A LATTICE BOLTZMANN METHOD MODEL OF DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING IN SKELETAL MUSCLE

BY

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THESIS

Submitted in partial fulfillment of the requirements for the degree of Master of Science in Mechanical Engineering in the Graduate College of the University of Illinois at Urbana-Champaign, 2016

Urbana, Illinois

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ABSTRACT

Aging and obesity is associated with reduction in muscle mass and increase in fat mass, leading to decline in both physical function and health. Probing the cellular microstructure of skeletal muscle with noninvasive methods is paramount in developing effective therapeutic procedures for the elderly, such as physical exercise. Using special proton magnetic resonance imaging (MRI) protocols we can investigate non-invasively diffusion phenomena within skeletal muscle. This project focuses on the numerical study of the effect of microstructure on the effective diffusion coefficient via a Lattice Boltzmann model (LBM). Specifically, we aim to characterize how variations in microstructure and mass transport properties affect the local apparent diffusion coefficient of water measured with Diffusion Tensor Imaging (DTI).

A numerical model is developed to solve the Bloch-Torrey equation in a periodic domain containing muscle cells surrounded by permeable membranes. This model is shown to be convergent in both time and space at the theoretical truncation error rate and to agree with analytical solutions of limiting cases. The effect of membrane permeability is investigated and found to be consistent in trend with prior experimental investigations.

A simpler two-compartment exchange model is also investigated and compared with the LBM model. It is found that qualitative agreement exists in terms of variations in ellipticity and permeability, however, there is qualitative disagreement in the model for changes in cell volume fraction. This disagreement is investigated systematically and the numerical source of the disagreement between the two models is identified. Our results demonstrate that the continuum LBM model is superior to the two-compartmental model for human muscle MRI.
To my parents.

*Without their love, guidance and patience I would not be here today.*
I would like to thank my academic and research advisor Professor John Georgiadis for providing me the opportunity to come to the University of Illinois. His support and guidance has been instrumental in helping me navigate graduate school and form an understanding of my research interests. He has introduced me to a fascinating synthesis of physiology, medical imaging and mechanical engineering so which I owe him a debt of gratitude.

I would like to thank Professor Brad Sutton of the Bioengineering department for his insightful advice and guidance this last year, Caroline Tennyson who performed much of the initial development of this work and Aaron Anderson for his technical help as well as advice on navigating graduate life. I wish to also acknowledge the National Science Foundation grant CBET-1236451, which has funded this project.

I wish to thank my family and many friends who have supported and encouraged me these last two years. In particular I would like to thank the men of Fever house as well as my good friends in ARG. Finally, I wish to thank God for the many gifts and opportunities provided to me these last two years.
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CHAPTER 1
INTRODUCTION

1.1 Effects of Obesity, Aging and Exercise on Skeletal Muscle

Age related loss of muscle mass, known as sarcopenia, is a major determinant of frailty in elderly persons [1]. At the same time an obesity epidemic, characterized by the percentage of persons with a body mass index (BMI) \( \geq 30 \text{ kg/m}^2 \), has impacted all age groups in the United States [2]. Both the total number and percentage of older persons who are obese has increased substantially, and this is a more common occurrence in women than men [2, 3]. Nearly 70% of women over 60 years of age are overweight or obese [2]. Further exacerbated by aging, obesity leads to reductions in mobility, decline of physical condition [4] and increased nursing home admissions [5]. The efficacy of various therapeutic interventions to combat this condition, like physical exercise or diet, hinges on quantifying their effects on skeletal muscle microstructure and health.

Especially in older adults where obesity and sarcopenia coexist, BMI is a poor predictor of the health effects of obesity. Distribution of fat is more important than the absolute amount of fat. According to exercise physiology, fit muscle metabolizes lipids efficiently in order to avoid depletion of carbohydrate depots [6]. Research has shown that lipids associated with the muscle, specifically intramyocellular triglycerides, are permanently relocated to the interior of the muscle fiber in obese individuals [7, 8]. These lipids can alter the compartmentalization of the muscle cell due to muscle loss and fat infiltration during aging [9], thus affecting metabolism and muscle cell contraction.

The role of therapeutic interventions in muscle quality was explored in a recent noninvasive, in vivo study [10, 11] that involved the measurement of...
the water diffusion tensor using Diffusion Tensor Imaging (DTI) and the distribution of intramyocellular and extramyocellular lipids in human thigh muscles by Magnetic Resonance Spectroscopy (MRS). Both techniques involved water proton MRI, which encodes the position and state of water molecules in Fourier space in a temporally convolved manner. These measurements were correlated with muscle strength measurements of elderly women differing in adiposity and habitual physical activity, after they were exposed to four months of exercise training or diet. The study showed that exercise impacts muscle quality more than body fatness or weight loss in the elderly. Muscle quality has been defined as leg strength normalized by the mineral free lean mass of the leg [12, 13]. 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.

Interpreting the MRI results (irrespective of the specific method of weighting the signal) requires the solution of an inverse problem from Fourier space to real space. When MRI is used to encode water diffusion (as is the case for DTI), the inversion problem is based on the diffusion equation. A diffusion model using random permeable barriers has been employed in a study of short term changes in healthy and pathological human calf muscle following treadmill exertion [14]. The model predictions, which were extracted from diffusion-weighted signal decays, indicated that free diffusion increased by 5.8%, muscle fiber diameter increased by 19.7%, and that the apparent sarcolemma permeability decreased by 7% in healthy controls.

Invasive experiments in animal models (involving immuno-histological analysis of rats and mice muscle samples) demonstrated that there is a two-fold increase in Aquaporin-4 (AQP4) accumulation in fast-twitch muscle in proportion with increased physical exercise [15]. Ex vivo measurements in these animal models revealed a concomitant increase in myocyte membrane (sarcolemma) permeability to water following long term physical exercise.

Taken together, the above experimental investigations of the effect of exercise on the microstructure of skeletal muscle indicate that the following intrinsic parameters are affected by intervention: local water diffusivity tensor, myocyte diameter and sarcolemma permeability. The overarching aim of this project is to examine the influence of these parameters on diffusion-weighted MRI (DTI) signal by building a numerical model to simulate both
water diffusion and MRI physics at the level of the myocyte.

1.2 Diffusion Tensor Imaging and Computational Diffusion Models

Understanding the biomechanics of force generation in skeletal muscle requires connecting muscle microstructure with muscle function. Due to muscle’s complex hierarchical fiber nature, determination of its microstructure requires high-resolution probing techniques. Currently, the highly invasive technique of muscle biopsy is the major method used to investigate muscle microstructure; however, non-invasive methods capable of probing these fine spatial scales are being developed. In particular, diffusion tensor imaging (DTI), a modality of magnetic resonance imaging (MRI), allows in vivo measurement of the directional diffusion coefficient of water in muscle. Water has a known free diffusion coefficient, however, within muscle the free diffusion of water is restricted by various microstructures. This results in an apparent diffusion coefficient (ADC) averaged over the voxel, which is measured by DTI.

Individual DTI pulse sequences have extrinsic parameters (pulse duration and strength) with corresponding effective diffusion times that determine the spatial scale (1-10 \( \mu \)m) at which the pulse is sensitive to barriers to diffusion. This makes DTI sensitive to tissue microstructure on the cellular scale. Using a combination of different pulse sequences and directions makes it possible to use DTI measurements to infer microstructural information. DTI has also been used to probe the orientation of muscle fibers in calf muscle, as well as other muscles [10, 16].

DTI has a practical voxel resolution limit of \( \sim 1 \) mm\(^3\) due to technological limitations; all structural information below this spatial scale is “smeared”. This implies that cell level information is lost when acquiring the signal in each voxel. However, by taking advantage of the highly hierarchical organization of skeletal muscle and by using computational models, it is possible to recover this microstructural information at sub-voxel levels. Human skeletal muscle consists of bundles of fascicles (each 1 – 2 mm wide), each composed of bundles of myocytes (each 10 – 100 \( \mu \)m wide). Each myocyte is in turn made up of an array of hundreds of parallel myofibrils as well as a network of
tubules, mitochondria, and lipid inclusions distributed throughout the cell. It has been hypothesized that this structure, including the multiple levels of tethering between different spatial scales, is intimately related to the generation of shear strain during muscle deformation [17]. Additionally, research indicates that subcellular barriers, such as intracellular lipid distribution, restrict the diffusive transport of molecules that are important for metabolism [18].

The bibliography for the computational diffusion models used to interpret MRI measurements inside and outside cells starts with a two-compartment exchange model presented by McConnell [19]. Käger [20] extended this model to describe diffusion-weighted MRI, and Stanisz et al. [21] added the effect of different $T_2$-relaxation rates between the compartments. Nilsson et al. [22] presents a comprehensive review of further developments. Most relevant to DTI experiments on human muscle is the work of Karampinos et al. [23] who modified the two-compartment exchange model of Stanisz [24] to accommodate anisotropic diffusion on the plane perpendicular to the myocytes. Although this reproduced the DTI anisotropy, it did not explain the effect of intervention on the intrinsic properties of the muscle.

Seeking to recover more complex microstructural physics, continuum models based on the integration of the partial differential equations describing MRI physics (Bloch-Torrey equations) on more realistic cell geometries have been introduced. Fieremans et al. [25] have performed a Monte Carlo simulation of the Bloch-Torrey equation for arrays of parallel cylinders (mimicking axons) and compared the results with the predictions of the two-compartment exchange models. Monte Carlo simulations are computationally expensive since the tracking of the random walk across multiple boundaries is very tedious for large systems. Xu et al. [26] obviated these difficulties by using an improved finite difference scheme instead. More recently, by introducing a Lattice Boltzmann scheme to simulate the Bloch-Torrey equations, Tennyson [27] addressed the problem of two dimensional water diffusion in a single myocyte delineated by a semi-permeable membrane and surrounded by a periodic arrangement of identical myocytes. The present research project aims to improve and expand this model by accommodating more complex physics and microstructure.
1.3 Thesis Objectives and Outline

This work further describes the Lattice Boltzmann method (LBM) scheme for numerically simulating microstructural restrictions of water diffusion in skeletal muscle, and relating these restrictions to the measured diffusion-weighted imaging signal obtained via DTI. This allows the investigation of the subvoxel structure of muscle, ultimately enabling a relationship to be developed between measures of muscle quality, diffusion-weighted imaging of skeletal muscle, and the microstructural properties of skeletal muscle. The establishment of this relationship will lead to a better understanding of how microstructural properties of muscle affect force generation within muscle and overall health, an important relationship for both clinicians and researchers alike.

This thesis is organized as follows: Chapter 2 presents the theoretical background related to the numerical integration of the Lattice Boltzmann method (LBM) model of DTI measurements, as well as the two-compartment exchange model employed. Chapter 3 describes the computational domain in the context of muscle microarchitecture. Chapter 4 presents the results of the LBM simulations, including validation of the numerical code, and discusses the effects of both extrinsic (MRI pulse sequences) and intrinsic (muscle) parameters on the local diffusion coefficient. Chapter 5 compares the predictions of the LBM model with those of the two-compartment model, while Chapter 6 gives the final conclusions and future research needs.
2.1 Diffusion-Weighted Magnetic Resonance Imaging

2.1.1 The Bloch-Torrey Equation

Diffusion refers to the incoherent (random walk) movement of a species from an area of high concentration to low concentration. Diffusion can be characterized by Fick’s first law of diffusion,

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

(2.1)

where \( \phi \) is the concentration of the species, \( t \) is time, \( D \) is the diffusion coefficient and \( \nabla \) is the gradient operator. In the absence of a diffusion gradient, molecules, in this context referring to water molecules, still undergo random thermal motion, even if at thermal equilibrium. This random motion of molecules, known as Brownian motion, was first observed by Brown in 1828 and mathematically described by Einstein in 1905; the motion is incoherent and is due to the thermal energy inherent in all molecules [28].

MR imaging relies on inducing resonance in proton spins to produce an electrical signal on the receiver (RF coil). When large numbers of protons resonate, their collective behavior can be represented by the vector quantity of their magnetization, \( \mathbf{M} \), which is the macroscopic summation of the microscopic nuclear magnetic moments of individual protons in a system. The MR signal is proportional to the transverse component of \( \mathbf{M} \), which in turn expresses the coherence of the phase of the precessing nuclear spins. Brownian motion causes the spins to lose phase coherence, leading to irrecoverable signal attenuation [29]. This signal loss is measurable and the basis of diffusion-weighted imaging.
Signal attenuation due to diffusion is not accounted for in the Bloch equation. To account for signal loss from diffusion one starts with the standard convection equation,

\[
\frac{\partial \phi}{\partial t} + \mathbf{V} \cdot \nabla \phi = \nabla \cdot (D \nabla \phi) + S
\]  

(2.2)

where \( \mathbf{V} \) is the species velocity and \( S \) is the source term. Setting the source term to zero and assuming isotropic diffusion the equation reduces to,

\[
\frac{\partial \phi}{\partial t} + \mathbf{V} \cdot \nabla \phi = D \nabla^2 \phi
\]  

(2.3)

Recalling that \( \phi \) represents the species concentration of water molecules, which is proportional to the macroscopic magnetic vector, \( \mathbf{M} \), the above equation can then be combined with the standard Bloch equation to describe how diffusion relates to signal attenuation.

\[
\frac{\partial \mathbf{M}}{\partial t} = \gamma \mathbf{M} \times \mathbf{B}_{\text{ext}} - \frac{M_x \mathbf{i} + M_y \mathbf{j}}{T_2} - \frac{(M_z - M_z^0) \mathbf{k}}{T_1} + \nabla \cdot (D \nabla \mathbf{M}_\perp) + \mathbf{V} \cdot \nabla \mathbf{M}_\perp
\]  

(2.4)

where \( \mathbf{B}_{\text{ext}} \) is the externally applied magnetic field, \( T_2 \) and \( T_1 \) are relaxation times and \( \mathbf{M}_\perp \) is the magnetic signal in the transverse plane perpendicular to the applied external field. The latter is the only component that can be measured by MR receiver coils. Equation 2.4 is the Bloch-Torrey equation and was first developed by Torrey in 1956 [30]. The Bloch-Torrey equation allows for diffusion based contrast imaging as well as determination of the effective diffusion coefficient within a domain.

Equation 2.4 can be written in terms of its Cartesian components as

\[
\frac{\partial M_x}{\partial t} = \gamma B_z M_y - \frac{M_x}{T_2} + D \left( \frac{\partial^2 M_x}{\partial x^2} + \frac{\partial^2 M_x}{\partial y^2} \right) + V_x \frac{\partial M_x}{\partial x} + V_y \frac{\partial M_x}{\partial y}
\]  

(2.5)

\[
\frac{\partial M_y}{\partial t} = \gamma B_z M_x - \frac{M_y}{T_2} + D \left( \frac{\partial^2 M_y}{\partial x^2} + \frac{\partial^2 M_y}{\partial y^2} \right) + V_x \frac{\partial M_y}{\partial x} + V_y \frac{\partial M_y}{\partial y}
\]  

(2.6)

\[
\frac{\partial M_z}{\partial t} = - \frac{M_z - M_z^0}{T_1}
\]  

(2.7)
2.1.2 Diffusion-Weighted Pulse Sequences

To determine the apparent diffusion coefficient (ADC), a pulse sequence of magnetic gradients is used. One of the most popular sequences is the pulsed-gradient spin-echo (PGSE) sequence which is shown in Figure 2.1.

![Figure 2.1: Schematic of a pulsed-gradient spin-echo (PGSE) sequence. ∆ and δ are timing parameters of the pulse.](image)

In the PGSE sequence a diffusion gradient (G) is applied to the slice. This causes the spins in the slice to move out of phase as the precession frequency of the spins becomes spatially dependent. These spins are then allowed to self-diffuse for some time ∆ before a gradient in the opposite direction is applied. After this second gradient is applied, if the spins were stationary they would return to their original phase. However, because of diffusion the spins lose phase coherence, which is associated with signal attenuation. The resulting signal is found to be

$$ S = PD(1 - e^{-\frac{TR}{T1}})e^{-\frac{TE}{T2}} e^{-bD} $$

(2.8)

where PD is the proton density, TR and TE are the repetition time and echo time, respectively, D is the diffusion coefficient and b is the b-value which is

$$ b = \gamma \int_0^T F(t)^2 dt $$

(2.9)

where F(t) is the summation of the applied gradients (G) as a function of
time,

$$F(t) = \int_{0}^{t} G(t')dt' \quad (2.10)$$

For PGSE sequences, \(b\) is given to be 

$$b = \gamma^2 G^2 \delta^2 (\Delta - \frac{\delta}{3})$$

where \(\delta\) and \(\Delta\) are timing parameters of the PGSE sequence shown in Figure 2.1. By setting the terms not dependent on the applied gradient in equation 2.8 to be a constant \((S_0)\) 2.8 can be reduced to

$$S = S_0 e^{-bD} \quad (2.11)$$

There are a number of other diffusion-weighted pulse sequences available, such as oscillating-gradient pulsed-echo (OGSE) which utilizes sine waves instead of rectangular pulses to obtain diffusion measurements with shorter diffusion times.

Equation 2.11 can be used to determine the diffusion coefficient by treating \(S_0\) as a constant and taking two measurements with different \(b\)-values. By comparing the resulting signals, the apparent diffusion coefficient (ADC) along the applied gradient axis can be calculated via

$$ADC = \frac{-\ln(\frac{S_2}{S_1})}{b_2 - b_1} \quad (2.12)$$

The calculated diffusion coefficient is referred to as the apparent diffusion coefficient because the value found is different from the unrestricted diffusion coefficient of the species being measured. This is because there are often microstructural barriers which inhibit diffusion and lead to a reduced value. The measured ADC represents the cumulative influence of the effects these barriers have on self-diffusion within each voxel. If there are not microstructural restrictions, or the restrictions are not preferential to a direction, then only one measurement is needed to characterize the diffusion within the domain. If the microstructural restrictions are direction-dependent, leading to anisotropic diffusion, it is necessary to take multiple measurements to calculate the diffusion tensor. This MRI modality is known as Diffusion Tensor Imaging (DTI).
2.1.3 Diffusion Tensor Imaging (DTI)

Anisotropic diffusion often occurs within fibers because cell membranes restrict the diffusion of water perpendicular to the axis of the fiber, leading to reduced apparent diffusion coefficients. This restriction is less important parallel to the fiber axis, leading to larger diffusion coefficients in this direction. The directions of the axes of fibers are often unknown before imaging and rarely line up with the laboratory axes, so a non-orientation dependent imaging method is needed. By taking multiple measurements in different, non-collinear, non-coplanar directions, one can construct an ellipsoid which has a major axis that corresponds to the axis of the greatest diffusion coefficient and thus the axis of the fiber. At least six different measurements are needed, though more measurements result in more accuracy [31]. If six measurements are taken, their values can be set as the coefficients of the equation of an ellipsoid, $ax^2 + by^2 + cz^2 + dyz + exz + fxy = 1$. These values can also be written in a 3x3 matrix that represents the diffusion tensor,

$$D_{eff} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$ (2.13)

This matrix also describes the ellipsoid, with the off-diagonal terms being symmetric about the diagonal ($D_{ij} = D_{ji}$) so there are only six degrees of freedom, not nine. Subjecting this tensor to diagonalization yields three eigenvectors and three corresponding eigenvalues. The eigenvectors correspond to the direction of the major and two minor axes while the eigenvalues are the diffusion coefficients along those respective axes. Finally, $D_{eff}$ can be evaluated from the equation $D_{eff}E = E\Lambda$ where $E$ is the matrix of eigenvectors and $\Lambda$ is the diagonalized matrix of eigenvalues [31].

$$E = (\epsilon_1, \epsilon_2, \epsilon_3); \quad \Lambda = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$$

In anisotropic fibers the eigenvector that corresponds to the largest eigenvalue represents the fiber-tract axis. As mentioned, the anisotropic diffusion can also be thought of as an ellipsoid. Each voxel will contain its own ellipsoid that can be plotted to show the axis of the fiber-tracts in each voxel.
If there is isotropic diffusion, then all the eigenvalues will be equal and the diffusion ellipsoid will reduce to a sphere.

In the case of skeletal muscle, the cells can be modeled as a series of parallel, infinitely long cylinders surrounded by a semi-permeable membrane. The underlying transport phenomena involves self diffusion of water with no advection. Since the cross-sectional shape of the cylinders is of primary interest, it is possible to restrict our attention to a two dimensional model which aligns the major axis of the cell with the direction of the externally applied magnetic field. This allows the transverse magnetization signal to be modeled as

$$M_{\perp} = M_x + M_y i$$

where $M_x$ and $M_y$ are found by solving the coupled system of equations 2.5 and 2.6.

2.2 The Lattice Boltzmann Method

2.2.1 Development of LBM equations

The coupled differential equations 2.5 and 2.6 are discretized using the Lattice Boltzmann Method (LBM). The Lattice Boltzmann Method is a mesoscale numerical scheme that can simulate transport phenomena on a discrete grid. It has been shown to be an accurate method for solving the advection-diffusion equation [32, 33]. In this work the Bhtnagar-Gross-Krook (BGK) model is utilized with a single relaxation time to solve the Bloch-Torrey equation.

In this setup, a two dimension, five speed model (D2Q5) is used, as shown in Figure 2.2. The model is defined by a lattice in two dimensions and a set of discrete velocities given as

$$e_i = \begin{cases} (0, 0) & (i = 0) \\ \pm (0, 1), (0, 0) & (i = 1, 2, 3, 4) \end{cases}$$

(2.15)

Using this lattice stencil, an equilibrium distribution function, $g_{eq}$, can be constructed by assigning each lattice direction a weighting factor, $\omega_i$, which
Figure 2.2: Schematic of two dimensional, five speed lattice (D2Q5)

relates to its contribution to the motion in a particular direction at each node:

\[ \omega_i = \begin{cases} \epsilon_D & (i = 0) \\ \frac{\epsilon_D}{4} & (i = 1, 2, 3, 4) \end{cases} \]  \hspace{1cm} (2.16)

The weighting factors, \( \omega_i \), are chosen such that the center particle is the most heavily weighted (\( \epsilon_D \)) while the velocities in the axial directions are weighted by \( \frac{\epsilon_D}{4} \). For the D2Q5 model the constant \( \epsilon_D \) equal 1/3.

The equilibrium distribution is:

\[ g_i^{eq}(x, t) = \left( \omega_i + \frac{\delta t v_j}{\delta x \epsilon_D} e_{ij} \omega_i \right) \phi(x, t) \quad (0 \leq i \leq 4) \]  \hspace{1cm} (2.17)

which, because there is no advection, can be reduced to

\[ g_i^{eq}(x, t) = \omega_i \phi(x, t) \quad (0 \leq i \leq 4) \]  \hspace{1cm} (2.18)

where \( \omega_i \) is the weighting factor for the different lattice directions, \( x \) is the location of the lattice grid point in the computational domain, \( \delta t \) is the time step, \( \delta x \) is the grid spacing, \( v_j \) is the velocity in each dimensional direction, and \( \phi(x, t) \) is the species distribution, in this case \( M_x \) and \( M_y \). At this point, the lattice BGK equation is introduced which represents the discretization of particle movement in time and space and is updated via an iterative process [34]. The BGK equation is given as
\[ g_i(x + e_i \cdot \delta t, t + \delta t) - g_i(x, t) = -\frac{1}{\tau} [g_i(x, t) - g_{iq}^i(x, t)] \] (2.19)

where \( g_i \) is the particle distribution and \( \tau \) is the relaxation time parameter, which is a function of \( \delta t, \delta x, \epsilon_D \), and the diffusion coefficient, D, as defined in equation 2.20.

\[ \tau = \frac{1}{2} + \frac{\delta t}{\epsilon_D (\delta x)^2} D \] (2.20)

The lattice BGK equation (2.19) can be integrated in two steps, commonly referred to as the collision and streaming steps. The lattice BGK collision operator is

\[ \hat{g}_i(x, t) = g_i(x, t) - \frac{1}{\tau} [g_i(x, t) - g_{iq}^i(x, t)] \] (2.21)

where \( g_i \) is the initial particle distribution at each time step, \( g_{iq}^i \) is the equilibrium particle distribution from 2.18, and \( \hat{g}_i \) is the particle distribution function following the collision step. \( \hat{g}_i \) is used as the input to the streaming step. The lattice BGK streaming operator is defined as

\[ g'_i(x + e_i \cdot \delta t, t) = \hat{g}_i(x, t) \] (2.22)

Summing the lattice values allows for the calculation of the magnetization vector \( M' \) after one iteration of the lattice BGK equation.

\[ M'(x, t) = \sum_{i=0}^{4} g'_{i_z}(x, t) + \sum_{i=0}^{4} g'_{i_y}(x, t) \] (2.23)

It is now necessary to consider the effects of \( T_2 \) relaxation and forced precession from the magnetic gradient on the signal. Utilizing an explicit forward-time centered space discretization of the Bloch-Torrey equation, the transverse magnetization can be expressed as [26],

\[ M(x, t + \delta t) = \exp \left( -\frac{\delta t}{T_{2e}} \right) \exp(-i\gamma G^n r_i \delta t) \cdot M'(x, t) \] (2.24)

where \( r_i \) is the position vector \( i \) in the direction of the applied gradient, \( G^n \) is the value of the gradient applied at time \( t = n \) and \( \gamma \) is the gyromagnetic
ratio of hydrogen. Equation 2.24 can be modified to be compatible with the Lattice Boltzmann scheme by substituting equation 2.23 into 2.24 and expanding out the summation. The effects of $T_2$-relaxation and precession on the non-equilibrium distribution can be written as

$$g_i(x, t + \delta t) = \exp\left(-\frac{\delta t}{T_{2x}}\right) \exp(-i\gamma Gn r_i \delta t) \cdot \left(g'_{ix}(x, t) + ig'_{iy}(x, t)\right)$$  \hspace{1cm} (2.25)$$

Hwang at al. propose letting $r_i = (i - \frac{N}{2}) \delta x \delta t$ such that

$$\Delta \varphi = \gamma Gn \left(i - \frac{N}{2}\right) \delta x \delta t$$  \hspace{1cm} (2.26)$$

where $N$ is the number of nodes in the gradient direction [35]. This centers the gradient on the center of the domain in the direction of the gradient. Assuming the gradient is applied along the x-axis, equation 2.25 can we rearranged and separated into its constitutive parts:

$$g_{ix}(x, t + \delta t) = \left[ g'_{ix}(x, t) \cos(\Delta \varphi) - g'_{iy}(x, t) \sin(\Delta \varphi) \right] \exp(-\delta t/T_{2x})$$  \hspace{1cm} (2.27)$$
$$g_{iy}(x, t + \delta t) = \left[ g'_{iy}(x, t) \cos(\Delta \varphi) + g'_{ix}(x, t) \sin(\Delta \varphi) \right] \exp(-\delta t/T_{2x})$$  \hspace{1cm} (2.28)$$

$g_{ix}(x, t + \delta t)$ and $g_{iy}(x, t + \delta t)$ are the solutions to one iteration of the LB scheme. They can be combined and used to calculate the macroscopic magnetic vector similar to 2.23.

$$M(x, t) = \sum_{i=0}^{4} g_{ix}(x, t) + i \sum_{i=0}^{4} g_{iy}(x, t)$$  \hspace{1cm} (2.29)$$

By running two different simulations with different b-values, equation 2.29 can inputted into equation 2.12 to calculated the ADC of the domain.

### 2.2.2 Boundary Conditions

Three different boundary conditions are implemented on various boundaries of the domain. These conditions are a periodic condition, a modified periodic condition and a membrane permeability condition. The three boundary conditions are defined as follows.
2.2.2.1 Periodic Boundary Condition

A periodic boundary condition is employed on the boundaries which lie parallel to the direction of the applied diffusion sensitizing gradient. As can be seen from equation 2.26, the effects of the diffusion gradient are location dependent in the direction of the diffusion sensitizing gradient but not in the perpendicular direction. Because of this, a periodic condition accurately represents the physics of the computational domain modeled as a unit cell of a larger periodic domain. The boundary condition is

\[ g'_i(x_{\text{dist}}, t) = g_i(x_{\text{src}}, t) \]  

(2.30)

where \( x_{\text{dist}} \) represents the location of the destination boundary and \( x_{\text{src}} \) represents the location of the source boundary and the relationship between them is \( x_{\text{src}} = x_{\text{dist}} + N\delta x \). The boundary condition is imposed between the collision and the streaming steps for nodes where the post collision value arrives from outside the domain (i.e. \( x_{\text{dist}} + e_i\delta x \)).

2.2.2.2 Modified Periodic Boundary Condition

On boundaries that are normal to the diffusion sensitizing gradient, the periodic boundary condition breaks down. The gradient applied causes the local magnetization vector to be become dependent on location. This magnetization vector then undergoes diffusion, creating a condition where neither the magnetization at the boundary nor the magnetization fluxes are predictable. As such, the three typical boundary conditions, Dirichlet, Newman and periodic, are all inapplicable. This problem can be dealt with by placing an impermeable barrier at this boundary. However, this restriction of diffusion creates large amounts of error at the boundary due to the imposition of highly restricted diffusion near the boundary. The effects of the impermeable membrane, the so called edge-effects [35], create a solution where only about the middle third of the computational domain is free from error. This means that greater than 65% of the computational area is wasted, which is computationally expensive. Xu et al. proposed a revised periodic boundary condition for finite difference methods which resolves this conflict and exactly predicts the behavior of a periodic domain at the boundary [26]. This modified periodic boundary condition has been adapted here to a Lattice Boltzmann scheme.
The boundary condition they derive for a finite difference scheme is:

\[ M_0 = \exp \left[ -i\alpha \gamma \sum_{k=1}^{n} G^k \delta t \right] M_N \]  

(2.31)

\[ M_{N+1} = \exp \left[ i\alpha \gamma \sum_{k=1}^{n} G^k \delta t \right] M_1 \]  

(2.32)

In the LB scheme this boundary condition becomes

\[ g_{i0} = \exp \left[ -i\alpha \gamma \sum_{k=1}^{n} G^k \delta t \right] g_{iN} \]  

(2.33)

\[ g_{iN+1} = \exp \left[ i\alpha \gamma \sum_{k=1}^{n} G^k \delta t \right] g_{iN} \]  

(2.34)

where \( \alpha \) is the domain length, \( G^k \) is the summation of the gradient applied up to time \( (t = n) \) and \( \delta t \) is the time step. This modified periodic boundary condition is applied at the end of each iteration of the Lattice Boltzmann scheme.

2.2.2.3 Semi-Permeable Membrane Boundary Condition

Muscle cells are surrounded by the sarcolemma, which involves semi-permeable membranes. 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 intercepted by the membrane is depicted in Figure 2.3 [32]. The distance from the lattice point in the intracellular region to the point at which the membrane cuts the lattice link is denoted by \( \Delta \) as shown in Figure 2.3. By normalizing the lattice grid size to unity, the distance from the lattice point in the extracellular region to the membrane is given by \( \Delta^{\text{ex}} = 1 - \Delta \). The membrane boundary condition is enforced at the end of the collision step. The direction of the particle distribution towards the membrane is denoted by the subscript \( i \), and the direction of the particle distribution away from the membrane is denoted by the subscript \( \overline{i} \). \( \Phi_n \) denotes the flux normal to the membrane.

The Neumann and Dirichlet boundary conditions used to derive the
Figure 2.3: Schematic depiction of the lattice link intersected by the membrane

boundary condition are based on the scheme developed by Li, Mei and Klausner [32]. 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 \( g_i'(x_e, t) \) and \( g_i'(x_f, t) \), respectively. This is presented in detail by Tennyson [27]. The membrane boundary conditions are found to be

\[
\left( \frac{2\Delta + 1}{2} \right) \left\{ g_i'(x_f, t) - \hat{g}_i(x_f, t) - \left( \frac{2\Delta - 1}{2\Delta + 1} \right) \left[ \hat{g}_i(x_f, t) - \hat{g}_i(x_{ff}, t) \right] \right\} \\
= \left( \frac{3 - 2\Delta}{2} \right) \left\{ -g_i'(x_e, t) + \hat{g}_i(x_e, t) + \left( \frac{1 - 2\Delta}{3 - 2\Delta} \right) \left[ \hat{g}_i(x_e, t) - \hat{g}_i(x_{ee}, t) \right] \right\} \\
(2.35)
\]

and
\[
\frac{K}{\epsilon_D} \left( \frac{3 - 2\Delta}{2\Delta + 1} \right) \left\{ g_i'(x_e, t) - 2\Delta \hat{g}_i(x_e, t) + \frac{(1 - 2\Delta)^2}{3 - 2\Delta} \hat{g}_i(x_{ee}, t) - 2 \left( \frac{1 - 2\Delta}{3 - 2\Delta} \right) \hat{g}_i(x_e, t) \right\} - \\
\frac{K}{\epsilon_D} \left( \frac{2\Delta + 1}{3 - 2\Delta} \right) \left\{ g_i'(x_f, t) - 2(\Delta - 1) \hat{g}_i(x_f, t) + \frac{(2\Delta - 1)^2}{2\Delta + 1} \hat{g}_i(x_{ff}, t) - 2 \left( \frac{2\Delta - 1}{2\Delta + 1} \right) \hat{g}_i(x_f, t) \right\} = \\
\frac{\delta x}{\delta t} \left( \frac{2\Delta + 1}{2} \right) \left\{ g_i'(x_f, t) - \hat{g}_i(x_f, t) - \left( \frac{2\Delta - 1}{2\Delta + 1} \right) [\hat{g}_i(x_f, t) - \hat{g}_i(x_{ff}, t)] \right\}
\] (2.36)

where \( K \) is the permeability coefficient of the cell membrane. \( g_i'(x_f, t) \) and \( g_i'(x_e, t) \) can now be determined by solving equations 2.35 and 2.36 as a system of linear equations.

For a simplified case of \( \Delta = 0.5 \) and using \( \epsilon_D = 1/3 \) for a D2Q5 LBM model, equations 2.35 and 2.36 become,

\[
g_i'(x_f, t) - \hat{g}_i(x_f, t) + g_i'(x_e, t) - \hat{g}_i(x_f, t) = 0 \tag{2.37}
\]

and

\[
3K \left\{ -g_i'(x_f, t) - \hat{g}_i(x_f, t) + g_i'(x_e, t) - \hat{g}_i(x_f, t) \right\} = \\
\frac{\delta x}{\delta t} \{ g_i'(x_f, t) - \hat{g}_i(x_f, t) \} \tag{2.38}
\]

For finite permeability values of \( K \) and \( \Delta = 0.5 \), equations 2.37 and 2.38 can be subtracted from each other and rearranged to get

\[
\left( 1 + \frac{1}{6K} \frac{\delta x}{\delta t} \right) g_i'(x_f, t) = \hat{g}_i(x_e, t) + \frac{1}{6K} \frac{\delta x}{\delta t} \hat{g}_i(x_f, t) \tag{2.39}
\]

Now let us define a parameter, \( P = \frac{1}{6K} \frac{\delta x}{\delta t} \). Then equation 2.39 becomes,

\[
g_i'(x_f, t) = \frac{1}{1 + P} \hat{g}_i(x_e, t) + \frac{P}{1 + P} \hat{g}_i(x_f, t) \tag{2.40}
\]

Substituting equation 2.40 into equation 2.37 gives,
\[ g_i'(x_e, t) = \frac{P}{1+P} \hat{g}_i(x_e, t) + \frac{1}{1+P} \hat{g}_i(x_f, t) \] (2.41)

Equations 2.40 and 2.41 therefore describe the particle distribution functions across the membrane, \( g_i'(x_e, t) \) and \( g_i'(x_f, t) \), at the end of the streaming step for finite permeability values of \( K \) and the assumption of \( \Delta = 0.5 \). For the more general case with variable \( \Delta \) at each lattice link, the particle distribution functions \( g_i'(x_e, t) \) and \( g_i'(x_f, t) \) are determined by directly solving equations 2.35 and 2.36.

For the special case of infinite permeability, \( K \to \infty \) and \( \Delta = 0.5 \), equation 2.38 reduces to

\[ -g_i'(x_f, t) - \hat{g}_i(x_f, t) + g_i'(x_e, t) - \hat{g}_i(x_f, t) = 0 \] (2.42)

Coupling equations 2.37 and 2.42 yields

\[ g_i'(x_f, t) = \hat{g}_i(x_e, t) \] (2.43)
\[ g_i'(x_e, t) = \hat{g}_i(x_f, t) \] (2.44)

Equations 2.43 and 2.44 imply that after the collision step of the LBM algorithm, the particle distribution function \( \hat{g}_i \) crosses the membrane unaltered during the streaming step for permeability \( K \to \infty \) and \( \Delta = 0.5 \).

### 2.2.3 Parallelization of Numerical Scheme

In order to investigate how cell membrane permeability and variations in intracellular and extracellular diffusion coefficients affect the diffusion-weighted signal, it is necessary to have a spatial scale small enough to refine the intracellular and extracellular space and distinguish magnetization gradients within each. Considering the small dimensions of skeletal muscle fiber (\( \sim 80 \mu m \) in diameter) and relatively large size of a DTI voxel (\( \sim 1 \text{ mm}^3 \)) fully simulating in two dimensions just one voxel would be a very large problem (\( 10^6 \to 10^8 \) nodes). Though it is believed that the hierarchical nature of muscle can be exploited to reduce the size of this problem, it is still necessary to develop an efficient computational algorithm to solve this problem.

To do this, a parallelization scheme is introduced. Parallelization breaks
up the domain into multiple sections, which are solved concurrently. Each section is assigned as a separate process, which in turn is assigned its own independent core so it can run in parallel with the other processes. Only one process is assigned to each core. To maximize parallel computational efficiency two quantities must be minimized, the number of different processes each individual process must communicate with, and the amount of information passed between each process. The implemented model focused on minimizing the number of processes each individual processes must talk to while holding the amount of data passed to be constant. It is recognized that this method will lead to a computational penalty for simulations using large number of cores, however, for the relatively small number of cores used (≤ 8) the penalty is believed to not be severe.

In the presented model, the 2D domain is partitioned into strips and each strip is assigned to a process, which in turn is assigned to its own core. Each core solves one time step of the LBM algorithm, swapping boundary information with adjacent strips every time step. The two strips at the edges of the domain also swap boundary information. The strips are oriented lengthwise in the direction of the diffusion gradient. This allows the edge strips to swap information with each other using the periodic boundary condition. Each strip also swaps boundary information within itself on its shorter edges according to the modified boundary condition. This distributed parallelization method minimizes the number of different processes with which each individual process needs to talk to (two other processes), however, the contact area between each strip is fixed for increasing numbers of processes. For large numbers of processors the parallelization scheme will need to be rewritten to also decrease the contact area of each process as well.

Based on this scheme, a parallel code was developed using Fortran 90 with a GCC v5.1.0 compiler and Open MPI v1.8.6. Simulations were run on a MacPro with 2 2.66GHz Quad-Core Intel Xeon processors, 16 GB of RAM and running OS X 10.10.5 (Yosemite). The code was run to investigate speedup due to parallelization. A single periodic cell with square packing was simulated with a domain length of 80 µm, a simulation time (TE) of 56 ms, δx was 0.8 µm, and δt was 40 µs. Time is shown in Figure 2.4. Simulation with 8 cores is 2.6x faster than with 2 cores (due to MPI implementation it is not possible to run the code with only one core). There is clearly a degradation in the measured speedup as the number of cores increases, which will need
to be investigated before larger simulation sizes are attempted.

![Figure 2.4: Execution time vs number of cores used](image)

2.3 Two-Compartment Exchange Model

Karampinos et al. employed a composite medium model based on Kärger [36] that accounts for water diffusion in the space within the muscle fiber and the extracellular region [23]. It is assumed that there are two main compartments contributing to the diffusion properties of the composite medium: the intracellular and extracellular space. As with the numerical model, the effect of intracellular restrictions is accounted for by use of a diffusion coefficient lower than free water. The model takes an approach analogous to the lumped capacitance method of heat transfer. It is assumed that the intracellular regions can be modeled as simple lumped models, meaning the signal distribution within the cell is uniform. Returning to the Kärger model, the
time evolution of the intra- and extracellular compartments, $S_{in}$ and $S_{ex}$, respectively, is governed by the system of differential equations [36]

$$\frac{dS_{in}}{dt} = -4\pi^2 q^2 D_{in} S_{in} - \frac{1}{\tau_{in}} S_{in} + \frac{1}{\tau_{ex}} S_{ex} - \frac{1}{T_{2,in}} S_{in} \quad (2.45)$$

$$\frac{dS_{ex}}{dt} = -4\pi^2 q^2 D_{ex} S_{ex} - \frac{1}{\tau_{ex}} S_{ex} + \frac{1}{\tau_{in}} S_{in} - \frac{1}{T_{2,ex}} S_{ex} \quad (2.46)$$

where $q = (\gamma/2\pi)\delta g$ and $\gamma$ is the gyromagnetic ratio of hydrogen, $g$ is the gradient amplitude and $\delta$ is the duration of the applied gradient. $D_{in}^{app}$ and $D_{ex}^{app}$ are the apparent diffusion coefficients of the intra- and extracellular compartments respectively, $\tau_{in}$ and $\tau_{ex}$ are the mean residence times of spins in the two compartments and $T_{2,in}$ and $T_{2,ex}$ are the $T_2$ relaxation time of the two compartments.

The model assumes equal spin distribution at $t=0$ which leads to the initial conditions:

$$S_{in}(t = 0) = \nu_{in} \quad (2.47)$$

$$S_{ex}(t = 0) = \nu_{ex} \quad (2.48)$$

$$\frac{1}{\tau_{in}} S_{in}(t = 0) = \frac{1}{\tau_{ex}} S_{ex}(t = 0) \quad (2.49)$$

where $\nu_{in}$ and $\nu_{ex}$ are the cell fractions of the two compartments such that $\nu_{in} + \nu_{ex} = 1$. Using this formulation, the total signal attenuation of the system can be expressed as the linear superposition of the solutions to the two compartments:

$$S(q, t) = S_{in}(q, t) + S_{ex}(q, t) \quad (2.50)$$

This system of ODEs has a closed-form solution:

$$S(q, t) = \nu_{in} \exp(-4\pi^2 q^2 t^2 D_{in}') + \nu_{ex}' \exp(-4\pi^2 q^2 t^2 D_{ex}') \quad (2.51)$$

where $\nu'$ and $D'$ represent modified volume fractions and diffusion coefficients as defined in Karampinos et al. [23].
Figure 3.1: Skeletal muscle in a male mouse. Shown is a stained cross-section of a lumbar muscle [37] The diameter of each fiber is approximately 50 microns

Diffusion Tensor Imaging has a practical spatial resolution limit of \(~1 \text{ mm}^3\) due to technological limitations. Below this spatial scale, all structural information which influences the diffusion-weighted signal contributes to the apparent diffusion coefficient. To investigate how permeability of sarcolemma membrane, as well as other microstructural features of muscle cells such as ellipticity and cell packing arrangement, affect the measured diffusion-weighted signal, it is necessary to have a spatial resolution sufficient to resolve
Figure 3.2: Periodic muscle fiber model consisting of infinitely long cylindrical muscle fibers contained by a semi-permeable sarcolemma membrane and surrounded by the endomysium.

not only individual muscle cells but also magnetization gradients within and surrounding these cells. Myocytes have typical diameters of 10 - 100 µm, requiring a spatial resolution on the order of 1 micron. As mentioned, to fully simulate just one voxel would be a very large computational problem (>10^6 nodes). However, by taking advantage of the highly hierarchical organization and long range order of skeletal muscle, it is possible to probe microstructure at sub-voxel levels using periodic computational models. By modeling just a few myocytes and applying periodic boundary conditions, it is possible to simulate the underlying physics in the central section of a bundle of myocytes. This is a much less computationally expensive approach.

The model proposed here consists of intra- and extracellular regions. The intracellular region represents the myocyte. Each myocyte is made up of an array of hundreds of parallel myofibrils as well as a network of tubules, mitochondria, and lipid inclusions distributed throughout the cell. The extracellular endomysium region is inhabited by a collagen network. Both of these regions have subcellular restriction to diffusion, however, such restrictions cannot be modeled at the current spatial scale. Instead they are accounted for through the use of reduced diffusion coefficients \((D_{in} \text{ and } D_{ex})\) which are representations of the effective diffusion coefficients of the two regions due to
subcellular restrictions to diffusion.

We adopt here the model of myocytes consisting of arrays of infinitely long cylinders with elliptical cross-sections [38] and extend it to account for various packing arrangements and finite sarcolemma permeability. The length of the muscle cell is much longer than the cross-sectional diameter, which implies that under fairly general conditions, the diffusion along the length of the cell is simply the summation of the intra- and extracellular diffusion coefficients weighted by their respective volume fractions.

\[ D_{axial} = \nu_{in}D_{in} + \nu_{ex}D_{ex} \]  

This enables the reduction of the problem to that of diffusion on the two dimensional cross-sectional plane. Utilizing periodic (and appropriately modified periodic) boundary conditions allows the modeling of the domain for various packing arrangements. The myocyte is modeled as an elliptic cell, with a special case when the major and minor diameters are equal, whereby the cell reduces to a circular disk. Elliptic ratios of 0.4 to 1.0 were investigated as well as cell inclusion fractions from 0.4 to 0.86.

3.1 Periodic Square Array

The periodic square array is the result of replicating a cell by translating it in the x and y directions. This model is the simplest packing arrangement possible and is useful to investigate the accuracy of the periodic and modified periodic boundary conditions. Square packing has limitations in that it has a maximum cell inclusion fraction of 0.7854. Figure 3.3 shows the simulated unit cell for periodic square packing of a circular disk. Elliptic cross-sectional cells were also simulated.

3.2 Periodic Hexagonal Array

Periodic hexagonal packing is the densest possible packing arrangement for circular disks with a maximum cell density of 0.9069. Figure 3.4 shows the simulated unit cell used for this packing arrangement. In comparison with a square packing pattern, hexagonal packing has a more uniform median
Figure 3.3: Schematic of unit cell for periodic square packing of a circular disk. The red domain represents the intracellular region and the blue domain represents the extracellular domain.

Figure 3.4: Schematic of unit cell for periodic hexagonal packing of a circular disk. The red domain represents the intracellular region and the blue domain represents the extracellular domain.
distance between cells compared with the large concentrations of extracellular region which develop in the corners of the unit cell in square packing. Such uniform distance between cells more closely mimics histological images of skeletal muscle cells (Figure 3.1).

3.3 Randomly Packed Array

As Figure 3.1 shows, skeletal muscle does not consist of a perfectly periodic array of muscle fibers; the muscle fibers feature cross-sections with rounded polygonal shapes which are randomly packed together. A random packing algorithm was developed to simulate more realistic muscle structure in 2D. This algorithm begins with a sparsely packed periodic array and then proceeds to move each cell in a random direction until it overlaps another cell. In this way the originally periodic array is perturbed, or “jiggled”, out of its original ordered array. This perturbation is performed many times with additional cells added anytime there is room for a cell in the corners of the domain. Cells are added because the original domain is sparsely packed and adding cells allows an increase in cell fraction. The domain begins sparsely packed because it allows the cells to move without becoming immediately jammed, as would happen if the perturbations happened for a densely packed system. After the system has been fully perturbed, cells are added to any open spaces that have developed due to jamming of cells. This is done because such holes do not exist in skeletal muscle and are an artifact of the packing method.

Unlike the periodic arrays, it is not possible to create a unit cell of randomly packed domain, instead, a larger domain is used as a pseudo-unit cell by applying periodic boundary conditions to the domain. Solving this problem results in a solution where the pseudo-periodic nature of the domain effects the edges of the domain but, if the domain is large enough, the periodic boundary effects will not reach the middle of the domain. This is because diffusion is only measured over a finite diffusion time, so if the domain is large enough the geometric effects of diffusion at the edge of the domain will not have time to propagate to the center of the domain and affect the signal there. Using this independent center region, a signal can be measured which accurately represent the expected signal from an infinite randomly packed domain. Figures 3.5 and 3.6 show two random packing configurations for
circular and elliptic disks, respectively.

Figure 3.5: Randomly packed domain of circular disk that have been undergone 100 perturbations

Figure 3.6: Randomly packed domain of elliptic disk (ellipticity ratio of 0.7) that have been undergone 100 perturbations
CHAPTER 4

LATTICE BOLTZMANN METHOD
RESULTS

4.1 Numerical Convergence and Stability of Lattice Boltzmann Method

4.1.1 Homogeneous domain

The magnetization signal evolves according to equations 2.5 and 2.6. These equations were simulated with the Lattice Boltzmann scheme in a homogeneous periodic domain using a PGSE-finite pulse sequence [39] with TE = 100 ms, Δ = TE/2 ms and δ = Δ/2. Two different b-values were used, b = 1 s mm\(^{-2}\) and 1000 s mm\(^{-2}\). The domain size was 80 µm x 80 µm. The relaxation time was held constant at τ = 0.875, while the node spacing and time step was changed according to equation 2.20 in order to maintain this value. The remaining intrinsic parameters of the domain were assumed to be \(T_2 = 110\) ms and D = 2.0 µm\(^2\) ms\(^{-1}\). The apparent diffusion coefficient (ADC) was calculated by averaging the signal simulated over the domain and inputting this value into equation 2.12.

Figures 4.2 and 4.1 are plots of the relative error in the simulated ADC (expressed as \(\frac{ADC-D}{D}\)) with respect to time step and grid size, δt and δx, respectively. As Figure 4.2 indicates, error convergence is second order with respect to time, while according to Figure 4.1, error convergence is fourth order with respect to space. Recall that δx and δt are not varied independently but changed so that τ is constant, which implies that δx\(^2\) ~ δt and so second order convergence in time will be fourth order in space. One can also see that the b-value has a large effect on error, with a larger b-value (1000 s mm\(^{-2}\)) yielding an error several orders of magnitude larger than when a small b-value (1 s mm\(^{-2}\)) is used. As Xu et al. observed [26], this increase in error is due to the increased gradient size, resulting in larger spatial gradients.
Figure 4.1: Relative Error in ADC vs time step for $b = 1$ s mm$^{-2}$ and $b = 1000$ s mm$^{-2}$. Dashed lines represent quadratic fits to the data.

Figure 4.2: Relative Error in ADC vs spatial resolution for $b = 1$ s mm$^{-2}$ and $b = 1000$ s mm$^{-2}$. Dashed lines represent quartic fits to the data.
The effect of pulse timing parameters was also investigated. A PGSE-finite pulse was utilized with TE ranging from 4 to 500 ms. A 2-D homogeneous domain of 80 µm x 80 µm was used with δx = 0.4 µm, δt = 10 µs, and τ = 0.875. Four different b-values of 1, 10, 100, and 1000 s mm\(^{-1}\) were investigated. Results of the relative error in the ADC compared with the actual diffusion coefficient are presented in Figure 4.3. It can be seen that error decreases as TE increases. The results shown are for constant b-value, which for a PGSE pulse is \(b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)\). For constant \(b\) as TE increases \(\Delta\) also increases (\(\Delta = TE/2\)). This increase in \(\Delta\) causes a related decrease in the gradient strength (\(G\)). It is believed that the observed decrease in error is due to the decrease in the gradient strength that occurs from the correlated increase in \(\Delta\). Lower gradient values relate to lower relative error [26]. This is shown in Figure 4.4, which shows a linear relationship between the relative error in ADC and b-value where the only parameter varied is the gradient strength.

Figure 4.3: Relative Error in ADC vs TE (seconds) for different b-values.
Figure 4.4: Relative Error in ADC vs b-value (s mm$^{-2}$) for various TE. Simulation was of a 2-D homogeneous domain of 80 µm x 80 µm with $\delta x = 0.4$ µm, $\delta t = 10$ µs, $\tau = 0.875$. A PGSE-finite pulse sequence was used.

Figure 4.5: Diagram of simulation geometry depicting the 1x1 and 7x7 square domains. Simulations were also performed for a 3x3 domain.
4.1.2 Verification of Periodic Boundary Condition

To verify the accuracy of the modified periodic boundary condition, simulations were run with increasing domain size, all encompassing the same periodic array of cylinders. Simulations were performed for a single unit cell, as well as a 3x3 and 7x7 array of cells situated within a square extracellular domain. The signal in the central unit cell of the 3x3 and 7x7 simulations (given as $\ln(S/S_0)$) was compared with the signal from the entire domain, as well as the single unit cell simulation. For these simulations double precision real numbers were used to calculate the magnetization signal in the domain. Double precision real numbers have an accuracy of 15 decimal places. It is found that the different simulations are identical to the 14th decimal place (Table 4.1), which can be attributed to accumulated round off error. This result shows that the modified periodic boundary condition accurately replicates the periodic effects desired, allowing one unit cell to be sufficient to simulate periodic arrays.

<table>
<thead>
<tr>
<th>Total Cells</th>
<th>Simulated Cells</th>
<th>$\ln\left(\frac{S}{S_0}\right)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x1</td>
<td>1x1</td>
<td>-0.176889150221239</td>
</tr>
<tr>
<td>3x3</td>
<td>1x1</td>
<td>-0.176889150221239</td>
</tr>
<tr>
<td>3x3</td>
<td>3x3</td>
<td>-0.176889150221246</td>
</tr>
<tr>
<td>7x7</td>
<td>1x1</td>
<td>-0.176889150221239</td>
</tr>
<tr>
<td>7x7</td>
<td>7x7</td>
<td>-0.176889150221266</td>
</tr>
</tbody>
</table>

4.2 Comparison with Analytical Results

4.2.1 Periodic Square Array of Cylinder with Infinite Membrane Permeability

Convergence of the LBM model was also checked against the analytical solution for a square array of cylinders with infinite permeability. The asymptotic solution of the thermal diffusion equation for perfectly conducting cylinders was derived analytically by Perrins [40]. Due to the analogy between heat
transfer and species diffusion, the apparent diffusion coefficient of cylinders with perfectly permeable membranes and sufficiently small cell fraction is found to be:

\[
\text{ADC}(\Delta \to \infty) = D_{\text{out}} \left[ 1 - \frac{2f}{T + f - \frac{0.305827f^4T}{T^2 - 1.402958f^8} - \frac{0.013362f^8}{T}} \right]
\]  \quad (4.1)

where \( T = \left( 1 + \frac{D_{\text{in}}}{D_{\text{out}}} \right) / \left( 1 - \frac{D_{\text{in}}}{D_{\text{out}}} \right) \) and \( f \) is the cell fraction. The solution given above is only accurate given certain values of \( T \) and \( f \). For our purposes, comparisons will be made for \( f \leq 0.52 \) and \( T < 2 \), in which case, the analytical solution is accurate to four decimal places.

Two PGSE-finite pulses were used, TE = 100 and 200 ms. The investigated domain contained a 60 \( \mu \)m diameter cylinder within an 80 \( \mu \)m x 80 \( \mu \)m periodic domain, which is representative of a single muscle fiber. The diffusion coefficients were \( D_{\text{in}} = 1.5 \mu m^2 \text{ms}^{-1} \) and \( D_{\text{ex}} = 2.0 \mu m^2 \text{ms}^{-1} \). \( \delta x \) and \( \delta t \) were adjusted such that \( \tau = 0.875 \) for inside the cylinder and \( \tau = 0.78125 \) for outside the cylinder. Simulations were performed for b-values of 1, 500 and 1000 s mm\(^{-2}\). Results for these simulations are shown in Figures 4.6 and 4.7.

As can be seen in Figures 4.6 and 4.7, convergence of the solution is dependent on both TE and b-value. For a given TE and b-value, the solution converges to a value that is offset by some amount from the analytical solution. Larger b-values cause the converged upon value to decrease, while longer TE times cause the converged upon solution to approach the analytical solution. Longer TE times mean longer \( \Delta \) values (\( \Delta = TE/2 \)). The analytic solution used is only valid for \( \Delta \to \infty \) and so, as \( \Delta \) increases, the offset error decreases. Figure 4.8 illustrates this for simulations using \( b = 1 \) and 1000 s mm\(^{-2}\).

Figures 4.6 and 4.7 also show that, as with the homogeneous domain, simulations with smaller b-values have more rapid convergence than large b-values. Larger b-values correspond to larger applied gradients, leading to higher spatial resolution being needed to fully resolve these gradients.

Figure 4.9 shows results for multiple cell fractions. For these simulations the domain area was held constant while the size of the cylinder was varied. Simulations were performed for TE = 100 ms with b = 1, 100, and 1000 s
Figure 4.6: Relative Error in ADC vs time step for a periodic array of square cylinders. Positive relative error relates to an ADC that is larger than the analytical solution.

Figure 4.7: Relative Error in ADC vs spatial resolution for a periodic array of square cylinders.
Figure 4.8: Relative error in ADC vs TE (seconds). As TE increases, ADC approaches the analytical solution. Simulation parameters were the same as for Figures 4.6 and 4.7.

Figure 4.9: Relative error in ADC vs cell fraction.
mm$^{-2}$ and $\text{TE} = 500 \ \text{ms}$ with $b = 1 \ \text{s mm}^{-2}$. As previously discussed, the error in the simulation with $\text{TE} = 500 \ \text{ms}$ is lower than the simulation with $\text{TE} = 100 \ \text{ms}$ and a similar $b$-value. Error increases as cell fraction increases, for smaller cell fractions the solution approaches that of a homogeneous domain, which has less spatial variation and consequently less spatial error.

### 4.2.2 Cylinder with Impermeable Boundary

The model was compared with the analytical solution for a cylinder surrounded by an impermeable membrane. The analytical solution is given in [41] as:

$$\frac{S}{S_0}(q, \Delta \to \infty) = \frac{[2J_1(2\pi qR)]^2}{(2\pi qR)^2} \quad (4.2)$$

where $q = (\gamma/2\pi)\delta g$.

![Figure 4.10: ln(S/S₀) vs b-value (s mm$^{-2}$) for impermeable membrane. The simulated solution (solid squares) begins to diverge from the analytical solution (solid line) at higher b-values, however, the corresponding b-values are not of practical interest.](image)
The domain used for this simulation was an 8.8 µm diameter cylinder with an impermeable boundary. Only the cylinder was simulated (i.e. only the intracellular domain) with \( D = 2.0 \, \mu m^2 \, ms^{-1} \) and \( T_2 = 110 \, ms \). This setup was used because the analytical solution assumes \( D\Delta/R^2 \gg 1 \) and \( \delta \to 0 \) while \( g \to \infty \) (the short-gradient-approximation). A PGSE pulse was used with timing parameters \( TE = 200 \, ms \), \( \Delta = 100 \, ms \) and \( \delta = 0.3 \, ms \). The simulations were run with \( \delta t = 10 \, \mu s \) and \( \delta x = 0.4 \, \mu m \). The simulated result, as well as the analytical solution, is shown in Figure 4.10.

### 4.3 Simulations of Periodic Arrays

#### 4.3.1 Square Array of Cylinders with Permeable Membrane

Simulations were performed on an 80 µm x 80 µm periodic domain containing a 76 µm diameter cylinder for a range of permeability values (K). The employed \( \delta t \) was 10 µs and \( \delta x \) was 0.4 µm. A PGSE pulse was used with \( TE = 56 \, ms \), \( \Delta = 40 \, ms \) and \( \delta = 16 \, ms \).

Four different cases were investigated with input parameters listed in Table 4.2. For each case, seven different permeability values were employed: \( K = 0, 1, 10, 100, 1000, 10000 \) and \( \infty \) µm s\(^{-1} \). Simulations were performed over a range of b-values and a linear curve fit was used to determine the ADC from equation 2.12.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_{in} ) (µm(^2) s(^{-1}))</td>
<td>2.0</td>
<td>2.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>( D_{ex} ) (µm(^2) s(^{-1}))</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>( T_{2, in} ) (ms)</td>
<td>110</td>
<td>30</td>
<td>110</td>
<td>30</td>
</tr>
<tr>
<td>( T_{2, ex} ) (ms)</td>
<td>110</td>
<td>110</td>
<td>110</td>
<td>110</td>
</tr>
</tbody>
</table>

The results of the simulation outcome (ADC) are shown in Table 4.3, while Figure 4.11 depicts the resulting ln\((S/S_0)\) for cases 1-4. For small K values, the differences in \( T_2 \) values for the intra- and extracellular regions do not appear to have much effect, however, as K increases, the results begin to diverge. Increasing the permeability results in an increased intermixing
Figure 4.11: $\ln(S/S_0)$ vs b-value (s mm$^{-2}$) for multiple circular disk configurations. Results for $K = 0, 1$ and $10$ $\mu$m s$^{-1}$ are too similar to be distinguished from each other.

The relationship between ADC and membrane permeability is shown in Figure 4.12.
Table 4.3: ADCs for various permeability values (K)

<table>
<thead>
<tr>
<th>K (µm s⁻¹)</th>
<th>ADC (µm² s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
</tr>
<tr>
<td>0</td>
<td>1.39004</td>
</tr>
<tr>
<td>1</td>
<td>1.39060</td>
</tr>
<tr>
<td>10</td>
<td>1.39557</td>
</tr>
<tr>
<td>100</td>
<td>1.44133</td>
</tr>
<tr>
<td>1000</td>
<td>1.68475</td>
</tr>
<tr>
<td>10000</td>
<td>1.94061</td>
</tr>
<tr>
<td>∞</td>
<td>2.00109</td>
</tr>
</tbody>
</table>

Figure 4.12: ADC vs Membrane Permeability (log scale). Notice how the results for case 1 and 2, as well as for case 3 and 4, are similar at low K values but diverge as membrane permeability increases.
4.3.2 Periodic Square Array of Elliptical Cylinders with Permeable Membrane

Elliptical cylinders with variable permeabilities were investigated. An 80 µm x 80 µm periodic domain was employed, containing an ellipse with a major-axis diameter of 76 µm and an ellipticity ratio of 0.7. δt was 10 µs and δx was 0.4 µm. A PGSE pulse was used with TE = 56 ms, ∆ = 40 ms and δ = 16 ms. Simulation parameters were $D_{in} = 1.5$ µm s$^{-1}$, $D_{out} = 2.0$ µm s$^{-1}$, and $T_2 = 110$ ms. Simulations were performed with the gradient aligned perpendicular to the major-axis (Case A) and parallel to the major-axis (Case B). Additionally, a simulation of a circular cylinder with a diameter 63.56 µm within an 80 µm x 80 µm periodic domain was performed (Case C), this case had the same cell fraction as Cases A and B.

![Figure 4.13: ln(S/S₀) vs b-value (s mm$^{-2}$) for elliptic disk configuration.](image)

Results for $K = 0, 1$ and 10 µm s$^{-1}$ are too similar to be distinguished from each other.

Figure 4.13a and 4.13b show the results of Cases A and B respectively. It can be seen that there is a wider distribution of solutions for the gradient applied perpendicular to the major-axis (Case A) than when the gradient is applied parallel to the major-axis (Case B). The difference between the computed ADC for Case A and B (Figure 4.14) is large for small $K$ values and becomes negligible as $K$ increases. Since diffusion is only measured in the direction of the gradient, Case A introduces a larger cross-sectional...
barrier to diffusion than Case B, and so the ADC is lower for Case A when permeability is low. ADC increases with permeability and this is consistent with predictions by Harkins et al. [42]. For low permeability values, Case C is between Cases A and B. The domain cross-section perpendicular to the gradient in Case C is between the cross-sections in Cases A and B suggesting that at low permeabilities this cross-section is affecting ADC. However, as permeability increases, all three cases appear to converge upon a single value. Since all three cases have the same cell fraction it appears that at large permeabilities ADC is more influenced by the cell fraction than cellular cross-section.

Figure 4.14: LBM results expressed as ADC (solid symbols) vs Membrane Permeability for Case A, B and C (log scale). The solid lines are numerical fits.

4.4 Randomly Packed Domain

The LBM scheme was also used to solve the 2D Bloch-Torrey equation in a randomly packed domain. A PGSE pulse with timing parameters of TE =
56 ms, $\Delta = 40$ ms and $\delta = 16$ ms was used. The simulation involved a 160 x 136 $\mu m^2$ domain with $\delta x = 1.6 \mu m$ and $\delta t = 40 \mu s$, and cells with ellipticity ratios of 0.7 packed randomly, with a cell inclusion fraction of 0.6398. The field map of the magnetization signal for an applied b-value of 572 s/mm$^2$ is shown in Figure 4.15. The ADC was calculated by averaging the signal over central sections of the domain of varying size in order to study the effect of domain truncation. Results are shown in Table 4.4, which indicates ADC varies by less than 1%. Consequently, the simulation domain can be decreased to 1/3 the original size without penalty.

Table 4.4: Calculated ADC from using only signal in center of domain

<table>
<thead>
<tr>
<th>Middle Fraction Analyzed</th>
<th>ADC ($\mu m^2$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3</td>
<td>1.4111</td>
</tr>
<tr>
<td>1/2</td>
<td>1.4085</td>
</tr>
<tr>
<td>2/3</td>
<td>1.4011</td>
</tr>
<tr>
<td>1</td>
<td>1.4116</td>
</tr>
</tbody>
</table>

Figure 4.15: Field map of magnetization signal for applied b-value of 572 s/mm$^2$
4.5 Comparison of LBM Predictions with Experimental Results

The well-established observation that the DTI tensor is anisotropic in muscle [43] has bolstered the hypothesis that this anisotropy is a manifestation of microstructural anisotropy on the cellular level. Here the LBM model is used to re-interpret prior DTI results obtained in vivo on a cohort of older obese women following exercise intervention over a four-month period [44]. For purpose of completeness, a description of the experiment is given here. A total of nineteen obese, elderly women (BMI: 33 ± 3, Age: 65 ± 6 years) were randomly separated into two groups, one of which involved exercise-based (EX) intervention combining endurance and strength training [44]. An imaging volume around the midpoint of the left thigh of the EX group subjects was scanned both pre- and post-intervention using a 3T Siemens Trio scanner. The DTI acquisition consisted of a single-shot twice-refocused spin-echo EPI sequence with TR/TE = 3000/71 ms, seven axial slices (10mm), 10 averages, 30 directions and a b-value of 550 s mm\(^{-2}\).

The LBM was employed with similar pulse timing parameters in a square periodic array with cell ellipticity of 0.7. The cell has a major-axis length of 78 µm. Intra- and extra-cellular diffusion coefficients are 1.6 and 2.0 µm\(^2\) ms\(^{-1}\) respectively with T\(_2\) relaxation time of 110 ms over the entire domain and the sarcolemma permeability varying in the range 10-90 µm s\(^{-1}\). A PGSE pulse was utilized with TE = 56 ms, ∆ = 40 ms, δ = 16 ms and b = 500 s mm\(^{-1}\). The gradient direction was applied parallel to the major-axis direction. Simulation resolution was δx = 0.8 µm and δt = 40 µs.

Table 4.5: Experimental DTI values with p-values. The units of ADC are µm\(^2\) s\(^{-1}\). * denotes statistical relevance.
Figure 4.16: Simulated Fractional Anisotropy (FA), Planar Index (CP) and Ellipsoid Eccentricity (e) vs. membrane permeability

An ROI was placed on all seven slices of the vastus medialis muscle, the ROI-averaged apparent diffusion coefficient (ADC), and three non-dimensional DTI measures, the fractional anisotropy (FA), planar index (CP), and ellipsoid eccentricity (e) were computed from the three DTI eigenvalues $\lambda_1$, $\lambda_2$, $\lambda_3$. Comparisons between pre- and post-intervention measures were performed for the EX group with a Students t-test using unequal variances and a one-tailed distribution. The results and p-values are tabulated in Table 4.5, which indicates that all dimensionless measures, FA, CP and e decrease significantly with exercise, while there is no significant change in ADC. As indicated in Figures 4.16 and 4.17, the numerical simulation results agree qualitatively with the experimental evidence: all non-dimensional ADI measures decrease with increasing permeability.

Despite the idealized (elliptical) cross-sectional geometry of the myocyte, the numerical results based on a continuum LBM model can account for the
Figure 4.17: Simulated DTI eigenvalues and associated ADC vs. membrane permeability of the muscle fiber. $\lambda_1$ is defined by the volume-averaged value of the intra- and extra-cellular diffusion coefficients, and it remains constant since the myocyte cross-section is constant. Both $\lambda_2$ and $\lambda_3$ increase with membrane permeability.

decrease of the dimensionless DTI measures with increasing scarcolemma permeability. The decrease of these measures corresponds to decreasing DTI tensor anisotropy, which is plausible given that the myocyte membrane becomes more permeable to water. No attempt was made to match additional biophysical parameters, so the numerical results agree with the experiment only in terms of trends. As corroborated by animal studies (AQP4 measurements [15]), these trends can become permanent and can be putatively linked to the effect of physical exercise. Our results bolster the view that an economical model incorporating intracellular barriers can increase the specificity of human muscle MR imaging, especially in older obese adults.
4.6 Discussion

The simulations presented in this section give evidence that the proposed Lattice Boltzmann Method model is an accurate method to solve the Bloch-Torrey equation in restricted diffusion domains. Solving the LBM model over a homogeneous domain showed that the model converges to the exact solution. The periodic and modified periodic boundary conditions are also found to be accurate in the sense that they reproduce the result of simulating a larger domain.

Comparison with the LBM solution for completely permeable cylinders arranged in a square packing array demonstrated converged results with less than 0.5 % difference from the analytical solution. Additionally, these differences were investigated as a function of simulation time (TE) and were found to decrease substantially as TE increased. This further supports the accuracy of the model because the analytical model is true in the limit of $\Delta \to \infty$ and so, at shorter TE times, it is only a good approximation. That the LBM model approaches the analytical solution in the long time limit suggests that at shorter TE the LBM model may, in fact, be a more accurate solution than that given by the analytical solution. The LBM results were also compared with the analytical solution for varying cell fractions. It was found that it approaches the analytical solution for lower cell fractions, and the difference between the analytical solution and the LBM results is always less that 0.5 %.

The LBM solution was also compared with the analytical solution for diffusion within an impermeable disk. The simulation closely matches the analytical solution except for high b-values. The range of b-values at which the two models start to diverge are not relevant in practice since these high values correspond with impractically high gradient strengths. These results imply that the LBM model is able to accurately simulate restricted diffusion.

The LBM model was then used to investigate the effect of permeability on diffusion-weighted signal. There was found to be a linear relationship between $\ln(S/S_0)$ and b-value which can be used to determine ADC. Investigating the effect of ellipticity on permeable cells also yielded a linear relationship between $\ln(S/S_0)$ and b-value, however, the difference between the calculated ADC for low and high permeability is found to be dependent on the direction of the applied gradient. Finally, solving over a large, randomly
packed domain shows the ability of the LBM model to simulate domains in a randomly packed configuration. It is also shown that the average value of the signal in this random packing configuration is independent of the section of the domain measured, giving support to the domain actually being randomly packed. The ability to solve over such a domain shows that the LBM model is capable of solving geometry configurations that more closely approximate muscle anatomy.

This LBM model allows the solution of diffusion within skeletal muscle. This problem does not have an analytical solution. A number of researchers have proposed simplified solutions to this problem which rely on a number of assumptions. With our more complete validated model we will now be able to examine these assumptions to find if they are accurate.

Our results were obtained for a number of assumptions which, although plausible, are not derived from the experiments on the women cohort that motivated this study. One assumption made is of the strength of the impermeable membrane barrier between the intra- and extracellular regions. Figures 4.12 and 4.14 suggest that this membrane affects the ADC value for permeabilities below 10 $\mu$m/s. Literature reports permeability values of 13 $\mu$m/s [25] and a range of 23 - 30 $\mu$m/s [14].
CHAPTER 5

COMPARISON OF LATTICE BOLTZMANN METHOD AND TWO-COMPARTMENT EXCHANGE MODELS

Comparisons were made between the two proposed models, the Lattice Boltzmann Method (LBM) model and the two-compartment exchange (2CE) model. The latter has only been compared with a Monte Carlo model [25] of the Bloch-Torrey equation in axons in the white matter of the brain. For our comparisons, a Pulsed Gradient Spin Echo (PGSE) pulse was employed with extrinsic parameters: TE = 56 ms, Δ = 40 ms, δ = 16 ms and b-value = 572 s/mm². The diffusion coefficients of the intracellular and extracellular domains were assumed to be 1.6 µm²/ms and 2.0 µm²/ms, respectively. The T₂-relaxation times of the intracellular and extracellular domains were taken as 32 ms and 110 ms respectively. The mean diameter was \( d_m = \frac{d_l + d_s}{2} = 80 \mu m \) (where \( d_l \) and \( d_s \) are the long and short diameters of the ellipse, respectively). The time step was 10 µs and the grid size was 0.5 µm. The cells were arranged in a periodic hexagonal packing array (as shown in Fig 3.3) and the simulation domain containing a single cell with periodic boundary conditions.

5.1 Variation in Membrane Permeability for Fixed Cell Faction and Ellipticity Ratio

Comparisons were made between the 2CE and LBM predictions for different values of the myocyte permeability (Figure 5.1). Simulations were performed for cross-sections with ellipticity ratios of 1.0 (circular disk) and 0.7. The membrane permeability was assumed to be 15 µm/s and the cell fraction was 0.711.

Figure 5.1 shows that the LBM model is more sensitive to variations in membrane permeability than the 2CE model. For the 0.7 ellipticity case, it can also be seen that the difference between the two models is smallest.
for $\lambda_3$ and largest for $\lambda_2$. Framing this observation geometrically, the $\lambda_3$ eigenvalue is the apparent diffusion coefficient in the direction of the shorter cell diameter, while $\lambda_2$ is the ADC in the direction of the longer cell diameter. As the staggered arrangement of Figure 3.4 implies, for elliptical cases $\lambda_3$ corresponds to the longest (tortuous) diffusion path in the continuous (extracellular) phase, compared to $\lambda_2$. Any increase in the membrane permeability affects the model used to compute $\lambda_3$ more strongly than $\lambda_2$. As such, $\lambda_3$ has a longer cell diameter laying perpendicular to the measured diffusion direction, thus causing a larger obstruction to diffusion due to the semi-permeable membrane, whereas the $\lambda_2$ measurement has the least amount of obstruction in the direction of the applied gradient and subsequently a higher ADC.

The 2CE model can be thought of in analogous terms to the lumped capacitance model used in heat transfer. This model considers two compartments (intra- and extracellular regions) and then ”lumps” (homogenizes) the
magnetization field in each compartment with little concern for the actual geometry of the domain. The model does not account for how gradients naturally develop within the domain due to the different diffusion coefficients and $T_2$-relaxation times. Making the comparison to lumped capacitance heat transfer theory requires introducing the Biot number, which is defined as $Bi = hL_c/k$, where $h$ is the convective heat transfer coefficient, $L_c$ is the characteristic length and $k$ is the thermal conductivity. The Biot number is proportional to the characteristic length scale and lumped capacitance holds only for small Biot number. In the context of the Bloch-Torrey equation, the Biot number can be recast as $Bi_D = h_D L_c/D$, with $h_D$ representing an unknown parameter which characterizes diffusion between the intra- and extracellular domains, similar to the convective heat transfer coefficient, and $D$ being the diffusion coefficient. The characteristic length of this problem is the cell diameter that is parallel to the direction of the measured ADC. In the 0.7 ellipticity case, the characteristic length is larger and there is also greater difference between the LBM and 2CE results, suggesting that for larger characteristic lengths this lumped capacitance approach begins to break down similarly to how it breaks down in heat transfer for increasing characteristic lengths.

5.2 Variation of Cellular Ellipticity Ratio for Fixed Cell Fraction

The effect of the cellular ellipticity ratio was also considered (Figure 5.2 and 5.3). The ellipticity ratio is defined as the ratio of the shorter diameter to the longer diameter. Two different cell fraction values were considered, 0.711 and 0.818. The permeability of the cellular membrane was 15 $\mu$m/s.

Figures 5.2 and 5.3 show that there is a quantitative difference between the LBM and 2CE models which is greater for the 0.818 cell fraction than for the 0.711 cell fraction. This difference is relatively constant across the range of investigated ellipticities, increasing slightly for lower ellipticities. If this offset difference is taken into account (particularly with the 0.818 cell fraction wherein the offset is greatest), the two models appear to agree relatively well with each other. This suggests the the 2CE model handles the effect of ellipticity well and that differences in the two models arise more as
a function of cell fraction than ellipticity.

Figure 5.2: Comparison of DTI $\lambda_2$ and $\lambda_3$ eigenvalues vs ellipticity between 2CE and LBM models for cell fraction of 0.711.

Figure 5.3: Comparison of DTI $\lambda_2$ and $\lambda_3$ eigenvalues vs ellipticity between 2CE and LBM models for cell fraction of 0.818.
5.3 Parametric Study of Differences Between LBM and 2CE models

To determine how the LBM and 2CE models compare over a combination of parameters, the relative difference of the predicted $\lambda_2$ and $\lambda_3$ was plotted by varying both ellipticity ratio and membrane permeability for a fixed cell fraction. This was performed for cell fractions of 0.711, 0.818 and 0.860. Taken together, Figures 5.4, 5.5 and 5.6 show that the relative difference between the two models is heavily influenced by cell fraction over variations in both parameters. It can also be seen that the difference is more influenced by changes in ellipticity than by changes in permeability. Simulations with low permeability and low ellipticity ratios show the most difference. The interpretation is that, as the cross-sectional area increases, the difference between the two models increases. However, it can also be seen that for very low ellipticities there is also an increase in the differences between the two models.

![Figure 5.4: Relative difference between 2CE and LBM models for cell fraction of 0.711 and variations in ellipticity ratio and membrane permeability.](image)

(a) Relative difference in $\lambda_2$  (b) Relative difference in $\lambda_3$
5.4 Variations in Cell Fraction

Simulations of varying cell fractions were also performed and the differences between the two models are plotted in Figure 5.7. Two cellular ellipticity ratios were considered, 0.7 and 1.0. The membrane permeability was set at 15 $\mu$m/s and cell fraction variation between 0.6 and 0.86 was considered. Note that the maximum cell fraction attainable with hexagonal periodic packing is 0.9069.

Figure 5.7 shows that for lower cell fractions ($\lesssim 0.7$) the LBM and 2CE models qualitatively agree, though there is an offset difference (similar to
the results in Figures 5.2 and 5.3. The LBM model continues to decrease linearly as cell fraction increases, but, around a cell fraction of 0.7, the 2CE prediction exhibits a minimum point and begins to increase. At this point the two models are qualitatively different. It appears that for the current setup the two models are comparable for cell fractions up to 0.7. Skeletal muscle is made up of tightly packed myocytes which will generally have higher cell fractions than 0.7, which suggests the 2CE model is not suited for investigation of such phenomena. This does not mean that the 2CE model has no use. It is clear that there are particular ranges that the model is an accurate approximation of the full LBM simulation. Determining these ranges will yield insight to when the 2CE model can be used in place of a full simulation of the problem.

To determine what causes the change in the 2CE model it is noted that the 2CE model can be broken up into 4 different terms, $S_{in}$, $S_{ex}$, $S_{0,in}$, and $S_{0,ex}$. These terms represent the signal in the two different compartments

Figure 5.7: $\lambda_2$ and $\lambda_3$ Eigenvalues vs cell fraction ellipticity of 0.7 and 1.0 for both 2CE and LBM models.
(intra- and extracellular) calculated for an applied gradient \((S_{in} \text{ and } S_{ex})\), as well as with no applied gradient \((S_{0,in} \text{ and } S_{0,ex})\). These terms are combined via superposition in equation 2.50 to solve for the two signals \((S \text{ and } S_0)\) that are used to calculate the ADC averaged over the domain (equation 2.12). By investigating the 2CE model term by term and comparing these terms with the LBM model it is possible to identify which terms are similar with the LBM model and which terms are causes of the divergence between the two models.

Figures 5.8 and 5.9 show the four terms being investigated for both the 2CE and the LBM model. The terms are calculated for the LBM model by solving the entire domain and then averaging the intracellular and extracellular signals separately to obtain \(S_{in}\) and \(S_{ex}\). The 2CE terms are calculated using equation 2.51.

![Figures 5.8 and 5.9: S_{0,in} and S_{in} for both LBM and 2CE models over a range of cell fractions](image1)

![Figures 5.8 and 5.9: S_{0,ex} and S_{ex} for both LBM and 2CE models over a range of cell fractions](image2)

It is clear from Figures 5.8 and 5.9 that the qualitative deviation in the two models arises from the \(S_{ex}\) term. Further investigation of this term shows that it is a function of the extracellular exchange time \((\tau_{ex})\). \(\tau_{ex}\) is determined by the initial conditions (equations 2.47, 2.48, and 2.49). In these equations \(\tau_{in}\) is found from the equation [36]:

\[
\tau_{in} = \frac{(d_m/2)^2}{15D_{in}} + \frac{(d_m/2)^2}{3K} \tag{5.1}
\]

These four relations then cause \(\tau_{ex}\) to be defined as,
As the cell fraction \((\nu_{in})\) increases, the extracellular exchange time goes to zero, however, in the equation which defines the modified diffusion coefficient,

\[
D'_{in,ex} = \frac{1}{2} \left( D_{in}^{app} + D_{ex}^{app} + \frac{1}{4\pi^2 q^2} \left( \frac{1}{\tau_{in}} + \frac{1}{\tau_{ex}} + \frac{1}{T_{2,ex}} \right) \right)
\]

\[
\pm \frac{1}{2} \sqrt{ \left( D_{ex}^{app} - D_{in}^{app} + \frac{1}{4\pi^2 q^2} \left( \frac{1}{\tau_{ex}} - \frac{1}{\tau_{in}} + \frac{1}{T_{2,ex}} - \frac{1}{T_{2,ex}} \right) \right)^2 + \frac{1}{4\pi^2 q^4 \tau_{in} \tau_{ex}}} \]  

(5.3)

it is seen that the equation is dependent upon \(1/\tau_{ex}\) which diverges as the cell fraction approaches one. This causes the modified diffusion term, \(D_{ex}\), to become overly influenced by this exchange time and start to increase (note, this does not happen with the \(D_{in}\) term because the two terms of the equation cancel this effect). While it is true that the mean residence time in the extracellular region will approach zero as the cell fraction goes to one, it appears that the 2CE model over-amplifies this effect. The result is that there is a minimum point in the computed ADC which occurs when the decreasing mean residence time of the extracellular region becomes the dominate term in the solution.

One explanation of why the model is unable to accurately handle larger cell fractions is related to a geometrical interpretation. The two-compartment model works by approximating the domain as exactly that, two compartments. These compartments are assumed to be placed next to each other and that the relationship between the two can be thought of as the interaction of two independent values (again, it is illustrative to think of an analogy with lumped capacitance heat transfer). This works well for low cell fractions as there are large gaps between cells which can be approximated as separate compartments of extracellular space. As the cell fraction increases, however, these extracellular spaces start to look less like independent compartments and more like rings around the intracellular space. This causes a breakdown of the two-compartment model as it is not able to handle this nested rings setup. An interesting open question is how the model would compare with
square packing at high cell fractions, in this case, as the cell fraction increases, one does not end up with a nested rings geometry but rather retains separate compartments of intracellular and extracellular space. This study was not performed and also would be limited in its insight because the maximum cell fraction of a square array is 0.7854, which is only marginally above where the two model start to diverge from each other.

5.5 Discussion

Two different models of diffusion-weighted imaging of muscle cells were investigated. One model is the direct numerical solution of the governing PDE of diffusion imaging and the other is a simplified compartmental exchange model. The direct numerical model has been shown to give accurate solutions when compared with analytical solutions to simplified setups and, because it is a numerical solution of the governing physical laws, it is assumed to yield the correct answer to the investigated problem. The two-compartment model meanwhile makes a number of assumptions. These assumptions allow the model to be less computationally expensive than the direct numerical model, which makes the two-compartment model an attractive approach if it can be shown that the assumptions and simplifications made do not negatively effect the accuracy of the model.

It is seen that the 2CE model reasonably approximates the LBM model for changes in ellipticity and membrane permeability within physiologically relevant ranges. The 2CE model appears to be more accurate for smaller cellular cross-sections in the applied gradient direction, as the diameter increases, the difference between the two models grows as well (this partially effects the accuracy of highly elliptical simulations). It is also seen that the difference between the models is more sensitive to changes in ellipticity than permeability. What was not investigated was how changes in mean diameter affected the model. Finally, it is seen that the model is highly dependent on cell fraction. For cell fractions less than approximately 0.7 the model is qualitatively the same, however, above this threshold the two models diverge, rendering the 2CE model effectively useless in this range. It is shown that this divergence is due to the way in which the mean residence time of the extracellular region is calculated.
If a method of determining $\tau_{ex}$ which does not cause this blow up of the solution for larger cell fractions can be determined, then it may be possible that the agreement between the LBM and 2CE models seen at lower cell fractions can be exhibited at higher cell fractions. If the application of the 2CE model being explored is at a low enough cell fraction and with small enough cell diameters, it appears that the 2CE model is a reasonable substitute for direct numerical integration of the Bloch-Torrey equation. A key question here is what is “low enough”? As seen with the LBM model, it does not appear that there should be an inflection point in the calculated values as cell fraction increases. The ADC should continue to decrease as cell fraction increases. If it can be shown that in the region of interest, increase in the cell fraction does not lead to a minimum or continual increase of the ADC, then it is reasonable to believe the 2CE results will be moderately accurate, just as it is in the cases shown here for cell fractions below 0.7.
CHAPTER 6

CONCLUSION

This thesis reports a computational investigation of the effect of changes in muscle microstructure on diffusion-weighted MRI signal, involving a continuum model. A numerical scheme employing the Lattice Boltzmann Method (LBM) is developed to integrate the Bloch-Torrey equation, which is the governing PDE for the MRI signal evolution in space and time. The numerical scheme predicts the evolution of the signal in a heterogeneous domain consisting of multiple compartments separated by semi-permeable membranes. We consider a muscle model consisting of homogeneous extracellular and intracellular compartments, each with its own intrinsic diffusion coefficient representing the aggregate effect of diffusion barriers within each compartment. Both standard periodic and modified periodic boundary conditions are employed at the periphery of the computational domain. The modified periodic boundary condition is a special boundary conditions that accounts for the spatial dependence of the magnetic gradient across the domain. Additionally, an interfacial boundary condition which handles the effect of cellular membranes on diffusion is employed.

Three different geometric arrangements consisting of parallel cylinder arrays with elliptical cross-sections are used; periodic square packing, periodic hexagonal packing and random packing, all with ellipses aligned. Periodic square packing is the simplest packing arrangement and allows quantification of error in the simulation by comparison with analytical models. Hexagonal packing allows investigation of larger cell fractions, while random packing allows simulation of the cells which most closely approximates the microstructure of skeletal muscle.

In order to validate the numerical scheme, a number of self-consistency tests were performed. The LBM model was shown to converge at the rate predicted by truncation error analysis to the exact diffusion coefficient for a homogeneous domain as the time step and grid size was decreased. Addition-
ally, the modified periodic boundary condition was verified by showing that it provided the same result as simulating a larger domain and only measuring the inner section of the domain.

Different geometric arrangements were used to validate the LBM model against analytical solutions. Analytical solutions exist for conduction in an array of perfectly conducting cylinders. This is analogous to diffusion in the same array of cylinders with infinitely permeable boundaries. The LBM model was found to converge to the analytical solution with $\leq 1\%$ difference, which is consistent to truncation error estimates. It was also found that longer TE times provide a more accurate result, while increasing the cell fraction leads to more inaccuracies. The LBM predictions were also compared with the exact MRI signal in a cylinder surrounded by an impermeable membrane. Over a range of practically relevant b-values, the solution was found to be in good agreement with the analytical model. These comparisons with analytical models show that the LBM model accurately solves the Bloch-Torrey equation.

In order to study the effect of intrinsic (muscle) parameters, simulations were performed for various packing arrangements of identical cells with permeable membranes. A range of permeabilities were investigated for both square and hexagonal packing arrangements, and DTI experiments with multiple b-values were simulated to allow the calculation of the apparent diffusion coefficient (ADC). By exploring the relationship between the b-value and $\ln(S/S_0)$, it was found that a linear approximation fit the data well and no biexponential behavior was observed. A monotonic relationship between membrane permeability and ADC was observed. When different $T_2$ values were used for the intra- and extracellular compartments it was found that their effect was only discernible at large permeabilities. A simulation was also performed on a randomly packed domain of ellipses. By looking at how the measured ADC changed depending on what area of the domain was used to calculate it, it was found that the calculated ADC remained unaffected by the domain size, suggesting that the solution to a smaller section of a randomly packed domain is sufficient to provide an accurate approximation of the entire region.

The utility of any model is ultimately assessed by comparison with experiments. The well established observation that the DTI tensor is anisotropic in muscle has bolstered the hypothesis presented in [23] that this anisotropy is a
manifestation of microstructural anisotropy on the cellular level. Extending this work, our study considered variations in membrane permeability of the sarcolemma. Despite the idealized geometry of the myocyte, the numerical results based on the LBM scheme were found to be consistent with the experimentally observed decrease in several dimensionless DTI measures with increasing permeability, as reported in [10]. This decrease corresponds to decreasing DTI tensor anisotropy, which is plausible given experimental evidence that the myocyte membrane becomes more permeable to water with physical exercise.

The two-compartment exchange model (2CE) was compared with the LBM model over a range of parameters relevant to skeletal muscle physiology. The two models were compared over ranges of cellular ellipticity, membrane permeability and cell fraction. It was found that the two models were qualitatively similar when considering variations in ellipticity and permeability, but not in cell fraction. This difference in the models for changes in cell fraction suggest that the two-compartment exchange model is not sufficient to investigate diffusion-weighted imaging of skeletal muscle. We presented evidence that the 2CE model has a range of applicability over intrinsic parameter ranges that are not relevant to muscle physiology, but may be relevant to other applications.

The outcome of the work presented in this thesis is a verified numerical code which can simulate the diffusion-weighted MRI signal in a spatially periodic or randomly packed two-dimensional domain. The code can accurately model the effect of a permeable membrane wall and can handle a variety of different packing arrangements of cells within the domain.

There exist a number of directions forward along which this model can be expanded. From a numerical analysis perspective, the effect of variations in the LBM relaxation parameter is poorly understood. The range used here (0.5<τ<1.0) was chosen because previous work suggests that this yields stable solutions, however, a study of the effect of varying this parameter will give further insight into the stability of the LBM scheme. Additionally, the present model is only in two dimensions, expanding the model to three dimensions will allow new ranges of physical phenomena to be captured, from the effect of T1-relaxation to diffusion in the axial direction of the cell. Finally, the current model neglects advection owing to blood flow. Including advection will allow the investigation of blood perfusion in the muscle.
From a physiological perspective, there is still more work to be done in developing geometric models which more closely approximate the anatomy of skeletal muscle. Developing these models and determining accurate values of intra- and extracellular diffusion coefficients, as well as $T_2$-relaxation values, still remains to be done. Finally, there is a limited amount of consistent experimental data that can be used to fully validate such models. Developing an experimental validation of this model will give further weight to its predictions.
REFERENCES


