constant throughout the domain, and only the effect of the change in geometry is observed in the signal. The membrane between the interior and exterior regions of the myocyte is assumed to be completely permeable. The diffusion coefficient used for the simulation is \( D_{\text{in}} = D_{\text{ex}} = 2.0 \, \mu m^2/\text{ms} \) and the local spin-spin relaxation time used is \( T_{2,\text{in}} = T_{2,\text{ex}} = 110 \, \text{ms} \). The signal ratio is

![Figure 4.8](image)

**Figure 4.8.** \( \ln (S/S_0) \) vs. \( b \) value for Case 3 of the Elliptical Myocyte Model: Comparison between COMSOL simulations with ellipse inclusion fractions of 0.174 and 0.70 for gradients applied along \( x \) and \( y \) axes.
plotted as a function of $b$ value and compared with the case of inclusion fraction 0.70 for the same ellipticity and input parameters, as shown in Figure 4.8.

Unlike the biexponential behavior shown by the signal for the case of the geometry with inclusion fraction 0.70, the geometry with inclusion fraction 0.174 illustrates a monoexponential behavior. A linear fit can be obtained from the above plot for the low inclusion fraction geometry, from which an apparent diffusion coefficient can be determined based on the theoretical model in Equation (4.1). The apparent diffusion coefficient, $D_{\text{eff}}$ that is determined from the plot is approximately $2.049 \, \mu m^2/\text{ms}$ when the gradient is applied along the $x$ axis and $1.945 \, \mu m^2/\text{ms}$ when the gradient is applied along the $y$ axis. The values of the apparent diffusion coefficient when the gradients are applied along the $x$ and $y$ axes, vary relatively from the actual diffusion coefficient by 0.0245 and 0.0274 respectively. This analysis shows that if the myocyte is modeled such that it is located far from other neighboring muscle fibers, then the signal obtained from the myocyte and the corresponding apparent diffusion coefficient are independent of the diffusion processes in the neighboring muscle fibers. On the other hand, if the inclusion fraction of the myocyte is high, that is 0.70, then the diffusion process in neighboring muscle fibers play an important role in the signal behavior of the myocyte under study. The apparent diffusion coefficient deviates from the monoexponential nature of the theoretical model in Equation (4.1). Furthermore, for simplicity, the muscle fibers are assumed to be periodic and identical in geometry which is not the case in reality. In the future, a two dimensional array of randomized muscle fiber ellipse geometry can be modeled to more closely simulate the diffusion process within the muscle.

4.1.4 Case 4: Validation of $T_2$ Relaxation Effects on Model with Ellipticity 0.70, Inclusion Fraction 0.70, Same Diffusion Coefficient and Local Spin-Spin Relaxation Times (a) 30 ms and (b) 110 ms in Intracellular and Extracellular Domains

In order to verify that the effect of the local spin-spin relaxation time, $T_2$ on the signal obtained is modeled correctly in the LBM and FEM algorithms, the ellipse model with ellipticity 0.70 was simulated with a constant apparent diffusion coefficient in the whole computation domain. Therefore, the same diffusion coefficients, $D_{\text{in}} = D_{\text{ex}} = 2.0 \, \mu m^2/\text{ms}$ and local spin-spin
relaxation times are used in both the intracellular and extracellular domains with a fully permeable membrane. The simulations were carried out for two different values of $T_2$: (a) $T_{2,in} = T_{2,ex} = 30 \text{ ms}$ and (b) $T_{2,in} = T_{2,ex} = 110 \text{ ms}$. A plot of signal as a function of time was obtained using the two algorithms at $b = 0 \text{ s/mm}^2$ as only the relaxation time effect is seen in the signal at this $b$ value. Finally, an exponential fit of the simulation data was performed and compared to the theoretical equation given in Equation (4.6) to validate the $T_2$ effect.

$$S(t)_{b=0} = S(0)_{b=0} e^{-\frac{t}{T^2}}$$

(4.6)

where, $S(t)_{b=0}$ is the signal at time, $t$ with $b = 0 \text{ s/mm}^2$

and, $S(0)_{b=0}$ is the signal at time, $t = 0$ with $b = 0 \text{ s/mm}^2$.

Figure 4.9 and Figure 4.10 show the plots of signal obtained using COMSOL and LBM as functions of time. The simulation data is fit with an exponential curve and the equations are given in the figures. For the case of $T_2 = 30 \text{ ms}$, the coefficients obtained from the exponential fit

![Graph showing signal vs. time for Case 4(a) of the Elliptical Myocyte Model.](image)

Figure 4.9. Signal, $S$ vs. Time, $t$ for Case 4(a) of the Elliptical Myocyte Model.
are \( S_{0,FEM} = 0.9977 \) and \( \left( \frac{1}{T_2\rangle_{FEM} \right) = 0.03313 \) for the COMSOL solution, and \( S_{0,LBM} = 1.012 \) and \( \left( \frac{1}{T_2\rangle_{LBM} \right) = 0.03333 \) for the LBM solution. The \( T_2 \) values obtained from the data for the COMSOL and LBM solutions are therefore, \( T_{2,FEM} = 30.184 \text{ ms} \) and \( T_{2,LBM} = 30.003 \text{ ms} \) respectively. These vary from the theoretical \( T_2 \) value used in the model by \( 6.14 \times 10^{-3} \) and \( 1 \times 10^{-4} \) respectively. Also, \( S_0 \) varies from the theoretical initial signal value, \( S_0 = 1.0 \) that are used in the simulations by 0.0023 and 0.012 for the COMSOL and LBM solutions respectively.

Similarly, for the case of \( T_2 = 110 \text{ ms} \), the coefficients obtained from the exponential fit are \( S_{0,FEM} = 0.9999 \) and \( \left( \frac{1}{T_2\rangle_{FEM} \right) = 0.009088 \) for the COMSOL solution, and \( S_{0,LBM} = 1.012 \) and \( \left( \frac{1}{T_2\rangle_{LBM} \right) = 0.009091 \) for the LBM solution. The \( T_2 \) values obtained from the data for the COMSOL and LBM solutions are therefore, \( T_{2,FEM} = 110.035 \text{ ms} \) and \( T_{2,LBM} = 109.9989 \text{ ms} \) respectively. These vary from the theoretical \( T_2 \) value used in the model by \( 3.201 \times 10^{-3} \) and

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**Figure 4.10. Signal, \( S \) vs. Time, \( t \) for Case 4(b) of the Elliptical Myocyte Model.**
respectively. Also, $S_0$ varies from the theoretical initial signal value, $S_0 = 1.0$ that are used in the simulations by 0.0001 and 0.012 for the COMSOL and LBM solutions respectively. Since the maximum difference between the simulation exponential fit and theoretical $T_2$ values is of the order of magnitude of $10^{-3}$, this test has validated that the $T_2$ relaxation effect is indeed implemented in both the LBM and FEM models correctly.

4.1.5 Case 5: Simulation of 2D Myocyte Model with (a) Ellipticity 0.70 and (b) Ellipticity 0.38, Diffusion and Relaxation Time Parameters Characteristic of Intracellular and Extracellular Domains, and Finite Permeability, $K = 13 \, \mu m/s$

In all the simulations discussed previously, the membrane between the intracellular and extracellular regions of the myocyte was assumed to be completely permeable, and therefore no membrane boundary conditions were imposed. The effects of introducing a membrane boundary based on the theory explained in Chapter 2 is examined for the elliptical myocyte model with ellipticities 0.70 and 0.38. The geometric dimensions used for both ellipticity models is the same as those in Cases 1 and 2. The diffusion coefficients and local spin-spin relaxation times used for intracellular and extracellular domains of the muscle fiber are also the same as those used in Cases 1 and 2, that is, $D_{in} = 1.6 \, \mu m^2/ms$, $D_{ex} = 2.0 \, \mu m^2/ms$, $T_{2,in} = 30 \, ms$ and $T_{2,ex} = 110 \, ms$. The permeability value used for the modeling of the myocyte membrane is $K = 13 \, \mu m/s$ based on research conducted by Landis et al. in 1999 to determine the permeability of water in the thigh muscle sarcolemma [32].

Figure 4.11 illustrates the drop in the signal ratio as a function of $b$ value ranging from 0 – 1000 $s/mm^2$ for gradients applied along the $x$ and $y$ axes. The plot compares the results obtained using LBM and FEM. Just like the cases of diffusion with infinite sarcolemma permeability, the signal ratio exhibits a biexponential behavior with inflection points observed at around $b = 200 \, s/mm^2$ and $b = 600 \, s/mm^2$ when the gradient is applied along both the $x$ and $y$ axes. Also, there are differences in the behavior observed when the gradient is applied along $x$ and $y$ axes, which is again justified as the result of asymmetry in the elliptical model. The maximum relative error between the signal ratio results obtained using LBM and FEM is 0.0466 and 0.0284 when the gradient is applied along the $x$ and $y$ axes respectively.
Figure 4.11. $\ln (S/S_0)$ vs. $b$ value for Case 5(a) of the Elliptical Myocyte Model: Comparison between LBM & COMSOL simulations for ellipticity 0.70 for gradients applied along $x$ and $y$ axes.

Figure 4.12. $\ln (S/S_0)$ vs. $b$ value for Case 5(a) of the Elliptical Myocyte Model: Comparison between LBM simulations for ellipticity 0.70 with $K = \infty$ and $K = 13 \ \mu m/s$ sarcolemma permeability for gradients applied along $x$ and $y$ axes.
A comparison between the signal ratio results with the sarcolemma membrane having infinite permeability and finite permeability value of \( K = 13 \, \mu m/s \) is shown in Figure 4.12. The natural logarithm of the signal ratio becomes less negative as the permeability of the sarcolemma membrane decreases. This shows that a stronger signal with a higher value is obtained in the intracellular and extracellular regions when the sarcolemma membrane has finite permeability. The signal values are close to two distinct values in the two domains of the myocyte. This is because the diffusion across the membrane is now restricted by the permeability of the membrane while in the case with infinite membrane permeability, the diffusion across the two domains of the myocyte is unrestricted and free.

![Figure 4.13. Signal Domain for the Case of Ellipticity 0.70 at \( b = 63.5 \, s/mm^2 \) with Gradient Applied along x-axis using (a) COMSOL and (b) LBM.](image)

The more well defined signal values in the intracellular and extracellular regions than in the case of infinitely permeable membrane is illustrated in the signal domain maps of the elliptical myocyte obtained using COMSOL and LBM at \( b = 63.5 \, s/mm^2 \) in Figure 4.13. The signal value is closer to 0.50 in the extracellular domain while, while the signal in the intracellular domain is about 0.11. In the extracellular region, it is observed that the signal towards the east and west boundaries is on the lower end of the signal range. This discrepancy in the signal in the extracellular domain is probably caused due to the effect of the neighboring myocytes and the periodic boundary conditions that are imposed. The absolute error between the two signal domains is shown in Figure 4.14. The maximum and minimum absolute errors
between the signal results obtained using the two algorithms are 0.3228 and $5.4759 \times 10^{-8}$ respectively. From the error domain map it can be seen that the maximum error is observed at the membrane boundary. The large absolute error at the membrane is because of the different methods of imposing the membrane boundary condition in LBM and FEM which is discussed in detail in Chapter 2. The LBM membrane boundary condition is a combination of Dirichlet and Neumann boundary conditions while the FEM membrane boundary condition is imposed by creating a third membrane domain with a diffusion coefficient that corresponds to the membrane permeability.

![Error Domain Map](image)

**Figure 4.14.** Absolute Error between COMSOL and LBM for the Case of Ellipticity 0.70 at $b = 63.5 \text{ s/mm}^2$ with Gradient Applied along $x$-axis.

![Graph](image)

**Figure 4.15.** $\ln \left( \frac{S}{S_0} \right)$ vs. $b$ value for Case 5(b) of the Elliptical Myocyte Model: Comparison between LBM & COMSOL simulations for ellipticity 0.38 for gradients applied along $x$ and $y$ axes.
The same set of results is obtained for the elliptical myocyte geometry with ellipticity 0.38 with the same input parameters that were used for the ellipticity 0.70 case. The comparisons of the signal ratio as a function of $b$ value between the LBM and FEM algorithms and the infinite and finite permeability models simulated using the LBM algorithm are plotted in Figure 4.15 and Figure 4.16 respectively. The comparison between the signal ratios obtained using the two algorithms shows that the relative error increases with higher $b$ values. The maximum relative error between signal ratio results obtained using LBM and FEM are 0.0847 and 0.0509 for simulations run with gradients along the $x$ and $y$ axes respectively. The narrow elliptical geometry of the myocyte with ellipticity 0.38 that results in a longer diffusion length along the major axis combined with the difference in the methods of imposing membrane boundary conditions in the LBM and FEM models are potential causes for the larger discrepancy in the LBM and COMSOL results in comparison to the other cases.

![Figure 4.16. In (S/S0) vs. b value for Case 5(b) of the Elliptical Myocyte Model: Comparison between LBM simulations for ellipticity 0.38 with $K = \infty$ and $K = 13 \, \mu m/s$ sarcolemma permeability for gradients applied along $x$ and $y$ axes.](image)
The behavior of the signal ratio with finite membrane permeability follows a similar trend as that of the infinite permeability case for ellipticity 0.38. The drop in the natural logarithm of the signal ratio is less negative for the simulation run with membrane permeability, $K = 13 \ \mu m/s$ than the simulation with infinite membrane permeability. This result follows the same behavior as Case 5(a) with ellipticity 0.70. However, there is a more significant difference in the signal ratio drop when the gradient is applied along the $y$ axis in comparison to when the gradient is applied along the $x$ axis. The longer diffusion length along the $x$ axis, and periodic boundary conditions that simulate the effect of the neighboring myocytes is the most probable cause for this dissimilarity in the signal behavior between the two directions along which the gradient is applied.

![Figure 4.17. Signal Domain for the Case of Ellipticity 0.38 at $b = 63.5 \ s/mm^2$ with Gradient Applied along x-axis using (a) COMSOL and (b) LBM.](image)

The signal domain maps for the elliptical myocyte with ellipticity 0.38 and sarcolemma permeability of $K = 13 \ \mu m/s$ obtained using COMSOL and LBM at $b = 63.5 \ s/mm^2$ are shown in Figure 4.17. The maximum signal value in the extracellular domain obtained using COMSOL and LBM is 0.489 and 0.525 respectively. The signal value in the intracellular domain is approximately 0.140 using both numerical algorithms. The signal in the extracellular domain drops to the lower end of the signal range towards the east and west boundaries due to the diffusion effect of the periodic boundary conditions imposed on the model that simulate the behavior of neighboring myocytes. However, the signal is observed to be more uniform than the previous case with ellipticity 0.70. Figure 4.18 shows the domain map of the absolute error...
between the two signal domains in Figure 4.17. The maximum and minimum absolute errors between the signal results obtained using LBM and FEM are 0.3691 and $3.0832 \times 10^{-8}$ respectively. The errors are of the same order of magnitude as that of the previous permeable elliptical myocyte model with ellipticity 0.70. The error distribution shows that the maximum error is observed at the membrane boundary which is also similar to the case with ellipticity 0.70. The difference at the boundary arises due to the different methods used in imposing membrane boundary conditions in LBM and FEM.

### 4.2 Disc Myocyte Model

In order to study the behavior of the diffusion weighted signal in a symmetric domain, the muscle fibers were modeled two dimensionally with a circular transverse cross-section and a square shaped extracellular domain. The inclusion fraction of the disc shaped myocyte is chosen as 0.70, same as the inclusion fraction of the elliptical myocyte model. The dimensions of the disc myocyte model are defined based on the parameter definitions in Figure 3.2. These dimensions are determined based on the theory described in Chapter 3 and the surface area and volume of the myocyte model with ellipticity 0.70. Using Equations (3.3) and (3.4), the radius, $r$ of the disc and the side length, $S_{dom}$ of the extracellular domain are calculated to be 38.195 μm and 81.142 μm respectively. For the purpose of simplicity in computation, the dimensions of the disc myocyte geometry were chosen as $r = 38 \mu m$ and $S_{dom} = 80 \mu m$ respectively. The computed inclusion fraction for these dimensions is 0.71.

The simulation parameters including the diffusion coefficients and local spin-spin relaxation times used for the disc myocyte model are the same as those used in Cases 1 and 2 of the elliptical myocyte model. The diffusion coefficients used for intracellular and extracellular...
domains of the muscle fiber are \( D_{in} = 1.6 \mu m^2/ms \) and \( D_{ex} = 2.0 \mu m^2/ms \) respectively and, the local spin-spin relaxation times used are \( T_{2,in} = 30 ms \) and \( T_{2,ex} = 110 ms \) in the intracellular and extracellular regions respectively. The gradient duration in the pulse sequence is \( \delta = 16 ms \) and the start of the negative gradient pulse occurs at \( \Delta = 40 ms \) resulting in a total echo time of \( t_E = 56 ms \). Two sets of simulations were run for finite sarcolemma membrane permeability, \( K = 13 \mu m/s \) and infinite sarcolemma membrane permeability using both the LBM and FEM algorithms. A comparison between the LBM and FEM results for the finite membrane permeability is shown in Figure 4.19, while Figure 4.20 shows the comparison between the results obtained using LBM for finite and infinite sarcolemma membrane permeability.

The behavior of the signal ratio as a function of \( b \) value for the LBM and FEM simulations with finite membrane permeability as shown in Figure 4.19 is biexponential with inflection points observed at \( b = 200 s/mm^2 \) and \( b = 600 s/mm^2 \) for gradients applied along both the \( x \) and \( y \) axes. This behavior is similar to that which is observed in the elliptical myocyte
models with finite membrane permeability. However, unlike the elliptical myocyte model, it can be seen that the signal ratio plot for gradients applied along the $x$ and $y$ axes coincide with a maximum absolute difference of $3.5427 \times 10^{-7}$ for the LBM model and 0.0184 for the COMSOL model. This result is as expected due to the symmetric nature of the disc myocyte model. Moreover, this result confirms that the asymmetric nature of the ellipse cross-section is the reason for the differences in signal ratio trends between the results for gradients applied along $x$ and $y$ axes in the elliptical myocyte model. The maximum relative error between the signal ratio results obtained using LBM and FEM is 0.0337 and 0.0358 when the gradient is applied along the $x$ and $y$ axes respectively.

Just like the elliptical myocyte model, the natural logarithm of the signal ratio becomes less negative as the permeability of the sarcolemma membrane decreases which is illustrated in Figure 4.20. The signal drop is significantly less at higher $b$ values above $b = 600$ s/mm$^2$ approximately. The signal drop is also lesser at $b$ values ranging between $b = 90$ s/mm$^2$ and $b =$
240 s/mm$^2$. However, this difference is of the order of magnitude $10^{-2}$ while, at higher $b$ values, the difference is of the order of magnitude of $10^{-1}$. The less negative signal ratio drop further signifies that the diffusion is less for the simulation with finite membrane permeability. The diffusion process is restricted within the intracellular and extracellular regions of the domain due to the finite membrane permeability which limits the diffusive process across the membrane.

Figure 4.21 illustrates the two dimensional domain map of the signal obtained for simulations run using COMSOL and LBM at $b = 63.5$ s/mm$^2$ for the disc myocyte model. From the domain maps, it can be seen that the behavior of the signal in the disc myocyte model is very similar to the elliptical myocyte models. The signal obtained in the intracellular domain is mostly uniform across the interior of the myocyte and increases in value towards the membrane. The signal value in the intracellular part of the cell is approximately 0.140 using both algorithms while in the extracellular region, the maximum signal value obtained using COMSOL and LBM is 0.47 and 0.484 respectively. Similar to the cases studied for the elliptical myocyte model, it is observed that the signal is not uniform in the extracellular domain. Rather, the signal drops to a much lower value towards the east and west periodic boundaries and the north and south boundaries have a high signal value. The symmetric nature of the signal value at the boundaries combined with the drop in signal value towards one set of opposite boundaries indicates yet again that this is the consequence of the diffusion effect caused by the periodic boundary conditions.
conditions that simulate the behavior of neighboring myocytes. The absolute error between the FEM and LBM signal domain maps is illustrated in Figure 4.22. The maximum and minimum absolute error between the signal obtained using the two numerical algorithms is 0.316 and $8.414 \times 10^{-8}$ respectively. It is observed that the maximum error occurs only at the membrane. The large difference in signal at the membrane is due to the different methods used to apply the membrane boundary conditions in the two algorithms. The membrane boundary condition is imposed between two points that form a lattice link across which the membrane is assumed to pass in LBM while, a separate membrane domain is created in COMSOL over which the Bloch-Torrey equation is applied. These methods are described in detail in Chapter 2 and give rise to a large error of the order of $10^{-1}$.

4.3 Simple Vertical Membrane Model

The numerical stability of the two algorithms, and their effectiveness in simulating the diffusion process were analyzed by testing a model with simple geometry consisting of extracellular and intracellular domains separated by a permeable membrane. In this numerical model, only the diffusion process out of the three steps of diffusion, free precession and relaxation was simulated. The parameters used to describe the geometry are defined in Chapter 3. The dimensions of the geometry are chosen on the same scale of the dimensions of the myocyte with length, $L = 160 \, \mu m$ and width, $W = 80 \, \mu m$. The length of each domain – extracellular and intracellular is $80 \, \mu m$. The Dirichlet boundary conditions for the concentration, $\phi$ on the wall boundaries at $x = 0 \, \mu m$ and $x = L = 160 \, \mu m$ are $\phi(0,y) = 1.0$ and $\phi(L,y) = 0.5$. 

![Figure 4.22. Absolute Error between COMSOL and LBM for the Disc Myocyte Model at $b = 63.5 \, s/mm^2$ with Gradient Applied along x-axis.](image)
The diffusion coefficients used for intracellular and extracellular domains of the muscle fiber are $D_{in} = 1.6 \ \mu m^2/ms$ and $D_{ex} = 2.0 \ \mu m^2/ms$ respectively and the permeability of the membrane between the two domains was set to $K = 13 \ \mu m/s$. A steady state analytical solution was determined for this model based on Fick’s first law of diffusion and is given by Equation (4.7). The variables in the equation are illustrated below in Figure 4.23.

$$K(\phi_{mem,ex} - \phi_{mem,in}) = D_{ex}\left(\frac{\phi_{ex} - \phi_{mem,ex}}{L/2}\right) = -D_{in}\left(\frac{\phi_{in} - \phi_{mem,in}}{L/2}\right)$$  \hspace{1cm} (4.7)

where, $K$ is the membrane permeability,

$\phi_{mem,ex}$ and $\phi_{mem,in}$ are the concentrations at the membrane on the extracellular and intracellular domain sides respectively,

$\phi_{ex} = 1.0$ is the concentration on the boundary wall at $x = 0 \ \mu m$,

$\phi_{in} = 0.5$ is the concentration on the boundary wall at $x = 160 \ \mu m$,

$D_{ex} = 2.0 \ \mu m^2/ms$ is the extracellular diffusion coefficient,
\[ D_{in} = 1.6 \, \mu m^2/ms \] is the intracellular diffusion coefficient,
and, \( L \) is the overall diffusion length of the domain.

Solving the above equation using the diffusion and concentration parameters defined in the two domains, the analytical solution for the concentration \( \phi \) for the particular case of this simulation with the given diffusion parameters is given in Equation (4.8) and the domain map of the analytical solution is shown in Figure 4.24.

\[
\phi(x) = \begin{cases} 
-0.00149770x + 1.000000, & 0 < x \leq 80 \\
-0.00187212x + 0.799539, & 80 \leq x < 160 
\end{cases}
\]  

(4.8)

Figure 4.24. Domain Map of the Analytical Solution for the Vertical Membrane Model.

The solutions obtained using COMSOL and LBM at steady state are plotted in Figure 4.25(a) and (b) respectively. Steady state was achieved at \( t = 2 \, s \) beyond which the change in solution was of the order of magnitude \( 10^{-7} \). On comparing these domains with the analytical solution, the absolute error domain maps shown in Figure 4.26(a) and (b) are obtained for COMSOL and LBM respectively. Also, a line plot along the \( x \) direction comparing the concentration in the COMSOL, LBM and exact solution domains at \( y = 40 \, \mu m \) is illustrated in Figure 4.27. Just like the analytical solution, the results from both COMSOL and LBM indicate a
decrease in the concentration from the boundary at $x = 0 \mu m$ to the membrane boundary at $x = 80 \mu m$, a jump in the concentration at the boundary due to the presence of the membrane and a further decrease from the concentration at the membrane boundary to the boundary at $x = 160 \mu m$. The absolute error between the COMSOL solution and the analytical solution in Figure 4.26(a) shows a symmetrical behavior of the error about the membrane boundary. The absolute error is maximum at the membrane boundary and gradually decreases towards the east and west boundaries. The maximum error for the COMSOL solution is $2.793 \times 10^{-3}$ which is consistent with the second order error expected for the advection diffusion equation.

The absolute error between the LBM solution and the analytical solution, on the other hand, is asymmetrical in behavior across the domain as shown in Figure 4.26(b). The error exhibits a gradual increase in magnitude from the membrane at $x = 0 \mu m$ to a maximum absolute error of $9.3 \times 10^{-3}$ at the
membrane boundary at $x = 80 \mu m$. The error between the membrane boundary and the domain boundary at $x = 160 \mu m$ is nearly constant and remains at the lower end of the absolute error range for the LBM solution. The line plots in Figure 4.27 also illustrate this difference in the behavior of the error between the COMSOL and LBM solutions. While the COMSOL solution remains consistent with the analytical solution with a second order difference, the LBM solution shows a greater difference with the analytical solution between $x = 0 \mu m$ and $x = 80 \mu m$ than in the interval between $x = 80 \mu m$ and $x = 160 \mu m$. This study indicates that COMSOL is an effective and stable method to validate the LBM algorithm in the absence of an analytical solution. Further, the LBM algorithm shows asymmetric differences with the analytical solution indicating that the LBM program requires more development and validation before it can be expanded for more complicated modeling of the muscle and microvasculature.

Figure 4.27. Line Plots Comparing the COMSOL and LBM Solutions with the Analytical Solution along the x-axis at $y = 40 \mu m$. 
4.4 Wedged Membrane Model

The membrane between the extracellular and intracellular domains is modeled as a wedge with a sharp corner at different angles in order to analyze the numerical stability of the Lattice Boltzmann and Finite Element methods in modeling the diffusion process at parts of the domain where there are sharp gradient differences or more than one boundary condition that needs to be satisfied. Since there is no analytical solution for this case, the results of LBM and FEM at time, \( t = 2 \) s are compared with each other in order to validate the Lattice Boltzmann algorithm. The dimensions of the geometry are defined based on the parameters described in Section 3.4 of Chapter 3. The dimensions of the domain are the same as that of the simple vertical membrane model with length, \( L = 160 \, \mu m \) and width, \( W = 80 \, \mu m \). Simulations were run for three cases of membrane wedge angles, \( \theta = 30^\circ, 45^\circ, 60^\circ \). The Dirichlet boundary conditions for the concentration, \( \phi \) on the wall boundaries at \( x = 0 \, \mu m \) and \( x = L = 160 \, \mu m \) are \( \phi(0,y) = 1.0 \) and \( \phi(L,y) = 0.5 \). Similar to the simple membrane model, the diffusion coefficients used in the intracellular and extracellular domains are \( D_{in} = 1.6 \, \mu m^2/ms \) and \( D_{ex} = 2.0 \, \mu m^2/ms \) respectively, and the permeability of the membrane between the two domains \( K = 13 \, \mu m/s \).

The COMSOL and LBM domain maps of the concentration solution at \( t = 2 \) s when the membrane wedge angle is \( \theta = 30^\circ \) is given in Figure 4.28(a) and (b) respectively. The domain maps indicate that the COMSOL solution shows a gradual variation in concentration, \( \phi \) from the

(a)  
(b)

Figure 4.28. Signal Domain for the Wedged Membrane Model with Wedge Angle, \( \theta = 30^\circ \) and Membrane Permeability, \( K = 13 \, \mu m/s \) using (a) COMSOL and (b) LBM.
wall boundaries to the membrane boundary in the intracellular and extracellular domains. The concentration is also uniform across the vertical $y$ direction in each of the individual domains. The LBM solution shows the same gradual change in concentration from the wall boundaries to the membrane boundary. However, at the sharp membrane wedge and the corners that the membrane forms with the north and south boundaries, the LBM solution illustrates non-uniformity.

Therefore, on comparison with the COMSOL solution as shown in Figure 4.29, it is observed that the maximum absolute error of 0.173 occurs at the membrane boundary, especially at the sharp corners formed by the wedge in the membrane as well as the membrane and the north and south wall boundaries. The absolute error between COMSOL and LBM is nearly $10^3$ times higher than the simple vertical membrane model. This shows that the complicated nature of the geometry comprising of sharp boundaries introduces difficulties in both numerical methods. In COMSOL, a finer mesh has to be obtained at the membrane corners while in LBM, the solution at the membrane is not smooth owing to the uniform grid size.

The same simulation was carried out using both methods for larger angles between the membrane and the vertical membrane. The COMSOL and LBM solutions when the membrane wedge angle, $\theta = 45^\circ$ is provided in Figure 4.30(a) and (b) respectively. Similarly, the COMSOL and LBM solutions for the membrane wedge angle, $\theta = 60^\circ$ is given in Figure 4.31(a) and (b) respectively. Just like the previous case with $\theta = 30^\circ$, the COMSOL solution is more uniform at the corners and edges with the concentration, $\phi$ in comparison to the LBM solution for both simulation cases with $\theta = 45^\circ$ and $\theta = 60^\circ$. The domain map of the absolute error between the

![Figure 4.29. Absolute Error between the COMSOL and LBM Solutions for the Wedged Membrane Model at $\theta = 30^\circ$.](image)
COMSOL and LBM solution for the membrane wedge angles $\theta = 45^\circ$ and $\theta = 60^\circ$ are displayed in Figure 4.32(a) and (b) respectively. As the membrane wedge angle increases from $\theta = 30^\circ$ to $\theta = 45^\circ$ and $\theta = 60^\circ$, the maximum absolute error between the COMSOL and LBM solution decreases from 0.173 to 0.140 and 0.0896 respectively. The maximum absolute error is still observed at the membrane wedge and the sharp corners that the membrane forms with the wall boundaries. This is because of the different boundary conditions (periodic boundary condition and membrane boundary condition) that are imposed together at a single point. Furthermore, as discussed for the case of $\theta = 30^\circ$, the LBM grid size is uniform. This implies that the solution at

Figure 4.30. Signal Domain for the Wedged Membrane Model with Wedge Angle, $\theta = 45^\circ$ and Membrane Permeability, $K = 13 \, \mu m/s$ using (a) COMSOL and (b) LBM.

Figure 4.31. Signal Domain for the Wedged Membrane Model with Wedge Angle, $\theta = 60^\circ$ and Membrane Permeability, $K = 13 \, \mu m/s$ using (a) COMSOL and (b) LBM.
the boundaries where several conditions are imposed together is not as smooth as COMSOL where a mesh conforming to the geometry is created. The error domain maps in Figure 4.32 demonstrate that the behavior of the error is asymmetric just like the simple vertical membrane model and the asymmetry in the error increases with wedge angle. The most important point to note from this study is that the error in the LBM model depends on the extent of complexity in the geometry. Sharp corners and wedges in the geometry create large gradients in the solution which introduces greater errors. A detailed numerical study of the geometric effects on the stability of the LBM model solution will facilitate future computational work in modeling the diffusion process within the myocyte and microvasculature.

4.5 Vessel Flow Model

The goal of this model is to simulate the advection and diffusion processes in microvessels in the brain by modeling the Bloch-Torrey equation using LBM and FEM. The dimensions of the model are defined in Figure 3.6 in Chapter 3. The extravascular domain is initially modeled as a square with \( L = W = 100 \, \mu m \). The width of the vessel passing horizontally through the domain is \( W_{\text{vessel}} = 5 \, \mu m \) such that the vessel occupies 5% of the total area of the domain initially for the given characteristic length, \( L \).
The diffusion coefficients used for intravascular and extravascular domains of the microvessel are $D_{in} = 1.12 \ \mu m^2/ms$ and $D_{ex} = 2.0 \ \mu m^2/ms$ respectively. The intravascular diffusion coefficient is chosen based on the results of an experiment performed using IVIM EPI on a 70 year old man at 1.5 T [33], and the average value of a fitted diffusion parameter from analytical modeling of restricted diffusion in a bovine optic nerve [34]. The diffusion coefficient of water is used in the extravascular domain as the extravascular space is predominantly made of water. Similarly, the local spin-spin relaxation times used are $T_{2,in} = 150 \ ms$ and $T_{2,ex} = 80 \ ms$ in the intravascular and extravascular regions of the microvessel. Diffusion is the only process that occurs in the extravascular space, and there is no flow. The velocity in the extravascular space is therefore always set to $V_{ex} = 0 \ mm/s$. The intravascular velocity, $V_{in} = (U_i + 0j) \ mm/s$ is a constant along the horizontal $x$-direction and zero along the vertical $y$-direction. The value of the intravascular velocity, $V_{in}$ is varied for the different simulations based on the Péclet number. The Péclet number is defined as $Pe = UL/D_{in}$ and determines the numerical stability of the Lattice Boltzmann and Finite Element methods. The pulse sequence timings are different than in the myocyte models. The gradient duration, $\delta = 24.65 \ ms$, and the onset of the negative gradient occurs at $\Delta = 35.85 \ ms$ resulting in a total echo time of $t_E = 60.50 \ ms$. The blood brain barrier that forms a permeable membrane between the intravascular and extravascular space is assumed

![Image](72x31) ![Image](72x31)

(a) (b)

Figure 4.33. Signal Domain for the Vessel Flow Model with $U = 0 \ mm/s \ (Pe = 0)$ at $b = 15 \ s/mm^2$ with Gradient Applied along $x$-axis using (a) COMSOL and (b) LBM.
to be completely impermeable with $K = 0 \, \mu m/s$.

The first simulation is run for a characteristic length, $L = 100 \, \mu m$ and $U = 0 \, mm/s$ ($Pe = 0$) in order to establish a baseline condition for the model at zero velocity before introducing the vascular flow. The no flow simulation is carried out at $b = 15 \, s/mm^2$ in both LBM and COMSOL. The signal domain maps obtained are shown in Figure 4.33. At zero velocity, two distinct values of signal are expected in the intravascular and extravascular domains. From the domain maps, it is observed that distinct signal values are observed through the middle of the domain. At the edges, the signal values drop off towards the lower end of the signal value range. This is due to the periodic boundary conditions that are imposed on the wall boundaries indicating that the model is more stable away from the boundaries of the computational domain. The distinct signal value obtained by both numerical models is approximately 0.65 and 0.45 in the intravascular and extravascular space respectively. This shows that larger the diffusion coefficient, greater the signal drop in the domain.

![Signal Maps](image1)

**Figure 4.34.** Line Plots of the Signal for the Vessel Flow Model with $U = 0 \, mm/s$ ($Pe = 0$) at $b = 15 \, s/mm^2$ along (a) $x$-axis at $y = 50 \, \mu m$ and (b) $y$-axis at $x = 50 \, \mu m$.

Figure 4.34 illustrates the line plots along the horizontal $x$-axis at $y = 50 \, \mu m$ and vertical $y$-axis at $x = 50 \, \mu m$. The line plot along the horizontal $x$-axis illustrates the signal along the
intravascular domain from $x = 0 \mu m$ to $x = 100 \mu m$ in Figure 4.34(a). The line plot indicates that a constant signal value is obtained towards the middle in the intravascular domain between $x = 20 \mu m$ and $x = 80 \mu m$ when there is no flow. The signal drops towards the boundaries indicating that the model is valid towards the interior of the computational domain far away from the periodic boundaries. The line plot along the vertical $y$-axis in Figure 4.34(b) illustrates the signal in the extravascular and intravascular domains across the impermeable blood brain barrier. The jump in the signal shows that two distinct signal values are obtained in the intravascular and extravascular domain with the signal in the extravascular domain lower than the signal in the intravascular domain. This result indicates that higher the diffusion coefficient in the domain, lower the signal obtained from the domain due to the higher diffusion of spins that occurs in the domain.

The relative error between the signals obtained using the two numerical algorithms is shown in Figure 4.35. The error is on the lower end towards the middle of the domain as discussed before and fluctuates towards the east and west boundaries away from the middle of the computational domain. The maximum absolute error between the COMSOL and LBM algorithms is 0.0288 and occurs towards the east and west boundaries within the intravascular region. The minimum absolute error on the other hand is $2.904 \times 10^{-6}$. The error map shows that both numerical models are reliable far away from the boundaries of the computational domain.

Once the baseline for the simulation was established, the simulation was run for the same computational domain with characteristic length, $L = W = 100 \mu m$, but the intravascular velocity along the horizontal $x$-direction was increased to $U = 1.5 \ mm/s$. By doing so, the Péclet number
was increased to $Pe \approx 134$. The simulation was run at $b = 15 \text{ s/mm}^2$ with the same diffusion parameters and local spin-spin relaxation times as the previous simulation with no intravascular flow. Figure 4.36 shows the signal obtained across the computational domain using both COMSOL and LBM for the given conditions. Unlike the previous case with no intravascular velocity, the introduction of flow causes a wave-like behavior in the intravascular domain. Moreover, the signal behavior in the intravascular domain is asymmetric in nature and the

Figure 4.36. Signal Domain for the Vessel Flow Model with $U = 1.5 \text{ mm/s (Pe = 134)}$ at $b = 15 \text{ s/mm}^2$ with Gradient Applied along x-axis using (a) COMSOL and (b) LBM.

Figure 4.37. Line Plots of the Signal for the Vessel Flow Model with $U = 1.5 \text{ mm/s (Pe = 134)}$ at $b = 15 \text{ s/mm}^2$ along (a) x-axis at $y = 50 \mu m$ and (b) y-axis at $x = 50 \mu m$. 
COMSOL and LBM signal along the x-direction do not agree. This is further illustrated in the line plots shown in Figure 4.37. The signals obtained using COMSOL and LBM along the horizontal x-direction at y = 50 μm behave as waves in the intravascular domain as shown in Figure 4.37(a). However the signal waves obtained from the two numerical algorithms in the intravascular domain do not agree with each other with a maximum absolute error of 0.120. Similarly, the line plot along the vertical y-direction in Figure 4.37(b) shows that the signal values from COMSOL and LBM agree in the extravascular domain but differ in the intravascular domain. This is because there is no flow in the extravascular domain and therefore the problem remains the same as the previous simulation case.

The domain map of the absolute error between the COMSOL and LBM solutions is shown in Figure 4.38. The maximum absolute error between the two algorithms is 0.120 which is observed in the intravascular domain, while the minimum absolute error is $9.657 \times 10^{-7}$ which is observed across the extravascular domain and especially near the boundaries. The instability in the result in the intravascular domain is analyzed by solving the two dimensional steady state channel flow [28] with an analytical solution as described by Li et al., and studying the dependence of the computational schemes on the Péclet number which is associated with the flow.

The 2D steady state channel flow considers the flow of velocity, $V_x$ in a 2D channel of constant height, $H$. The convection diffusion equation for the temperature, $T$ inside the channel with diffusion coefficient, $D_t$ is,
\[ V_x \frac{\partial T}{\partial x} = D_t \left( \frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} \right) \] (4.9)

The Péclet number that characterizes this thermal flow problem is \( Pe = \frac{V_x H}{D_t} \). Setting the height of the channel as \( H = 64 \, \mu m \) and the diffusion coefficient, \( D_t = 2.0 \, \mu m^2/\text{ms} \), the velocity of the flow is determined to be \( V_x = 0.625 \, \text{mm/s} \) for an initial Péclet number, \( Pe = 20 \). Dirichlet boundary conditions are imposed on the walls at \( y = 0 \, \mu m \) and \( y = H = 64 \, \mu m \) given by,

\[ T(x, y = 0) = T(x, y = H) = \cos(kx) \] (4.10)

where, \( k = 2\pi/L \) and \( L = H = 64 \, \mu m \). The analytical solution for the thermal field is given in terms of complex variables as follows,

\[ T_{ex}(x, y) = \text{Real} \left[ e^{ikx} \left( \frac{1-e^{-\lambda H}}{e^{\lambda H} - e^{-\lambda H}} e^{\lambda y} - \frac{1-e^{\lambda H}}{e^{\lambda H} - e^{-\lambda H}} e^{-\lambda y} \right) \right] \] (4.11)

Figure 4.39. Exact Solution for the 2D Steady State Channel Flow at \( Pe = 20 \).
where, “Real” means taking the real part of a complex variable and \( \lambda = k \sqrt{1 + \frac{iU}{D_t k}} \). The temperature domain map of the analytical solution for \( Pe = 20 \) is shown in Figure 4.39. The domain maps of the absolute error between the analytical solution and the solutions obtained using COMSOL and LBM are provided in Figure 4.40(a) and (b). From the figure it can be seen that the maximum absolute error between the analytical solution and COMSOL is \( 3.0 \times 10^{-3} \) while the maximum absolute error between the analytical solution and LBM is 0.0438. The maximum error is observed at the boundaries on which the Dirichlet boundary condition in Equation (4.10) is imposed. Moreover, the behavior of the error follows the behavior of the solution for the temperature. The maximum absolute error between the analytical solution and the COMSOL and LBM solutions are \( 3.0 \times 10^{-3} \) and \( 4.38 \times 10^{-2} \) respectively.

![Figure 4.40. Domain Maps of the Absolute Error between the Analytical Solution and the Solutions Obtained Using (a) COMSOL, and (b) LBM for the 2D Steady State Channel Flow at Pe = 20.](image)

The Péclet number was then increased to \( Pe = 75 \) in order to study its effect on the error between the model and analytical solutions. For the same height of the channel, \( H = 64 \ \mu m \) and diffusion coefficient, \( D_t = 2.0 \ \mu m^2/ms \), the velocity of the flow is now \( V_x = 2.344 \ mm/s \) for \( Pe = 75 \). The analytical solution for the temperature domain at \( Pe = 75 \) is shown in Figure 4.41. In this case, the maximum absolute error between the analytical solution and COMSOL is 0.0126 while the maximum absolute error between the analytical solution and LBM is 0.3085 which can be
observed from Figure 4.42. The error in both solutions obtained using COMSOL and LBM has increased by one order of magnitude. From these results it can be inferred that the Péclet number plays an important role in the stability of the numerical model and the errors introduced into the model due to computational stability limitations.

Figure 4.41. Exact Solution for the 2D Steady State Channel Flow at $Pe = 75$.

Figure 4.42. Domain Maps of the Absolute Error between the Analytical Solution and the Solutions Obtained Using (a) COMSOL, and (b) LBM for the 2D Steady State Channel Flow at $Pe = 20$. 
Therefore, from this analysis of the 2D steady state channel flow problem indicates that the Péclet number that was used in the vessel flow model, \( Pe = 134 \) is too high. The Péclet number is then reduced to \( Pe = 10 \) and the model is simulated again in COMSOL and LBM. The low Péclet number is achieved by reducing the length and width of the geometry to \( L = W = 50 \mu m \). The width of the vessel that passes horizontally through the domain remains the same, that is, \( W_{\text{vessel}} = 5 \mu m \). However, now the vessel occupies 10% of the total area of the domain for the given characteristic length, \( L \). The model parameters such as the diffusion coefficient, local spin-spin relaxation times, pulse sequence timings and the permeability of the blood-brain barrier are all the same as before. The intravascular velocity corresponding to the reduced Péclet number is \( U = 0.224 \, \text{mm/s} \). The signal over the domain obtained using the two numerical algorithms for the reduced number Péclet number conditions is illustrated in Figure 4.43. Two almost distinct signal values are observed in the intravascular and extravascular domains with the intravascular signal approximately close to 0.66 and the extravascular signal approximately close to 0.44 for solutions obtained using both COMSOL and LBM. The drop in the signal value towards the east

\[ \text{Figure 4.43. Signal Domain for the Vessel Flow Model with } U = 0.224 \, \text{mm/s (Pe = 10)} \text{ at } b = 15 \, \text{s/mm}^2 \text{ with Gradient Applied along } x\text{-axis using (a) COMSOL and (b) LBM.} \]
and west boundaries is more gradual than in the case with Péclet number, $Pe = 134$. The signal behaves as a wave in the intravascular domain where the velocity is imposed, and there is closer agreement between the COMSOL and LBM solutions for the low Péclet number than for the previous simulation with $Pe = 134$. The line plot in Figure 4.44(a) shows the wave behavior of the signal in the intravascular domain along the x-axis at $y = 50 \, \mu m$ for both COMSOL and LBM. The maximum error along the line plot between the two solutions. The maximum absolute error between the COMSOL and LBM solutions along the horizontal in the intravascular domain is $1.6 \times 10^{-3}$. On the other hand, the line plot in Figure 4.44(b) shows the signal along the vertical $y$-direction at $x = 50 \, \mu m$ across the two domains for both numerical algorithms. The maximum absolute error in this case is $7.9 \times 10^{-3}$. Two different signal values are observed in the intravascular and extravascular domains due to the different diffusion coefficients in the two domains. Moreover, the intravascular signal is higher than the extravascular signal since the intravascular diffusion coefficient is lower than the extravascular diffusion coefficient.

The domain map of the absolute error between the signals obtained using the two numerical model is provided in Figure 4.45. In the extravascular domain, the error lies towards the lower end of the error range with a minimum error of $9.069 \times 10^{-6}$. The maximum error is
observed in the intravascular domain and has a value of $7.9 \times 10^{-3}$. The error in the intravascular domain is asymmetric and exhibits wave-like behavior with the higher error occurring towards the $x = 0 \mu m$ boundary.

Lastly, the change in the domain signal behavior with an increase in $b$ value was studied for the two numerical models in COMSOL and LBM. The change in the behavior of the error between the signals obtained using the two methods is also studied. The signal domains obtained at different $b$ values ranging from $b = 0 \, s/mm^2$ to $b = 240.2 \, s/mm^2$ is illustrated in Figure 4.46 and Figure 4.47 for the COMSOL and LBM solutions respectively. The absolute error between the solutions from the two numerical methods is illustrated as a function of $b$ value in Figure 4.48. At $b = 0 \, s/mm^2$, two distinct signal values close to 0.668 and 0.470 are observed in the intravascular and extravascular domains respectively in both COMSOL and LBM as shown in the figure. The maximum absolute error between the two signal domains at $b = 0 \, s/mm^2$ is $2.0 \times 10^{-3}$ and is observed in the extravascular region. The minimum absolute error for the same $b$ value is $1.324 \times 10^{-4}$ and is observed in the intravascular region. When the $b$ value is increased the signal values no longer remain constant in the two domains. In the extravascular domain, the signal value becomes constant only towards the middle of the computational domain and drops in value towards the east and west boundaries with an increase in $b$ value. The signal in the intravascular domain deviates from the constant value due to the flow condition imposed and demonstrates an asymmetric wave behavior. The stability of the wave gradually decreases with the COMSOL and LBM solutions gradually showing large differences between the signal values with increase in $b$ value. Beyond $b = 30.1 \, s/mm^2$, the order of magnitude of the error increases beyond $10^{-3}$. The high differences between the COMSOL and LBM results at higher $b$ values.
indicates that both models are unstable at higher $b$ values in addition to higher Péclet values and require an improvement in the computational method to accommodate these instabilities.

Figure 4.46. Signal Domain for the Vessel Flow Model with $U = 0.224 \, mm/s \ (Pe = 10)$ at Different $b$ Values with Gradient Applied along $x$-axis using COMSOL.
Figure 4.47. Signal Domain for the Vessel Flow Model with $U = 0.224$ mm/s (Pe = 10) at Different $b$ Values with Gradient Applied along x-axis using LBM.
Figure 4.48. Absolute Error between COMSOL and LBM for the Vessel Flow Model with $U = 0.175 \text{ mm/s (Pe = 10)}$ at $b = 15 \text{ s/mm}^2$ with Gradient Applied along $x$-axis.
CHAPTER 5: CONCLUSION

This thesis focuses on the solution of the Bloch Torrey equation in two dimensions with a home grown Lattice Boltzmann code and its validation with a commercial code based on the Finite Element Method (COMSOL). The Bloch Torrey equation relates the diffusion advection process with the MRI magnetization in motion encoded sequences. Two physiological models are employed. The first corresponds to a basic representative microstructural model of the muscle fiber consisting of a periodic array of myocytes. The myocyte cross-section was first modeled as an ellipse embedded in a rectangular shaped extracellular domain, with spatial periodicity imposed on all boundaries. The simulation was performed for two cases of ellipticity (minor over major axis), 0.70 and 0.38, with an inclusion fraction of 0.70 (percentage of space occupied by the myocyte). Further simulations were run to study the effect of the inclusion fraction of the intracellular region of the myocyte on the diffusion process by reducing the inclusion fraction to 0.174. Also, the change in the signal with the presence and absence of a semi-permeable membrane of permeability, $K = 13 \, \mu m/s$ between the intracellular and extracellular regions of the myocyte is studied. For the ellipse models (ellipticity 0.70 and 0.38), with infinitely permeable membrane, the signal behavior obtained when the gradients are applied along the $x$ and $y$ axes is different. This is because of the asymmetry in the geometry of the ellipse with the diffusion length along the $x$-axis being longer than that along the $y$-axis. The change in ellipticity from 0.70 to 0.38 results in a lack of inflection in the signal ratio drop with the increase in $b$ value when the gradient is applied along the $y$ direction. The natural logarithm of the signal drop as a function of the $b$ value shows a biexponential behavior indicating that extraction of an apparent diffusion coefficient is impossible using a linear fit of the logarithmic curve. Moreover, the change in the inclusion fraction of the geometry from 0.70 to 0.174 demonstrated a change in the behavior of the signal drop with increase in $b$ vale from biexponential to monoexponential, thereby indicating that an apparent diffusion coefficient for the process can be determined using a linear fit of the logarithmic signal curve. Therefore, the geometry of the myocyte plays an important role in the diffusion pattern within the muscle cell in terms of shape of the myocyte as well as its inclusion fraction. Detailed parametrization of the
diffusion process with respect to myocyte geometry shape and inclusion fraction would help in the two dimensional parallelization of the model in addition to expanding the model to three dimensions. Lastly, the comparison between the models with and without the semipermeable membrane showed that the presence of a permeable membrane resulted in more restricted diffusion within the intracellular and extracellular domains. Less diffusion causes a higher signal resulting in the natural logarithm of the signal ratio becoming less negative than in the model with infinitely permeable membrane.

In order to further verify that the cause for different signal behavior when the gradients are applied along the $x$ and $y$ axes is the asymmetric nature of the elliptical myocyte model, the myocyte cross-section was then modeled as a disc within a square extracellular domain to achieve a symmetric geometry. For this case with infinitely permeable membrane, it was found that the natural logarithm of the signal ratio as a function of $b$ value was approximately the same when the gradients are applied along the $x$ and $y$ axes. This validates the previous conclusion that the geometry indeed plays an important role in determining the diffusion pattern when the MRI gradient is applied along different axes. Furthermore, repetition of this test for the case with permeable membrane also gave the same results with the signal ratio behavior when gradients are applied along the $x$ and $y$ direction being the same, and the natural logarithm of the signal ratio being less negative than in the case of the infinitely permeable membrane.

In order to further isolate the performance of the COMSOL and LBM codes in the vicinity of the myocyte membrane, a simple vertical membrane model possessing an analytical solution was adopted. On comparing the results from the COMSOL and LBM models with the analytical solution, it was found that the COMSOL solution differs from the analytical solution by an error which is of second order in grid size. The LBM error on the contrary is higher, which implies that there is still further development needed in the way LBM handles boundaries. Also, the LBM solution resulted in a higher error (order of magnitude of $10^{-3}$) in comparison to the COMSOL solution. A possible reason for this difference between COMSOL and LBM is that the COMSOL mesh is created to conform to the geometry, while the LBM grid is uniform. This causes a lack of a smooth solution at the boundaries. Next the effect of geometry complexity on
the diffusion process and the effectiveness of the models in capturing this effect was examined. The oblique membrane model features a semipermeable membrane between two domains in the form of a wedge inclined from the vertical at three different angles. COMSOL provided a more uniform solution across the vertical direction in the domain, while LBM showed instability and inaccuracy near the sharp corners of the membrane. The maximum error was observed at the membrane corners forming the wedge and connecting to the periodic wall boundaries. An increase in the angle of inclination from the vertical caused the maximum error to decrease. A numerical study of the error due to the LBM algorithm should incorporate effects of the uniform LBM grid, and geometry with sharp corners and wedges that create large gradients.

The second physiological model pertains to the flow of blood within the cerebral microvasculature. A single two dimensional vessel surrounded by homogenous brain parenchyma was considered. The mass transport problem involves an advection diffusion process, whose complexity is characterized by the Péclet number. High Péclet number and domain sizes cause numerical instability which is manifested in spurious oscillations in the solution. Additionally, high b values (beyond $b = 30.1 \text{ s/mm}^2$) also cause instability in the COMSOL and LBM solutions.

The myocyte diffusion model using the Lattice Boltzmann Method has been successful in accommodating barriers to diffusion in the form of semipermeable membranes. The model can be readily expanded to include lipid domains in order to study their effects to the signal. Once the two dimensional model with both semipermeable membranes and lipids has been created, the model can be parallelized and extended in three dimensions. The next major step in the study of muscle diffusion would be to connect the DTI and MRS signals with the characteristic parameters of the water filled interstitial space of the myocyte in order to interpret the experimental data. The microvessel flow model is developed and requires a number of key improvements. These include conducting a variable Péclet number study in order to define the velocity and grid limitations on the LBM model, and careful study of the effect of vessel alignment with the LBM grid.
REFERENCES


