

# A Complete Brain Model (fix)

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September 7, 2017

## Abstract

Here is some abstract text

## 1 Introduction

Introduction text.

## 2 Methods

### 2.1 Data Acquisition

- Images were acquired using.... on a healthy volunteer (self, 24 years of age, female), MRI sequence (MPRAGE), – OSIRIX documentation

### 2.2 Preprocessing of Images

#### 2.2.1 MRI Correction

- T1 and T2 images were preprocessed using FSL for bias field correction

#### 2.2.2 DTI

- DWI was preprocessed using DTIPrep which corrects for movement, badly acquired images, etc.
- DWI was converted to DTI using Slicer - (module) after registration.

#### 2.2.3 fMRI

- fMRI was preprocessed using the fcon\_1000 pipeline. (specific to the University of Utah), includes registration

#### 2.2.4 Registration

- Images were all registered to T1 MRI image
- T2 was already registered because the patient did not move in between scans
- DWI was registered by first stripping out the skull using FSL, the skull stripped image was cleaned up using Seg3D, then using an affine registration using Slicer.

### 2.3 MRI Segmentation of Tissues

(HOW MUCH MANUAL TIME???) - manual clean up requires to step through each slice in each direction (axial, sagittal, coronal), white matter took longest, then skull, then grey matter

- Volume was segmented into air, skin, skull, eyes, sinus, white matter, grey matter, and CSF.
- Brain was segmented using FSL fast after skull stripped using BET2 (part of FSL), this was superior to freesurfer, gave segmentations for white matter, grey matter, and CSF.
- Manual clean up of white matter was required after using FSL fast to add more accurate detail, remove grey matter and CSF regions.
- Manual clean up of grey matter was required after using FSL fast to fill any holes between the new white matter, thicken the back side of the brain, and to add grey matter nuclei that FSL fast could not differentiate. (figure??)
- After grey and white matter were segmented, a complete brain segmentation was made. White and grey matter were removed giving the CSF layer.
- Skin was segmented by thresholding the entire volume using Seg3D and removing the other layers afterwards.
- Skull segmentations are difficult when using an MRI scan because bone appears black, and the volunteer did not have a CT-scan. A pseudo-CT scan was provided by Angel Torrado-Carvajal et al. (REFERENCE HERE) which was made from an all female database (!!). Manual clean up was required using Seg3D. The pseduo-CT scan also provided a segmentation of the sinuses and esophagus. Sinuses are hard to segment due to the lack of CT-scan as well.
- Eyes were segmented using T2 image and thersholding.
- Air was segmented as anything left over.
- Checked and filled for holes.

### 2.4 Finite Element Mesh Generation

- Tetrahedral mesh was generated using Cleaver.
- Due to the complexity of the segmentation, with a sizing field of 0.7, a mesh was generated with no holes but with 80M elements.

- To reduce the size of the mesh, a mesh was made with a sizing field of 1.0. The sizing field was then manipulated using SCIRun to change the scaling of the data (by 27?), and then input back into Cleaver and cleaved a new mesh. This mesh is 15.6M elements with no holes. This mesh contains one flat tetrahedra.
- Mesh simplification?

### 3 Conductivity Preparation

- Homogeneous conductivities
- White matter inhomogeneous tensor conductivities - scaling, ratios

#### 3.1 Mathematical Modeling

#### 3.2 Numerical Methods

#### 3.3 Simulations

- Forward problem
- Include figures of SCIRun networks - how much detail??

END OF ALLY'S TEXT

##### 3.3.1 Experimental Methods

We induced episodes of acute, transient ischemia in anesthetized, open-chest swine ( $n = ??$ ) and canine ( $n = ??$ ) preparations. In each experiment, the heart was exposed and suspended in a pericardial cradle. A portion of the LAD was minimally dissected and fitted with a hydraulic occluder, which could be compressed to restrict coronary blood flow, thereby creating the transient ischemic condition, and then released to restore normal cardiac perfusion. Experimental protocols consisted of measuring extracellular potentials, both on the epicardial surface and within the myocardium, while applying stepwise increases of ischemic load.<sup>23</sup> To this end, two basic protocols were used to induce ischemia: 1) LAD blood flow was incrementally reduced by the occluder while maintaining a constant, often elevated, heart rate (supply ischemia) or 2) increases in the heart rate were applied while maintaining a constant, often restricted, LAD blood flow (demand ischemia). For purposes of this study, we do not consider the differences between supply and demand ischemia but rather focus on the size, shape, and location of the zones within the heart that show an electrical response to the ischemic condition. All studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Pub. No 85-23, Revised 1996).

Customized sock and needle electrodes were used to acquire electrical recordings of both epicardial and intramural electrical potentials. A 247-electrode, flexible sock array,<sup>24</sup> with recording electrodes evenly distributed across the ventricles, acquired epicardial electrogram recordings. Twenty-five (25) flexible fiberglass plunge needles<sup>25</sup> were used to record intramural electrical activity. Plunge needles were constructed with 10 evenly spaced electrodes at 1.6 mm intervals along the shaft. Needles were placed in and around the perfusion bed of the occluded LAD. Sock and needle

recordings were made periodically at a 1KHz sampling rate, the combination of which provided a *3-dimensional* electrical representation of the induced ischemic condition.

In addition to the acquisition of electrical recordings, digitized locations of sock electrodes and needle locations were extracted for postexperiment validation studies. After digitization, needle electrodes were removed and replaced with radio-opaque spacers prior to cardiac imaging in order to provide a registration reference.

Electrograms were calibrated, gain adjusted, and baseline corrected against control recordings, which had been taken immediately before each intervention. Poor quality electrograms, caused by broken lead connections or bad contacts, as well as electrograms without positive Q-wave deflections (identified as cavity electrodes) were discarded. The global root mean squared signal was computed from data recordings of both sock and needle electrodes. These signals were used to identify a point that lay at 40% of the distance between the J point and T wave peak (ST40%). Potential difference maps were generated at ST40%, which compared baseline recordings to those obtained during an ischemic episode. Potential differences, taken at ST40% during baseline conditions, were used to generate a threshold by which ischemic regions were identified as values exceeding two standard deviations. Sock recordings were used to validate simulation findings and will be addressed later. Needle electrodes were used to generate subject-specific ischemic zone geometries by identifying regions within a spatial neighborhood that met the above-mentioned ischemic thresholding criteria.<sup>26</sup>

### 3.4 Simulation Pipeline

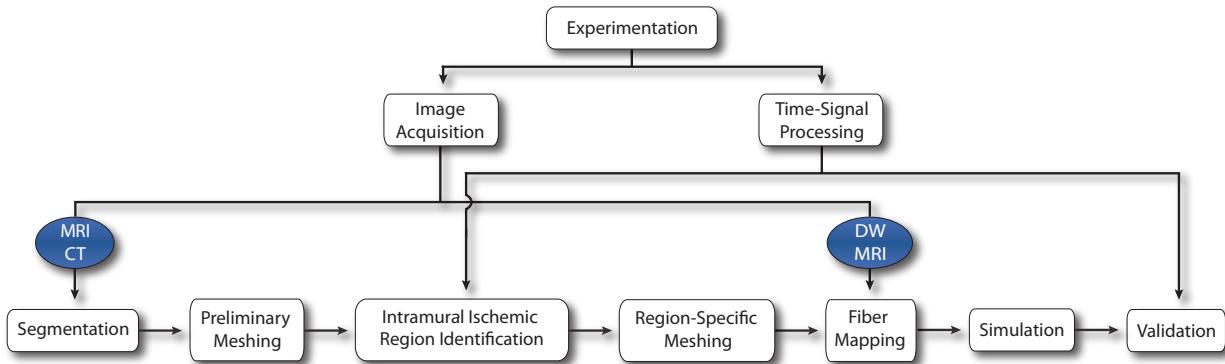


Figure 1: Ischemia Simulation Pipeline. Both image and time signals were extracted from experimental protocols of acute, induced ischemic preparations. Image data was used to generate geometries through segmentation and meshing. Intramural electrical data, recorded from plunge needles, were mapped to these meshes to define ischemic zone location. New meshes were generated with ischemic geometries imposed on which ischemic simulations were generated and validated against the original experimental data recorded from epicardial sock data.

A simulation pipeline was implemented in order to produce in silico models that were representative of experimental findings. Electrical data acquired during the experimental process, as well as imaging information acquired post experiment, were used to construct subject-specific, finite element, bioelectric simulations by way of the steps illustrated in Figure 1.

### 3.4.1 Imaging and Segmentation

After completion of the experimental protocol, each heart was excised and scanned with a 7 tesla MRI scanner using FISP and FLASH MRI sequences. Diffusion tensor images (DTI) were also acquired to determine fiber direction. FISP scans rendered consistent, albeit low, contrast throughout the tissue - preserving edges near the field of view boundaries. FLASH scans, in comparison, provided images of high contrast within the center of the volume, which diminished steeply near the field of view boundaries. The advantages of both FISP and FLASH were combined in order to produce realistic, geometric segmentations of blood, cardiac tissue, and needles, using the Seg3D\* open-source software package. Needle locations were readily identified within the scans as dark regions occupied by the radio-opaque spacers that were inserted at the end of the experimental phase. Diffusion-weighted MRI (DW-MRI) images were also obtained from which fiber orientation was derived.

### 3.4.2 Geometric Processing and Data Mapping

Segmentations were used to generate realistic *3-dimensional* geometries for use in subsequent finite element simulations (See Section 3.4.4). By using two open-source meshing packages, we were able to generate smooth, linear, subject-specific, boundary-conforming, tetrahedral meshes for use in simulations. First, segmentations were ported into the BioMesh3D\* software package to generate smoothed/tightened surface representations. BioMesh3D surface representations were used as input indicator functions to a second meshing package, Cleaver\*, from which the final mesh was derived. Cleaver is a multimaterial meshing package that produces structured meshes of tetrahedral elements with guaranteed minimum element angles,<sup>27</sup> resulting in quality meshes that require fewer computational resources. Cleaver, however, does not offer the surface-tightening features of BioMesh3D. As a result, meshes produced by Cleaver from standard MRI segmentations (with no surface tightening) would propagate the stair-stepped surfaces inherent in rasterized, volumetric data. By combining packages, we were able to produce smooth, structured meshes of guaranteed element quality.

Correspondence points derived from known sock and needle locations were used to register needle and sock electrode geometries within the cardiac mesh using the SCIRun problem-solving environment †. Processed data values were mapped to corresponding node locations within the cardiac mesh. Linear interpolation to local nodes was applied but restricted to the geometric convex hull of the needle locations. Extrapolation to outlying regions, not within the scope of needle locations, was not included.

To identify ischemic zones, potential difference maps were generated that removed baseline potentials from those observed during ischemic interventions. Difference map values within the specified needle region that exceeded a value greater than two standard deviations from baseline recordings were identified and labeled as ischemic. These new label masks were used to create a final mesh that contained three defined tissues (blood, healthy cardiac tissue, and ischemic cardiac tissue) that shared conforming surfaces - an important feature in static forward simulations when considering areas in proximity to potential sources.<sup>28</sup>

Finally, subject-specific fiber orientation was applied within the mesh. A vector field was defined by the principle eigenvector from DW-MRI images with all other cross-sectional fiber components regarded as isotropic. This vector field was normalized, aligned, and mapped to the cardiac mesh

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\*<http://sci.utah.edu/software.html>

using weighted-average interpolation to provide a basis for anisotropic conductivity.

### 3.4.3 Mathematical Modeling

The cardiac mesh, with associated fiber structure and ischemic region, was used to solve the bidomain passive current flow equation:

$$\nabla \cdot (\bar{\sigma}_e + \bar{\sigma}_i) \nabla \phi_e = -\nabla \cdot \bar{\sigma}_i \nabla V_m \quad (1)$$

where  $\sigma_e$  and  $\sigma_i$  represent the extracellular and intracellular conductivity tensors, respectively.  $\phi_e$  is the extracellular potentials, and  $V_m$  represents the transmembrane potential.

In this model, it was assumed that the heart was surrounded by a perfect insulator, leading to a Neumann boundary condition on the epicardial surface. The endocardium, in contrast, allowed for extracellular, but not intracellular, current flow into the ventricular blood pool. Initial blood potentials were defined by Cauchy boundary conditions along the endocardial surface as shown in Equation 2.

$$\begin{cases} \nabla \cdot (\bar{\sigma}_e + \bar{\sigma}_i) \nabla \phi_e = -\nabla \cdot \bar{\sigma}_i V_m & x \in \Omega_H \\ \vec{n}_{epi} \cdot (\bar{\sigma}_e + \bar{\sigma}_i) \nabla \phi_e = 0 & x \in \partial\Omega_{H,epi} \\ \vec{n}_{endo} \cdot (\bar{\sigma}_e \nabla \phi_e) = -\vec{n}_b \cdot (\bar{\sigma}_b \nabla \phi_b) & x \in \partial\Omega_{H,endo} \\ \phi_e = \phi_b & x \in \partial\Omega_{H,endo} \\ \phi_i = 0 & x \in \Omega_b \end{cases} \quad (2)$$

where  $\Omega_H$  represents the cardiac volume;  $\partial\Omega_{H,epi}$  and  $\partial\Omega_{H,endo}$  the epicardial and endocardial surfaces, respectively;  $\phi_e$  and  $\phi_b$  correspond to potentials in the extracellular space and the blood, respectively.  $\vec{n}$  represents the normal, outward unit vector along the epicardial (*epi*), endocardial (*endo*), and blood (*b*) surfaces. The first equation specifies the relationship between transmembrane and extracellular potentials within the cardiac domain. The following four equations define the handling of currents and potentials along the cardiac surfaces. The blood, in all studies, was completely enclosed within the cardiac region and considered to have isotropic conductivity (See Figure 2 and Table 1).

Conductivity values within the tissue, as well as the blood pool, were normalized with respect to extracellular longitudinal values and matched those used in previous studies.<sup>10,29,30</sup> Table 1 shows the conductivity values used for this study. These conductivity values were chosen to be consistent with those previously defined by Johnston and Kilpatrick.<sup>31</sup> Conductivities within the ischemic region were reduced with respect to healthy values corresponding to the first 5 - 15 minutes after ischemic onset.

We defined a fixed transmembrane potential value ( $V_m$ ) of 30mV as the potential source for our forward simulations. The reduced transmembrane potential mimics the delayed activation of diseased tissue under ischemic conditions during the ST-segment. Healthy tissue was assigned a value of 0 mV, typical of the relatively quiescent state of healthy cardiac activation during the ST segment. Between healthy and ischemic tissue, a border zone was defined in which potentials progressed from the diseased to healthy states.

The border zone, the region between healthy and ischemic tissue, has been determined to be a necessary, and problematic, region to include in simulation studies.<sup>10,29,32</sup> In this study, we defined the border zone as a piecewise, continuous function represented by Equation 3 in which a Gaussian function defines the region from the ischemic zone boundary to a specified transition point,  $S_1$ . At

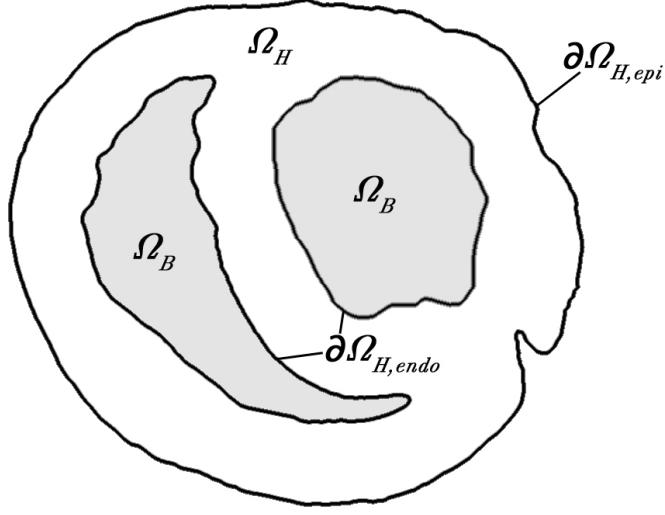


Figure 2: Bidomain equations are defined within the cardiac tissue  $\Omega_H$  and bounded by epicardial and endocardial boundaries  $\Omega_{H,epi}$  and  $\Omega_{H,endo}$ . Extracellular currents were allowed to flow into the blood volume  $\Omega_B$  along the endocardial boundary.

Table 1: Ratio applied to tensor conductivity values within healthy and ischemic regions.<sup>29</sup>

Labels	Conductivity	Healthy	Ischemic
		Conductivity Values	Conductivity Values
$\sigma_{el}$		1	1/2
$\sigma_{il}$		1	1
$\sigma_{et}$		1/3	1/4
$\sigma_{it}$		1/20	1/20
$\sigma_b$		3	3

$S_1$  the border transitions to a linear, decreasing function that reduces to 0 (the value assigned to healthy tissue) at  $S_2$ . It is important to note that not all models, found in the literature, have applied border zones. For the sake of consistency and uniformity, however, we have imposed border regions into all of the forward simulations constructed in this paper. Table 2 shows the values applied to Equation 3 for this study.

$$BZ = \begin{cases} V_m e^{\frac{-d^2}{2\sigma^2}} & d < S_1 \\ \Gamma - \frac{\Gamma}{S_2 - S_1} (d - S_1) & S_1 \leq d < S_2 \\ 0 & d \geq S_2 \end{cases} \quad (3)$$

$$\text{where } \Gamma = V_m e^{\frac{-(S_1)^2}{2\sigma^2}}$$

Table 2: Values Used In Border Zone Determination.

Label	Definition	Value
$V_m$	Transmembrane Potential	30 mV
$\sigma$	Gaussian RMS Width	5 mm
$S_1$	First Transition Distance	8 mm
$S_2$	Second Transition Distance	11 mm
$d$	<i>distance</i>	<i>variable</i>

### 3.4.4 Numerical Methods

Solutions to Equation 1 were computed using finite element methods. By applying Green's divergence theorem to Equation 1, the following weak formulation is generated

$$\int ((\bar{\sigma}_e + \bar{\sigma}_i) \nabla \phi_e) \cdot \nabla \psi(\bar{x}) d\bar{x} = - \int (\bar{\sigma}_i \nabla V_m) \cdot \nabla \psi(\bar{x}) d\bar{x}, \quad \forall \psi \in \Omega \quad (4)$$

where,  $\Omega$  (see Section Section 3.4.2) is the linear, finite element mesh,  $\psi$  represents the finite element basis functions characterized by local hat functions associated with mesh nodes. By applying this formulation to the finite dimensional mesh, we can reduce Equation 4 to a system of linear equations

$$A\phi_e = -RV_m \quad (5)$$

where  $A$  and  $R$  represent stiffness matrices defined by  $A_{j,k} = \langle \nabla \psi_j, (\bar{\sigma}_e + \bar{\sigma}_i) \nabla \psi_k \rangle_\Omega$  and  $R_{j,k} = \langle \nabla \psi_j, \bar{\sigma}_i \nabla V_m \rangle_\Omega$ , while  $\phi_e$  and  $V_m$  represent extracellular and transmembrane potentials, respectively.<sup>33</sup>

We used the open-source, SCIRun problem solving environment<sup>34</sup> to apply parameters and to solve Equation 5 numerically. Within the SCIRun environment, fiber orientation and conductivity tensors were applied to the mesh, initial and boundary conditions were defined, and border regions were generated in order to compute extracellular potentials by way of a conjugate gradient method with a Jacobi preconditioner.

### 3.4.5 Comparison Approaches

Epicardial potentials compared using CC, RMS Error, and DICE correlation...Do it first, then explain it.

### 3.4.6 Validation

In order to validate solutions of the ischemic condition, experimental data was compared to simulated solutions. Experimental data were mapped to the mesh by digitizing and later registering sock electrodes to points identified on the surface of the cardiac mesh. Potential data from sock electrodes were interpolated onto the ventricular surfaces and compared to simulated potentials on a node-to-node correspondence. RMS error and the correlation coefficient between simulated epicardial potentials and experimental sock data were generated to assess accuracy of simulation results.

## **4 Results**

## **5 Discussion**

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## **6 Conclusion**

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## **7 Acknowledgements**

Support for this research comes from the the NIH NCRR Center for Integrative Biomedical Computing ([www.sci.utah.edu/cibc](http://www.sci.utah.edu/cibc)), NIH NCRR Grant No. 5P41-RR012553-08, the Nora Eccles Treadwell Foundation, and the Richard A. and Nora Eccles Harrison Fund for Cardiovascular Research.

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