To Jose, Beatry & Silvia
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Myocardial fiber architecture largely determines the current pathways and current wavefront propagation in the heart. Disruption of this organization may give rise to severe chronic cardiac conditions related to electrical imbalances. In this study, underlying fiber direction information was obtained from DT-MRI data to predict intracellular electrical conductivity in cardiac tissue, and a finite element model of the heart was created to predict current pathways. Isotropic and anisotropic tissue properties were assigned to the heart tissue to compare the electrical behavior under different stimuli: (a) potential difference and (b) current point source stimulus. Significant differences in predicted current paths can be seen between isotropic and anisotropic cardiac models in response to both of the inputs. This DT-MRI modeling approach accounts for more realistic tissue properties that can more accurately predict the implications of myocardial infarction, which will be the focus of future studies. In addition, a preliminary time-dependent model was included to examine the implications of such simulations with a more realistic behavior.
CHAPTER 1
INTRODUCTION

Cardiac function is influenced by the three-dimensional organization of the myocardial fibers. Cardiac fibers are arranged in a circumferential, longitudinal, and a sheet-like fashion, forming counter-wound helices from the base to the apex of the heart.\textsuperscript{1} This fiber organization is responsible for the delicate balance between mechanical and electrical functioning of the heart. When electrical disruption of coordinated function occurs, this is associated with cardiac arrhythmias which may lead to more serious conditions like ventricular fibrillation.\textsuperscript{2,3} In case of a heart attack (myocardial infarction), blood supply to a section of the heart is interrupted, and this oxygen shortage (ischemia) causes damage and possibly death of heart tissue. Injured heart tissue conducts electricity slower than healthy heart tissue\textsuperscript{4,5} and this difference in conduction velocity often triggers a re-entry or a feedback loop. These re-entry waves and feedback loops are thought to be the cause of many lethal cardiac arrhythmias.\textsuperscript{2}

Previous studies have been conducted to reconstruct fiber architecture in the heart\textsuperscript{6}, but this anatomical reconstruction is labor intensive and time consuming. Such studies consist of perfusing, excising, and precisely cutting segments of the ventricular wall from which the architecture is then carefully measured. Other methods to incorporate fiber orientation in heart models have also been proposed\textsuperscript{7,8}. The method developed by Lorange \textit{et al.}\textsuperscript{7} consisted of nesting revolving ellipsoids from the endocardium to the epicardium, from 0\degree to 120\degree. Ellipsoid dimensions were taken from a computer tomography scan of a frozen human heart. Models developed by Vigmond and Leon\textsuperscript{8} also included the rotating fiber anisotropy. They modeled muscle fibers as a discrete cable network in a rectangular area. Within a plane, the fibers where all parallel and there was a fixed clockwise rotation of fiber orientation between planes. The use of this simplified geometry did not result in realistic echocardiograms (ECG). These methods
provide a solid foundation for the study of the structure-function relationship of myocardial
anisotropy, and provide approximations of the actual anatomical structure.

Recent studies used diffusion tensor magnetic resonance imaging (DT-MRI) to determine
the orientation of cardiac muscle fibers.\textsuperscript{9,10,11} This technique yields an average diffusion tensor
for water in the tissue over an image voxel where the eigenvalues and eigenvectors determine the
magnitude and principal directions of diffusion rates, respectively. The principal direction
corresponds to the fiber orientation parallel to the long axis of the muscle fiber.\textsuperscript{4}

Electrical conductivity is also a tensor, and it is predicted that electrical conductivity in
heart tissues is greatest along the cardiac muscle fiber direction.\textsuperscript{12} Cardiac fibers create a sheet-
like structure along the fiber direction. The next preferential direction for electrical conduction is
transverse to the fibers in the direction parallel with to the sheets. The least electrical conduction
occurs in the direction normal to the sheets.\textsuperscript{13}

In this study, the underlying fiber direction information from the water diffusivity tensor
as measured by DT-MRI was used to predict intracellular electrical conductivity in cardiac
tissue. Based on this information an electrical finite element model of the heart was created.
Initially a two-dimensional model was created for validation purposes. Then, a steady-state
analysis in three dimensions was done and intracellular current paths were predicted in the left
ventricle. The current pathlines and voltage distribution was compared between models using
anisotropic and isotropic conductivity properties.

Such simulations are useful for predicting current propagation and current density
distribution patterns, as well as voltage distribution and sensitivity to electrical impulse location.
This may useful for establishing defibrillation threshold values and as well as optimizing
electrode placement. Ultimately, such models may be used to understand the consequences of
myocardial infarction on the electrical functioning of the heart and defibrillation characteristics. Preliminary studies on a time-dependent model were prepared and analyzed against the steady-state cases.

Initially, a brief background is given on the topics necessary for a better understanding of the issues addressed. The topics of the background overview are: heart diseases, devices to overcome such diseased states, basic heart physiology, reconstruction of anatomy using DT-MRI and techniques used to measure electrical conductivity. Then, a detailed step-by-step description is presented on the creation of the computational heart model and the subsequent simulations. Following this description, the results of the simulations are analyzed. The implications of the results are provided along with an exploration of future studies. Lastly, conclusions are drawn and the results obtained are summarized.
CHAPTER 2
BACKGROUND

Heart Disease

Heart attacks are the leading cause of death in developing countries. In the United States alone, more than 10,000,000 are living with some form of heart disease. Every year, approximately 1,200,000 people suffer a coronary attack every year, and about 40% of them die as a result of this episode. This suggests that approximately every 65 seconds, a person in America dies of a coronary event.

Heart attack or myocardial infarction, is a medical condition that occurs when an insufficient blood supply reaches a certain region of the heart. This insufficient blood supply event is referred to as an ischemic episode. This insufficient blood supply or oxygen shortage produces damage or death to the cardiac tissue. This damaged tissue area is referred to as an ischemic area. When the ischemic area is small and does not compromise the electrical system of the heart, the likelihood that the patient will survive is very high. If the ischemic area is large, and a region of infarcted or dead tissue arises, then myocardial arrhythmias occur.

Cardiac arrhythmia makes reference to any cardiac condition that involves an abnormal electrical activity in the heart. These range from non-dangerous arrhythmias to severe arrhythmias such as ventricular fibrillation. Some examples of cardiac arrhythmias are: tachycardia, bradycardia and fibrillation. When the cardiac rhythm exceeds 100 beats per minute when at rest, this is classified as tachycardia. Extreme tachycardia makes the heart ventricles contract rapidly and therefore they do not completely fill with blood in every blood cycle and often leads to death.

On the other hand, when the cardiac rhythm is under 60 beats per minute, the condition is called bradycardia. In extreme bradycardia, the heart pumps the correct amount of blood, but so
sparsely that the quantity of oxygen that gets to the organs and tissues is not enough to properly oxygenate them. Cardiac fibrillation is present when there is an uncoordinated contraction of either the atria or the ventricles in the heart. Atrial fibrillation is more common than ventricular fibrillation. It often tends to become a chronic condition and leads to a small increase in the risk of death. On the other hand, ventricular fibrillation is severely dangerous and depending on the duration of the episode it often leads to a sudden death. These conditions are not diseases per se, but are often a reflection of underlying cardiac tissue damage.

Nevertheless, one out of three people that have a heart attack die before they can receive any type of medical treatment. Due to the frequency of sudden deaths, the development and improvement of ‘resuscitation’ techniques for treating cardiac arrhythmias is very important. Devices like external defibrillators and implantable cardioverter defibrillators need to be optimized as well as the drug therapies which follow these episodes.

**External Defibrillators and Implantable Cardioverter Defibrillators**

In general, defibrillators work by delivering an electrical impulse to the heart that simultaneously affects the majority of myocardial tissue cells and induces their simultaneous depolarization. After a successful defibrillation, the heart resets its electrical cycle reactivating the normal mechanical contractions starting with the atria and later with the ventricles. The success of the defibrillation depends on the patient’s condition as well as the amount of myocardium that reaches a certain voltage gradient threshold.

External defibrillation and electric cardioversion defibrillation are therapies that deliver an electrical shock to normalize abnormal rhythmic beatings of the heart. They are effective when used promptly after a cardiac episode. External defibrillation is used when a patient is experiencing ventricular fibrillation or ventricular tachycardia without a pulse. These two episodes are lethal if there is no intervention.
Electrical cardioversion is employed in order to revert any type of arrhythmia except for that mentioned above. The electric impulse sent is synchronized with the heart’s electrical activity and it can be administered either urgently during an extreme situation or selectively using implantable cardioverter defibrillators (ICD).

External defibrillators deliver the impulse through externally placed paddles. Paddle sizes have a wide range, but common dimensions are 6 to 12 cm diameter circular paddles. These paddles are placed directly on the thorax on the patient’s skin. There is a slight paddle-
placement dependence using these defibrillators as reported by Karlon et al. \textsuperscript{15}; but an overall positioning near the heart region obtains the desired results. These devices deliver a wide range of voltages, some deliver voltages within the high-voltage range from 700 V to 2000 V \textsuperscript{16}, while others deliver voltages within the low-voltage range from 100 V to 500 V.\textsuperscript{15}

Internal cardioverter-defibrillators deliver the electrical impulse on the heart’s endocardium. Usually, they are used in patients with recurrent arrhythmias or a chronic electrical disruption condition. Unlike external defibrillators, their implantation requires a surgical intervention. Most have two electrodes that are placed in the right atrium towards the base of the heart and in the left ventricle towards the apex of the heart. Since the electrical impulse is delivered directly on to the heart tissue, the magnitude of the shock required is smaller than that required when using external defibrillators.

![Image of Implantable Cardioverter-Defibrillator and Electrode Placement](image)

Figure 2-3. Implantable cardioverter defibrillator and electrode placement (image obtained from U.S. Department of Health and Human Services and NIH)

The dimensions of the electrodes that deliver the shock in ICDs are much smaller than the external defibrillator paddles. Their dimensions are small so that a transvenous implantation is possible, therefore the electrode placement within the heart has to be more precise.
Heart Anatomy and Electrophysiology

Heart Anatomy

The heart is the principal organ in the circulatory system. It is a striated muscle that acts as a pump to synchronously circulate blood and nutrients through the whole body. It is located slightly offset to the left in the middle of the thorax and it is surrounded by the pericardium. The pericardium is responsible for its insulation and lubrication, preventing it from wear during its normal mechanical functions. The heart consists of three main layers: the endocardium (the innermost layer), the myocardium and the epicardium (the outermost layer). The endocardium is a connective tissue membrane that covers inside of the heart and has direct contact with the blood. The myocardium is the layer consisting of cardiac muscle fibers that are responsible for the pumping mechanism. These cardiac muscle fibers are arranged in a circumferential, longitudinal, and a sheet-like fashion, forming counter-wound helices from the base to the apex of the heart. Surrounding the heart is the epicardium, (a part of the pericardium) responsible for producing the pericardial fluid used to lubricate the layers of the heart during its mechanical motion.

The heart has four main cavities, right and left atrium, and right and left ventricle (Figure 2-4). The right atrium receives deoxygenated blood from the body, pumps it to the left ventricle which then pumps it to the lungs. Due to the low resistance faced when circulating blood to the lungs, the right side of the heart does not have to exert the same amount of force as does the left side.

The left atrium receives oxygenated blood from the lungs and pushes it to the left ventricle through the mitral valve. The left ventricle then sends oxygenated blood to the whole body through the aortic artery.
Electrophysiology

Cardiac muscle is self-excitatory; it does not require an external stimulus to trigger its contractile functioning. Rhythmic contractions occur spontaneously, and the pace of these contractions is regulated by the sinoatrial (SA) node. It is located in the superior wall of the right atrium (Figure 2-5). The SA node produces an action potential, which is caused by the electric depolarization of its membrane due to a concentration imbalance of Na and K ions. The current produced by the SA node propagates slowly throughout the atria. Then, it passes to the ventricles through the atroventricular (AV) node which is located at the junction of both ventricles. Depolarization occurs more rapidly from the AV node across the ventricles and travels towards the apex of the heart. From the AV node, the depolarization wave propagates to the Bundle of His; then upward from the apex of the heart to the extremity branches of the Bundle of His. These fibers distribute the current to the ventricles through their terminal branches called Purkinje fibers.
Figure 2-5. Sequence schematic of the electrical propagation in the heart. A) location of nodes, B) electrical activity starting at the SA node, C) depolarization wave going across the atria, D) depolarization wave moving to the apex of the heart and E) depolarization wave spreading upward from the apex (imaged obtained from Anatomy and Physiology, Marieb 2000)

**Overview of DT-MRI**

Cardiac function is influenced by the three-dimensional organization of the myocardial fibers. This fiber organization is responsible for the delicate balance between mechanical and electrical functioning of the heart. Disruptions in normal fiber architecture are present in cardiac conditions such as cardiac ischemia and ventricular hyperthrophy \(^\text{17}\). Alterations to this fiber organization may induce abnormal electrical propagations which may lead to severe arrhythmic disruptions. In addition, devices like implantable cardioverter and external defibrillators rely on accurately delivering the correct amount of charge to a specific location and exciting the correct amount of mass percentage of the heart. Such tasks are influenced by the underlying fiber architecture of myocardial fibers. Therefore there is an overall need for quantifying fiber arrangement.

Recent studies used diffusion tensor magnetic resonance imaging (DT-MRI) to determine the orientation of cardiac muscle fibers.\(^9,10,11\) This technique yields an average diffusion tensor for water in the tissue over an image voxel, where the eigenvalues and eigenvectors determine the magnitude and principal directions of rate of diffusion, respectively.
In DT-MRI, a linearly varying pulsed magnetic field gradient is applied to the tissue. Two pulses in the same direction but opposite magnitude are applied. A reduction in signal happens due to the movement of the protons during this time interval, and it can be related to the amount of water diffusion through the following equation

\[ A = e^{-bD} \]  (2-1)

where \( A \) is the signal attenuation, \( D \) is the diffusion coefficient and \( b \) is a factor that characterizes the gradient’s shape, amplitude and timing.\(^{18}\) In anisotropic diffusion, the coefficient \( D \) is a symmetric rank-2 tensor. This tensor characterizes water molecule mobility along three axes that correspond to the MR machine’s axes. Therefore, in order to properly obtain the diffusion tensor one needs to take into account the tissue’s local coordinates.

**Measuring Tissue Electrical Conductivity**

When characterizing electrical properties of tissue, capacitive and resistive elements need to be specified. These two parameters vary with frequency \(^{19}\) but at the frequencies of present interest in the current study the effects of frequency dependence were disregarded. A more detailed explanation of this assumption will be given in the following paragraph.

Electrical conductivity, \( G \), (equal to \( 1/r \) where \( r \) is electrical resistivity), and permittivity, \( \varepsilon \), are needed to describe the electrical properties of tissue. These properties are commonly measured using the four-electrode technique.\(^{20}\) When using this technique, for an alternating current of frequency, \( f \), the ratio of voltage, \( V \), and current, \( I \), is proportional to specific impedance, \( Z \). This is a complex quantity and can be written as

\[ \frac{\Delta V}{I} = Z \]  (2-2)

where
In this equation, $\varepsilon_r$ is the permittivity of space which is a constant, $8.854 \times 10^{-12}$ F/m. The phase difference between current and voltage can be obtained by

$$\phi = \tan^{-1}\left(\frac{2\pi f \varepsilon\varepsilon_r}{G}\right)$$  \hspace{1cm} (2-4)$$

except for low frequencies, $G >> 2\pi\varepsilon\varepsilon_r$. Therefore, the magnitude of the ratio between voltage and current is approximately proportional to the tissue resistivity (1/electrical conductivity). Tissue resistivity is more commonly called, specific impedance.

The heart contracts by passing ionic current inside the muscle, therefore activating rhythmic contractions that circulate blood throughout the body. This ionic current is generated by the transport of Na$^+$ and K$^-$ ions through a semi-permeable membrane. Ions move through small cellular membrane gates which can either be open during an excitation state or closed at a resting state. This ionic movement generates an action potential.

Action potential propagation is a complex electrochemical phenomenon of ionic imbalance, but it can be described using the FitzHugh-Nagumo equations. This model is a two-dimensional simplification of the Hodgkin-Huxley model which models a spike generation in a neuronal axon. There are three characteristics that describe the behavior of excitable media, i.e. neurons and muscle cells: rest cell membrane potential, threshold for opening and closing ionic gates in the membrane, and the diffusive spreading of the electrical signals.

The following equations are a general form of this model

$$\frac{\partial u_1}{\partial t} = \Delta u + (\alpha - u_1)(u_1 - 1)u_1 - u_2$$

$$\frac{\partial u_2}{\partial t} = \varepsilon(\beta u_1 - \gamma u_2 - \delta)$$  \hspace{1cm} (2-5)$$
Here $u_1$ is an action potential that activates the media, $u_2$ is the gate regulator variable that inhibits the system, $\alpha$ gives the threshold for excitation, $\varepsilon$ is the excitability of the system, and $\beta, \gamma, \text{ and } \delta$ are the parameters that describe the resting state and dynamics of the system.

Previous studies have been done where cardiac electrical propagation is described using these equations. Filipini et al. found a strong correspondance between their model and with the electrical behavior of cardiac cells studied in vitro. However, since mechanical contractions were not introduced in this model, they aim to propose a model that includes them in future studies. This mathematical model describes the depolarization process of the cellular membrane that characterizes wave propagation in nervous and cardiac tissue. If the external stimulus exceeds a certain threshold value, the system initiates a wave propagation across the excitable media. If no such threshold is reached, no propagation occurs.
CHAPTER 3
METHODS

Animal Preparation and MR Imagining

Min Hwang, a Ph.D. student in the John Forder laboratory, was responsible for the animal experiments and the MR imaging procedure which was conducted at the McKnight Brain Institute at the University of Florida.

DT-MRI cardiac data was obtained from an exsanguinated white male rabbit. Rabbit surgery was conducted in accordance with the NIH guidelines on the use of animals in research and the regulations of the Animal Care and Use Committee of the University of Florida. An isolated and later arrested heart was used for this experiment because it maintains structural integrity of the vasculature. A New Zealand White male rabbit was be anesthetized using a mixture of ketamine/xylazine (40mg/kg: 10mg/kg, i.m.) followed by heparin (1000 U/kg, i.v.) and was later exsanguinated.

Figure 3-1. Experimental setup of isolated heart with the aorta cannulated. Left: perfused heart with STH, right: replaced with PFC emulsion. (Figure courtesy of Min-Sin Hwang Ph.D student, Biomedical Engineering Department, McKnight Brain Institute, University of Florida)

The excised heart was placed in a bath of cold cardioplegic solution (4°C). The heart was transferred to a Langendorff apparatus and perfused retrogradely. An initial perfusion period of 10 minutes washed the red blood cells out of the vascular space, permitted the heart to contract normally, and the aortic valve to remain intact. A thin (1 mm-OD) polyethylene tube was
inserted in the left ventricle (LV) serving as a vent to avoid excess hydrostatic pressure accumulation and distension of the left ventricle from Thebesian flow. Due to the sensitivity of diffusion weighted images to motion, the heart was arrested prior to imaging by switching perfusate to a modified St. Thomas’ Hospital cardioplegic solution (STH).

MR imaging experiments were performed on an 11.1 T/ 40 cm clear bore magnet (Magnex Instrument Inc. UK, Bruker Instrument console) with a loop-gap coil (32 mm diameter, 40 mm height) dual tuned to $^1\text{H}/^1\text{H}$ resonances. The temperature in the magnet was 28 - 29°C. Proton diffusion weighted images of the arrested rabbit heart with the cardioplegic solution were acquired by applying the gradients to give diffusion sensitizing factors (b values) of 80, 160, 250, 350, 460, 580, 710, 850, and 1000, in 6 directions with a standard spin echo pulse sequence. Imaging parameters were TR = 1.5 s, TE = 29 ms, one average for all scans using $\Delta = 16.5$ ms, $\delta = 5.5$ ms. Thus, a total of 55 scans were obtained per slice of 2 mm thickness each with in-plane resolution of $0.5 \times 0.5 \text{ mm}^2$ and data matrix of $80 \times 80$. MR images were processed with standard processing functions (Fourier transformation) and diffusion-weighted images were fit to a rank-2 tensor model of tissue diffusion.

**Tissue Segmentation**

Image segmentation can be defined as the division of a particular image into distinct regions, each having different properties. In this project, image segmentation was implemented on a voxel by voxel basis using a custom Matlab (Matlab v. 6.5.0, Mathworks) subroutine. The imaged volume was segmented into heart tissue and non-tissue regions. Such segmentation allowed us to correctly assign myocardial tissue properties and the desired properties for the surrounding regions.

A large number of image segmentation techniques are available in literature; however, there is no particular method that can be applied to all images or accepted for all imaged
subjects. In general, cardiac tissue segmentation has been implemented based on characteristic feature values, i.e. relative anisotropy or fractional anisotropy. These values are used in cardiac tissue segmentation because they describe the level of microstructure organization of the tissue. Since muscle tissue is highly organized, these parameters can accurately distinguish between tissue and non-tissue.

Fractional anisotropy (FA) values provide a measure of the extent of tissue anisotropy. These values were calculated from the DTI data using:

\[
FA = \frac{\sqrt{3} \sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}
\]

(3-1)

where \( \lambda \) is the mean diffusivity (\( \frac{1}{3} \text{tr}(D) \)) and \( \lambda_1, \lambda_2 \) and \( \lambda_3 \) are the principal eigenvalues of water diffusivity. FA was used to distinguish between aligned cardiac tissue (FA=1) and isotropic air (FA=0) surrounding the heart. Figure 3-2 shows the correspondence between an FA visualization map and the implemented segmentation. For FA values greater than 0.2, the voxel was characterized as non-tissue, for values less than 0.2 it was assigned electrical conductivity properties of heart tissue.

Figure 3-2. Tissue segmentation correspondence, (A) FA map of transverse image of the heart showing left and right ventricle walls. (B) Tissue segmentation (red=non-tissue, blue=heart tissue)
Assigning Properties for Electrical Conductivity

One should note that DTI measures the effective tensor of water diffusivity in tissue which is sensitive to the underlying tissue structure and $G$ measures intracellular conductivity properties. A strong correlation is assumed between the eigenvectors of the water diffusion tensor and the eigenvectors of the electrical conductivity tensor based on tissue microstructure in order to assign electrical propagation directionality. This ‘cross property’ relationship has been previously studied and assigned by Tuch et al.\textsuperscript{25}

DTI data was processed to assign fiber orientation to the electrical conductivity tensor along the longitudinal, transverse and normal directions of the tissue using a customized Matlab subroutine. This subroutine scanned every point of the DTI data and calculated the eigenvalues and eigenvectors at every location. After segmenting the tissue as mention above, the electrical conductivity tensor components in the local coordinate system of the heart were assigned to each node by sorting them in descending order and creating the matrix

\[
G = \begin{bmatrix}
g_{11} & 0 & 0 \\
0 & g_{22} & 0 \\
0 & 0 & g_{33}
\end{bmatrix}
\]  

(3-2)

where $g_{ii}$ are the conductivity eigenvalues and were obtained from Eason et al.\textsuperscript{26} Electrical conductivity was assigned values in the global coordinate system using

\[
G' = PGP^T
\]

(3-3)

where $P$ is the transformation matrix and the columns of $P$ are equivalent to the eigenvectors of the water diffusion tensor at each point. In this way, the principal directions of the water diffusion tensor provided the fiber orientation and the direction of maximum intracellular conductivity in the global coordinate system.
Finite Element Model of the Heart

The electrical conductivity tensor data was assigned on a voxel-by-voxel basis to the 3-dimensional model and on a pixel-by-pixel basis to the 2-dimensional model within the multiphysics software package, COMSOL (COMSOL Multiphysics v. 3.3, Stockholm, Sweden).

Two-dimensional Model

In this preliminary model, a rectangular area of 80 x 80 mm was selected and a quadrilateral mesh was implemented in which each pixel was assigned to an element in the mesh for a total of 6400 elements.

An isotropic model was first undertaken by selecting a particular transverse image of the heart near the base. For this case, the electrical conductivity tensor matrix was reduced to a single-non-zero scalar value of 0.6 S/m. A voltage difference of 0.1 V was applied between opposing boundaries and electrical insulation to the remaining 2 edges of the model (Figure 3-3).

Figure 3-3. Transverse image of the heart along the xy-plane, 2D isotropic model for validation studies. (red=isotropic heart tissue, blue=non-tissue surroundings).
This isotropic model was then compared to a similar model having anisotropic tissue properties. In the anisotropic model, the spatially-varying electrical conductivity values from the tensor transformation were used.

**Three-dimensional Model**

A rectangular volume corresponding to a truncated image array was created using 24,840 quadratic brick elements, with 212,877 degrees of freedom for the dependent variable, $V$, and electrical properties calculated for each voxel. Each brick element corresponds to an image voxel. To reduce computation time, the atria were disregarded and only the ventricles were modeled when brick elements were used. When the total mass of the heart was required, the modeling was done with ventricle and atria volumes.

![Figure 3-4. Mesh containing 24,840 brick elements corresponding to embedded ventricles and surrounding media.](image)

The continuity equation for conductive DC media yields a general form of Ohm’s law, which for a static case states that

$$\nabla \cdot J = -\nabla \cdot (G' \nabla V - J^e) = 0$$

(3-4)

where $J^e$ is an externally generated current density, $J$ is the induced current density, $V$ is the electric potential, and $G'$ is the electrical conductivity. A current source term, $Q$, was included, and the externally generated current density was eliminated. Therefore, the following generalized equation was used
Heart tissue was modeled as having isotropic and anisotropic electrical conductivity values according to fiber orientation. In literature, reported electrical conductivity values have a wide range. For the isotropic case, an electrical conductivity of 0.28 S/m was used throughout the tissue. This value is an approximation obtained from conductivities measured along the fiber direction, transverse to the fiber direction and blood vessel conductivity. For the anisotropic case, electrical conductivities were taken to be 0.625 S/m, 0.236 S/m and 0.11 S/m along the longitudinal, transverse and normal fiber directions, respectively. 13,26

Figure 3-5. Transverse slice images of the isotropic electrical heart model in FEM software, from apex=1 to base=12 of the heart (blue=heart tissue with isotropic conductivity, white=surrounding non-tissue)
Boundary conditions for the voltage difference simulation assumed electrical insulation on the lateral faces surrounding the heart, that is

\[ n \cdot J = 0 \]  \hspace{1cm} (3-6)

and a potential difference \( V_0 \) between the base and the apex of the heart.

When a current point source was modeled, electric insulation was used on all the faces surrounding the heart. A current point source was defined, namely \( Q_0 \), and a ground (zero potential) point was defined on the surface of the ventricles. This arrangement is important to determine electrode placement in the heart when defibrillation systems need to be implanted.
Steady-state equations were solved and studies compared (a) an input potential difference between the apex and the base of the heart, and (b) current point sources at different locations. In addition, modeling studies were done (c) that resemble external heart defibrillation using different voltage magnitudes, and (d) implantable cardioverter defibrillators by having a voltage point source within the left ventricle wall with different voltage magnitudes.

**Defibrillation Models**

Two types of defibrillators were modeled, external and implantable cardioverter defibrillators. For the external defibrillation simulation, a potential difference was applied between opposing faces of the rectangular model; namely the faces corresponding to the anterior and posterior planes of a human body. This paddle placement location is referred to as anterior-posterior paddle placement (APR3). Neumann boundary conditions were assigned to the remaining faces so that there was no current flowing out of the volume (Figure 3-7).

![External defibrillation model with anisotropic electrical conductivity properties.](image)

Figure 3-7. External defibrillation model with anisotropic electrical conductivity properties.

Implantable cardioverter defibrillations were modeled as voltage point sources located (by visual inspection) at the superior wall of the right atrium and on the lower wall of the right
ventricle. A potential difference between these points was applied and electrical insulation boundary conditions were assigned to all the boundaries in the volume (Figure 3-8).

Figure 3-8. Implantable cardioverter-defibrillation model with anisotropic electrical conductivity properties.

Preliminary Ischemic Model

Several studies have been conducted to characterize the remodeling of the myocardial architecture that occurs after myocardial infarction. However, the electrical implications of such remodeling are not clearly understood. Chen et al. suggested that infarcted heart tissue exhibits a 37% decrease in relative anisotropy. This value is not small enough to be considered as totally isotropic as water, but it does not exhibit the same level of organization as a healthy myocardium. Other studies suggest that according to the degree of myocardial ischemia, a mere decrease of electrical conductivity results, therefore slowing down the impulse propagation. In addition, these studies suggest a complete lack of propagation in the presence tissue necrosis.

A preliminary model of an ischemic heart was created. To do so, a simplified ischemic geometry was implemented by introducing a cone-shape volume within the posterior wall of the left ventricle (Figure 3-9). The ischemic region represented approximately 8% of the total heart
tissue. A low electrical conductivity of 0.18 S/m was assigned to this region and the tissue was assumed isotropic. Simulations where a potential difference input was applied were done in order to compare to the healthy heart tissue model.

Figure 3-9. Transverse slice images of anisotropic electrical heart model in FEM software with infarct region (dark blue), from apex=1 to base=5 of the heart. (red=parallel to xy-plane, blue=perpendicular)

**Time-Dependent Model**

A time-dependent model was implemented using a modified version of the FitzHugh-Nagumo equations for excitable media, Equation 3-7. A fully anisotropic electrical conductivity tensor $G'$ was implemented which has not been previously analyzes.

The electrical conductivity tensor affects the speed at which the tissue is excited as well as the speed at which the tissue depolarizes. Non-linear membrane kinetics were implemented by using modified FitzHugh-Nagumo equations for excitable media

$$\frac{\partial u_1}{\partial t} = \nabla \cdot G' \nabla u_1 + c_1 u_1 (u_1 - \alpha)(1 - u_1) - c_2 u_2$$

$$\frac{\partial u_2}{\partial t} = \varepsilon (u_1 - \alpha u - \gamma)$$

(3-7)

$G'$ is the electrical conductivity tensor and as well as in the general form of the equations, $u_1$ is an activation variable, $u_2$ is an inhibitor, $\alpha$ sets the excitation threshold, $\varepsilon$ the excitability, and $\beta, \gamma, \delta$ are the parameters that describe the resting state and dynamics of the system.
The boundary conditions for this simulation assumed that no current was flowing into or out of the control volume. Therefore, insulating Neumann boundary conditions were assigned to every face of the volume surrounding the heart. Initial conditions characterize an initial uniform potential of distribution of 1 V throughout a section of the model for the activation variable, while the adjacent sections remain at zero. For the inhibitor variable, the adjacent sections have a value of 0.3 V.

Values for $\varepsilon$, $\alpha$, $\beta$, $\gamma$ and $\delta$ were obtained from literature from an FEM model done by Filippi et al.²⁹ to be 0.01, 0.1, 0.5, 1 and 0 respectively, which are standard values used in simple FitzHugh-Nagumo models. Preliminary data from these models is presented.
CHAPTER 4
RESULTS

Two-dimensional Results of Validation Studies

2D heart model simulations were carried out solely for the purpose of visualizing if the data was being properly obtained from DT-MRI data, transformed into the correct coordinates, and corresponded to the expected underlying fiber tissue arrangement.

Figure 4-1. Transverse cuts of the heart obtained from slice 7 of the imaging sequence. A) Fiber orientation mapping using FLTView software. B) Electrical conductivity map in COMSOL Multiphysics software, red=parallel to the xy-plane, blue=perpendicular.

The red areas in Figure 4-1 (B) indicate the regions of larger electrical conductivity, this implies that along these areas the fibers are aligned parallel to the plane of the transverse cut. That is, the fibers are aligned almost horizontally. This inference can be validated when comparing it with the FLTView fiber orientation map (Figure 4-1 (A)). It can be seen that the fibers in this particular image and region of interest (red regions) are oriented parallel to the plane of the image. These results were also validated by comparing them to similar studies found in literature where the fiber architecture of the heart was reconstructed by histological measurements of the fiber angle orientation.6
Three-dimensional Results

Voltage Input and Current Input Simulations

Significant differences can be seen between isotropic and anisotropic cardiac models in response to the potential difference input. Figure 4-2 illustrates the current paths taken when traveling from the apex to the base of the heart. In the isotropic model, the current direction is largely perpendicular to the transverse cut; while in the anisotropic model, current follows a more helical path. In addition, it can be seen that the current tends to follow the fiber orientation of the left ventricular wall. Fibers tend to lie in planes parallel to the epicardium, then rotate counterclockwise over approximately 110° with increasing depth from the epicardium to the endocardium going through a horizontal alignment near the midwall.

Figure 4-2. Current direction for a potential difference between the apex and base within a transverse cut of the heart 12 mm from the base. Arrows correspond to the current direction.

The magnitude of the paths of selected current streamlines between two points was compared in both models. Significant differences in magnitude were obtained. Streamlines with
starting points at the base of the left ventricle at (37 mm, 43 mm, 0 mm), and at the apex of the left ventricle wall at (39 mm, 30 mm, 10 mm) were calculated for current point source and voltage difference input models. The results of the simulations are summarized in Table 4-1.

Table 4-1. Summary of the magnitude of current paths at between two points at different locations with the same seed point.

<table>
<thead>
<tr>
<th>Simulation input</th>
<th>Tissue property</th>
<th>Start Point (x,y,z) (mm)</th>
<th>End Point Avg (x,y,z) (mm)</th>
<th>Magnitude (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage</td>
<td>Isotropic</td>
<td>37, 43, 0</td>
<td>38,46,16</td>
<td>32.6</td>
</tr>
<tr>
<td></td>
<td>Anisotropic</td>
<td>37, 43, 0</td>
<td>38,44,16</td>
<td>36.3</td>
</tr>
<tr>
<td>Current</td>
<td>Isotropic</td>
<td>39,30,10</td>
<td>5,5,15</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Anisotropic</td>
<td>39,30,10</td>
<td>7,7,15</td>
<td>91</td>
</tr>
</tbody>
</table>

The magnitude of the distance between the same starting point and an average of three adjacent ending points of current paths was calculated in isotropic and anisotropic models. Anisotropic streamlines were found to be significantly longer. A plot of the averaged streamlines clearly delineates the differences between the current behavior in isotropic and anisotropic models (Figure 4-3).

Figure 4-3. Comparison between current streamlines in isotropic and anisotropic models. Average from the same seed point.
The following figure illustrates the paths current takes when a current point source was implemented as the input. This source was located in the exterior wall of the left ventricle. Path lines emerge from the point source in a slightly straight fashion in the isotropic model. Although the tissue has isotropic conductivity, the lines are not completely straight throughout the entire volume. Such behavior is attributed to the boundary effects at the edges of tissue and non-tissue regions.

On the other hand, current does not exhibit straight pathlines in the anisotropic model. This again, reflects the importance of the underlying fiber structure in electrical conduction in myocardial tissue.

Figure 4-4. Slice image of a transverse cut of the heart with current path lines. A) Isotropic model, red=uniform electrical conductivity. B) Anisotropic model, blue=perpendicular to the xy-plane, red=parallel to xy-plane.

Sensitivity Analysis

By definition, a sensitivity analysis is the study of how the output of a model varies when certain parameters in the model are changed. This concept was applied to this model by simulating external defibrillation and internal cardioversion.
Different voltage values were applied to simulate external defibrillators. As an overall trend, when the magnitude of input voltage was increased, the percentage of heart tissue nodes at certain voltage increased as well. After running these simulations, a Matlab subroutine (appendix b) was implemented in order to see how many tissue nodes had reached a certain voltage threshold under the different stimuli. The tissue and non-tissue nodes were segmented according to FA values in this case as well.

![Normalized number of nodes of heart tissue above 5 volts at different voltage inputs with a surface potential difference.](image)

**Figure 4-5.** External defibrillation at low range. Normalized number of nodes of heart tissue above 5 volts at different voltage inputs with a surface potential difference.

In external defibrillation models, different potentials were applied across the anterior and posterior faces of the heart for isotropic and anisotropic tissue properties. Significant differences could be observed at lower voltage inputs, 3 V to 10 V (Figure 4-5). The voltage input and the normalized number of nodes show an exponential relationship in the anisotropic case and a more linear relationship in the isotropic case.

On the other hand, at higher voltage input values the differences between isotropic and anisotropic responses are not as evident. From Figure 4-6, one can note that an approximately linear relationship exists between the voltage input and the normalized number of nodes in the
range of 15 V to 35 V. Outside this range the behavior is not quite linear as mentioned previously.

Figure 4-6. External defibrillation at high range. Normalized number of nodes of heart tissue above 5 volts at different voltage inputs with a surface potential difference.

A similar trend can be seen when modeling implantable cardioverter defibrillators. In internal defibrillation models, a point source voltage difference was applied between the right atrium and right ventricle. At low voltages (3 V to 10 V), there is a significant difference between the behavior of anisotropic and isotropic tissue. The percentage of nodes that reach a 5 V threshold in anisotropic tissue increases radically when the voltage input reaches approximately 9 V; while in the isotropic tissue model, a more linear behavior is observed.

Figure 4-7. Implantable cardioversion at low-range. Normalized number of nodes of heart tissue above 5 volts at different voltage with a point source input.
Significant differences can be observed between isotropic and anisotropic tissue models (Figure 4-8) when a voltage point source was modeled (internal cardioversion-defibrillation). In comparison to the results obtained when a surface potential difference was modeled at high-range voltages, the behavior under isotropic and anisotropic tissue properties is clearly different. There is a faster increase of the percentage of nodes above the defined threshold in the anisotropic tissue model than in the isotropic model.

![Graph showing normalized number of nodes vs. point source voltage input](image)

Figure 4-8. Implantable cardioversion at high range. Normalized number of nodes of heart tissue above 5 volts at different voltage with a point source input.

The differences seen at the high-range voltage input are more important when modeling point sources than when modeling surface potential difference. Better visualization of the results is seen on the following graph (Figure 4-9). Eighty percent of anisotropic tissue reaches a voltage threshold of 5 V at approximately 18 V of voltage point source input. When the tissue is isotropic with the same input, eighty percent of its nodes reach above the threshold at approximately 35 V of input. On the other hand, differences are not significant between isotropic point source and isotropic face models. Nevertheless, it can be observed that in the isotropic model, there is a faster increment of number of nodes than in the anisotropic model.
Ischemic Tissue Results

The ischemic model was compared to the healthy model with anisotropic tissue properties. As it can be inferred from Figure 4-10, the response difference between the healthy and the ischemic models is not major. Although healthy myocardium reached the voltage threshold at a lower voltage input, it does not exhibit a significant difference from the ischemic heart. Eighty percent of healthy heart tissue is excited above 5 V with a voltage input of approximately 28 V. On the other hand, 80% of heart tissue in the ischemic model surpasses such threshold at approximately 35 V. However, it should be pointed out that depending on the severity of the ischemia, the volume of infarcted heart tissue increases, and so does the disruption of electrical function.

A sensitivity analysis was done where different isotropic electrical conductivity values were assigned to the ischemic tissue region. They were done in order to better understand the how these values impacted the results. Electrical conductivity values of 0.35 S/m, 0.2 S/m, 0.18 S/m
and 0.15 S/m were assigned, and the normalized number of tissue nodes stimulated above a 5 V threshold results are summarized in Figure 4-11.

Figure 4-10. Comparison between healthy and infarcted heart tissue above a 5 V threshold for a

Figure 4-11. Sensitivity analysis of ischemic heart tissue with different electrical conductivity values.
Time-Dependent Model Results

Qualitative information was obtained from the time-dependent simulations. Although still in a developmental stage, differences could be observed between isotropic and anisotropic responses to the FitzHugh-Nagumo equations. Isotropic tissue was excited uniformly throughout the tissue and the wavefront propagation of action potential was nearly symmetric. On the other hand, anisotropic tissue presented varying shapes of wavefront propagation that are still under analysis.
Fiber architecture obtained from water diffusivity (DT-MRI) was used to predict electrical conductivity in cardiac tissue and an intracellular electrical finite element model of the heart was created. An isotropic model was also created in order to compare the paths taken by currents under different stimulations conditions. In this case, fiber orientation was disregarded and a uniform conductivity was assumed. Significant differences were seen between anisotropic and isotropic model current paths lines. Streamlines in the isotropic model follow the shortest path between two points, while in the anisotropic model they follow paths that reflect the underlying muscle fiber orientation. Current follows the higher conductivity direction when traveling between two points, and delineated the rotating organization of the fibers from the epicardium to the endocardium in the left ventricular wall.

Previous Studies

Other studies have modeled the significance of fiber architecture in electrical propagation in cardiac tissue. Knisley et al.\textsuperscript{30} examined the role of spatial variation of voltage gradients on the transmembrane voltage changes in rabbit hearts. They explored the voltages using a bidomain computer model. They incorporated 2D fiber orientation and approximated the orientation further away from the area of interest. In comparison, our study incorporates a high-resolution 3D fiber architecture and the corresponding electrical conductivities in the appropriate directions.

Wei et al.\textsuperscript{31} compared isotropic and anisotropic computer heart models in body surface electrocardiograms. Their model incorporated fiber arrangement by rotating fiber architecture counterclockwise from the epicardial layer to the endocardial layer a total of 90°. They modeled transient electrical conduction and saw no significant differences in surface ECGs between
models. Their study incorporated both the fiber architecture and the action potential propagation but only as an approximation. Its aim was to analyze the differences that could be detected in surface ECGs.

**Interpretation of Results and Applications**

The presented model attempts to specifically describe the behavior of current patterns and predict the percent of tissue stimulated when different stimuli are implemented. The modeling approach is also able to account for more realistic tissue properties that can more accurately predict the implications of an electrical imbalance which will be the focus of future studies.

This computational model may be useful for optimizing electrode placement and also for predicting defibrillation thresholds that minimize damage of tissue. Simulation results suggest a minimum and a maximum voltage range that a subject may undertake for successful defibrillation while not suffering permanent damages. At the time of implantation of the cardioverter defibrillators, safety-threshold testing is conducted. Ventricular fibrillation is induced at the time of implantation to test whether or not the arrhythmia is terminated. Such testing may cause permanent damages to the tissue and developing technologies to avoid such injury are potentially beneficial.

There exists a critical mass hypothesis stating that a way to end an episode of ventricular fibrillation is by electrically exciting a critical percentage mass of the heart. The exact amount of mass that needs to be electrically activated is unclear, but estimates have established a range of 75% to 100% of the myocardial tissue. In addition, it has been speculated that raising a critical mass of myocardium above 5 V/cm will defibrillate the heart. According to this theory, our developed modeling approach may predict DFTs for implantable cardioverter defibrillators before implantation. When modeling point source inputs in anisotropic tissue, our rabbit heart model (Figure 4-8) roughly shows a voltage range for successful defibrillation of 17 to 20 V.
This is significantly different if the tissue is assumed isotropic. In this case a voltage ranging from 30 V to 45 V would successfully defibrillate the tissue.

Simulation results obtained when a potential difference input was applied, mimic an external defibrillation. In an attempt to include the resistivity of the torso, without imbedding the heart model into a whole torso model, the resistivity of non-tissue surrounding the heart was very high (1e-6 S/m). With this assumption, we could see that when the heart was modeled as anisotropic, the voltage range that would defibrillate the heart was larger than when the heart was stimulated using a point source. In a rabbit heart model, voltages ranging from 45 V to 100 V would excite 90% of the mass above a threshold of 5 V. Standard external defibrillation voltage thresholds for human hearts range from 200 V to 1000 V depending on the weight and diseased condition of the patient. Compared to this range, our results do not seem to correspond, but one should note that the heart DT-MRI data used in our model was obtained from the heart of a rabbit which is smaller than for a human and may not directly apply to values obtained in human studies.

Analyzing the results of the infarcted myocardium model, several observations can also be made. Although the percentage of heart tissue stimulated in this case did not significantly differ from that of healthy tissue, it did exhibit a different voltage distribution. Areas around the infarcted region had increased voltage values compared to the rest of the heart tissue. This could be attributed to boundary effects between healthy and unhealthy regions. This behavior be of consequence due to the unorganized current propagation inside the infarcted region creating regions of current recirculation affecting the potential distribution around the edges of the infarct. Nevertheless, healthy and unhealthy myocardium exhibited a comparable percentage of tissue excitation for the different voltage inputs.
Future Work

Previous DT-MRI studies have found that infarcted myocardium exhibits an increase in the magnitude of water diffusivity. Future work will use DT-MRI-based models to account for regions of tissue damage to predict electrical propagation imbalance. Such models will be used to analyze various infarction scenarios and determine possible implications in the mechanical functioning of the heart.

The developed models may also be used to understand the implications of large external electrical fields on myocardial conduction. To implement this approach one may start modeling a magnetostatic case. When modeling electric behavior of biological tissue at very low frequencies, a quasistatic approximation is valid. The induced electric field can be written in terms of the magnetic vector potential $A$ and the electric scalar potential $\phi$ as

$$E = -\frac{\partial A}{\partial t} - \nabla \phi.$$  

(5-1)

The tissue volume is assumed a conductive medium following the general form of Ohm’s Law

$$J = \sigma E$$

(5-2)

where $J$ is the current density and $\sigma$ is the spatially varying conductivity tensor obtained from DTI data. In a quasistatic approximation, the divergence of the current density $J$ is zero, so we have

$$-\nabla \cdot (\sigma \nabla \phi) = 0.$$  

(5-3)

Combining equations (5-1)-(5-3), we obtain

$$-\nabla \cdot \left( \sigma \frac{\partial A}{\partial t} \right) - \nabla \cdot (\sigma \nabla \phi) = 0$$

(5-4)

Also, the constitutive equation for magnetic fields needs to be included. For biological tissues, the relative permeability is approximately 1, therefore
\[ B = \mu_0 H \]  \hspace{1cm} (5-5)

where \( B \) is the magnetic flux density or magnetic field, \( \mu_0 \) is the relative magnetic permeability and \( H \) is the magnetic field strength.

These equations aim to predict the effects that externally occurring electric and magnetic fields have on the electrical behavior of the heart. In addition, they may be useful to define a near-field electromagnetics standard in the presence of external electromagnetic forces. This field may be characterized by observing at what distance electrodes need to be from the heart, so that the effects of anisotropy can be ignored. Such analysis will be implemented in future studies.
CHAPTER 6
CONCLUSIONS

The overall goal of this project was to realistically model cardiac electrical anisotropy and run sensitivity analyzes for different input and boundary conditions. Such simulations were primarily done based on a steady-state case and preliminary studies were done on a time-dependent model. This project also included simulations of infarcted myocardium based on reported characteristics of such tissue. As a result, the general objectives of this project were achieved together with the possibility for expansion in many directions.

Although an accurate heart geometry was used, there are certain limitations to the model that need to be addressed. Heart tissue consists of different kinds of cells, i.e. Purkinje fibers, SA node cells etc. These cells have different electrical characteristics that were not taken into account. The tissue was assumed anisotropic throughout but with the same electrical excitation characteristics. This clearly affects the propagation patterns in heart tissue, but these issues will be addressed in future studies.
test3a_cuts_atria.m

%Get eigenvalues and eigenvectors from .flt file DTI data
%Output the G tensor
%and separate files containing the anisotropic matrix values
%Organizes these values in rows of 80 columns (or the size of the image) in
%the x-direction

%Cuts atria
%
 DT=openFLT('dti.flt');
eigen_vec=fopen('eigen_vec.txt','w');  %Eigenvector file
eigen_val=fopen('eigen_val.txt','w');  %Eigenvalues
Gtensor=fopen('Gtensor.txt', 'w');     %Conductivity tensor
e11=fopen('e11.txt','w');
e12=fopen('e12.txt','w');
e13=fopen('e13.txt','w');
e22=fopen('e22.txt','w');
e23=fopen('e23.txt','w');
e33=fopen('e33.txt','w');
sur=fopen('surface.txt','w');

%Electrical Conductivity
gl=0.625;    % (S/m)  Parallel to myofibers
gt=0.236;   % (S/m)  Transverse to myofibers but in the same plane
gn=0.1087;   % (S/m)  Normal to the layer

G=zeros(3,3);  %Initialize matrices
g=zeros(3,3);  %
D=zeros(80,80);
E11=zeros(1040,80);
E12=zeros(1040,80);
E13=zeros(1040,80);
E22=zeros(1040,80);
E23=zeros(1040,80);
E33=zeros(1040,80);

for k=1:5 %Number of slices
    for j=14:68 %Size of the region of interest where the image is
        for i=25:70 %Size of the region of interest where the image is
            if ((i-40)^2+(j-40)^2<=33^2)
                [v,l]=eig(matr(DT,i,j,k));%Function that gets eigenvalues and eigenvectors
                trace=(l(1,1)+l(2,2)+l(3,3))/3;
            end
        end
    end
end
\[ FA = \frac{\sqrt{3\left((l(1,1) - \text{trace})^2 + (l(2,2) - \text{trace})^2 + (l(3,3) - \text{trace})^2\right)}}{\sqrt{2 \left(l(1,1)^2 + l(2,2)^2 + l(3,3)^2\right)}}; \]

if (FA<0.2)
  \[ G(1,1)=0.0001; \]
  \[ G(1,2)=0.0001; \]
  \[ G(2,2)=0.0001; \]
elseif (FA>=0.2) % Sorts and assigns values
  diag=[l(1,1),l(2,2),l(3,3)];
  [lam,idxMax]=max(diag);
  [lam,idxMin]=min(diag);
  signEv=sign(diag);
  if idxMax==1
    if idxMin==2
      g(1,1)=gl;
      g(2,2)=gt;
      g(3,3)=gn;
    elseif idxMin==3
      g(1,1)=gl;
      g(2,2)=gn;
      g(3,3)=gt;
    end
  elseif idxMax==2
    if idxMin==1
      g(1,1)=gt;
      g(2,2)=gl;
      g(3,3)=gn;
    elseif idxMin==3
      g(1,1)=gt;
      g(2,2)=gl;
      g(3,3)=gn;
    end
  elseif idxMax==3
    if idxMin==2
      g(1,1)=gt;
      g(2,2)=gn;
      g(3,3)=gl;
    elseif idxMin==1
      g(1,1)=gn;
      g(2,2)=gt;
      g(3,3)=gl;
  end
G = v * g * v';

if (k == 6)
    if (FA >= 0.2)
        aa = 1;
    else
        aa = 2;
    end
    D(i, j) = aa;
    fprintf(sur, '%d %d %+15.6e
', i, j, aa);
end

E11(j + 80*(k-1), i) = G(1, 1);
E12(j + 80*(k-1), i) = G(1, 2);
E13(j + 80*(k-1), i) = G(1, 3);
E22(j + 80*(k-1), i) = G(2, 2);
E23(j + 80*(k-1), i) = G(2, 3);
E33(j + 80*(k-1), i) = G(3, 3);

fprintf(e11, '%+15.6e', G(1, 1));
fprintf(e12, '%+15.6e', G(1, 2));
fprintf(e13, '%+15.6e', G(1, 3));
fprintf(e22, '%+15.6e', G(2, 2));
fprintf(e23, '%+15.6e', G(2, 3));
fprintf(e33, '%+15.6e', G(3, 3));

fclose('all');
tiss_nontiss.m

% Program that evaluates nodal points

clear all
clc
format long;

fidEvec=fopen('infa-aniso-point5v.txt');
Det=fopen('conductivity-point-infa.txt');

tissue=0;
tissue1=0;
i=1;
for r=1:70920

[Evec, cnt] = fscanf(fidEvec,'%25e %25e %25e %25e\n',[1,4]);
E1=i;
E4=Evec(4);
vol{E1}=E4;

[Idx2, cnt] = fscanf(Det,'%25e',[1,3]);
[Evec2, cnt] = fscanf(Det,'%25e\n',[1,1]);

E11=i;
E41=Evec2(1);

con{E11}=E41;
i=i+1;
end

for q=1:70920
if ((0.65 > {q}) & ({q} > 0.18))
    tissue = tissue + 1;
    if (vol{q} >= 0.005)
        tissue1 = tissue1 + 1;
    end
end

fclose('all')
LIST OF REFERENCES


Ana Maria Saaibi was born in 1983 in Bucaramanga, Colombia, and in the fall of 2001 she received her high-school diploma from Colegio Panamericano in her home town. In the spring 2002, she began her engineering and her collegiate tennis career at Tulane University in New Orleans, Louisiana where she double majored in mechanical engineering and mathematics. She received her Bachelor of Science in Engineering degree in the fall of 2005. In 2006 after starting graduate school in the Biomedical Engineering department at Tulane University, she transferred to the Mechanical and Aerospace Engineering department at University of Florida. She will receive her Master of Science degree in mechanical engineering with a minor in biomedical engineering from the University of Florida in August 2008.