

# A Complete Brain Model (fix)

<sup>1</sup>Alexandra Warner, <sup>1</sup>Chris Johnson

<sup>1</sup>University of Utah, Salt Lake City UT; <sup>2</sup>Placeholder in case we need to put more refs

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## Abstract

Here is some abstract text

## 1 Introduction

Introduction text.

## 2 Methods

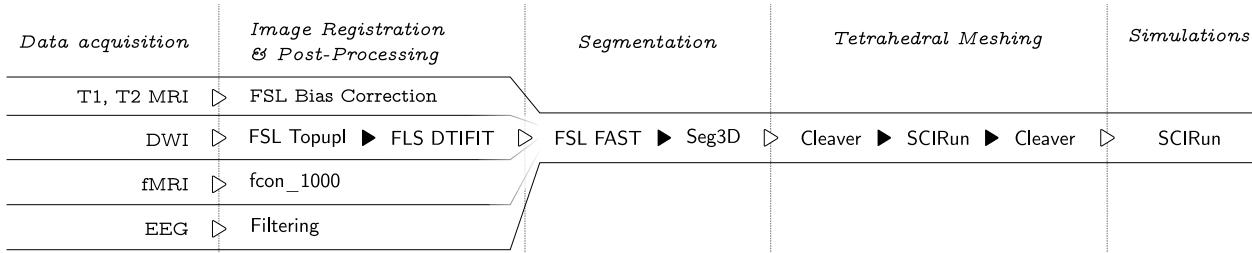


Figure 1: Head/Brain Model Pipeline

### 2.1 Data Acquisition

To construct a high-resolution, personalized, anisotropic volume conductor whole-head model,  $T_1$ -,  $T_2$ - weighted, diffusion weighted, and functional magnetic resonance (MRI) scans were acquired on a healthy, female volunteer who is 23 years of age on a Skyra 3T full-body scanner (Siemens Medical Solutions).

The  $T_1$ -weighted scan was performed with a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (Mugler and Brookman, 1990) – get this reference. The parameters used were as follows: echo time: 3.41ms, repetition time: 2500ms, flip angle: 7 °, resolution matrix size: 256x256 pixels, field of view: 256mm, 208 sagittal slices with a slice thickness of 1mm. Acquisition time was 10:42 minutes.

The  $T_2$ -weighted scan was performed with a sampling perfection with application-optimized contrast using different flip angle evolutions (check ref) (SPACE) sequence (Lichy et. al., 2005; Mugler et al., 2000). The parameters used were as follows: echo time: 406ms, repetition time: 3200ms, resolution matrix size: 256x256 pixels, field of view: 256mm, 208 sagittal slices with a slice thickness of 1mm. Acquisition time was 5:34 minutes. The subject did not move in between the two scans so the scans did not need to be registered.

The diffusion weighted images (DWI) were acquired with multiband two-dimensional echo-planar imaging (EPI). Both phase encoding directions were performed (anterior to posterior and posterior to anterior) with 64 diffusion directions each. Further sequence parameters for each scan was as follows: echo time: 76.8ms, repetition time: 4070ms, flip angle: 90 °, resolution matrix size: 104x104 pixels, field of view: 208mm, 60 slices with 2.5mm slice thickness. Acquisition time was 5:05 minutes each.

The function MRI (fMRI) scans were acquired with blood oxygenation level dependent contrast (BOLD). The following parameters were used: echo time: 76.8ms, repetition time: 780ms, flip angle: 55 °, resolution matrix size: 104x104 pixels, field of view: 210mm, 72 slices with 2mm slice thickness. Acquisition time was 10:32 minutes.

A continuous electroencephalogram (EEG) was recorded using a 256-channel HydroCel Geodesic Sensor Net that was connected to a NetAmps 400 amplifier and referenced online to a single vertex electrode shown in Figure 2. Channel impedances were kept at or below 50 kOhms and signals were sampled at 250Hz. The EEG was recorded while the subject sat quietly in a chair, alternating two minute epochs of eyes open and eyes closed for a total of 12 minutes.

All acquisition reports will be included with the dataset.



Figure 2: 256-channel HydroCel Geodesic Sensor Net on Subject

## 2.2 Preprocessing of Images

### 2.2.1 MRI Correction

Bias field signal is a low-frequency, smooth signal that corrupts MRI images due to inhomogeneities in the magnetic fields of the MRI machine by blurring images reducing the high frequencies of the images such as edges and contours. It changes the intensity values of image pixels so that the same tissue has a different distribution of grayscale intensities across the image. (ref) An estimated bias field correction on the  $T_1$  and  $T_2$  MRI's was done using FMRIB Software Library (FSL) FAST, and will be further described in the Segmentation section.

### 2.2.2 DWI Distortion Correction

Diffusion weighted images performed with EPI sequences are prone to distortions from rapid switching of diffusion weighting gradients, movement from the scanning table, and movement from the subject. The diffusion data was collected with reversed phase-encode blips (anterior to posterior (AP) and posterior to anterior(PA)), resulting in pairs of images with distortions going in opposite directions. From these pairs the susceptibility-induced off-resonance field was estimated using a method similar to that described in [Andersson 2003] as implemented in FSL [Smith 2004] and the two images were combined into a single corrected one. This was accounted for using FSL's topup and eddy command line tools.

Before running these tools, an acquisition parameters text file needs to be created with the FSL-defined total readout time. There are two parameters that are frequently needed when calculating and applying field maps: the effective echo spacing and the total readout time for an EPI sequence. "Effective" echo spacing was used, rather than the actual echo spacing, in order to include the effects of parallel imaging, phase oversampling, etc. Multiplying this by the size of the reconstructed image in the phase direction will give you the reciprocal of the effective echo spacing:

$$\text{Effective Echo Spacing (s)} = 1 / (\text{BandwidthPerPixelPhaseEncode} * \text{MatrixSizePhase})$$

The total readout time (FSL definition) is:

$$\text{Total readout time (FSL)} = (\text{MatrixSizePhase} - 1) * \text{EffectiveEchoSpacing}$$

MRICconvert (ref) is a software package that provides all of the acquisition information about a dicom series, as well as converts to a NiFTI format, including effective echo spacing and total readout time. To obtain this information, first load in the dicom series for either DWI acquisition. Choose "Options" to ensure that the DWI will be saved as a NiFTI, and click "Convert All." This will save all the files into the output directory specified upon opening MRICconvert. The text file will include the FSL-defined total readout time which should be contained in the acquisition parameter file in seconds. MRICconvert also outputs the b-values and b-vectors files, and they should be the same for both the DWI AP and DWI PA scans. The last input file needed is an "index.txt" file. This text file contains one column with 65 rows (for 64 directions plus the b0 image) of 1's.

(MRICconvert, Options, and text file figures) (acquisition parameters file and index file)(maybe a figure out the outputs in finder)

Create a separate folder for topup results and include the following files: the acquisition parameters file, the index file, b-values, b-vectors, and the DWI AP and DWI PA files. In the following

instructions, DWI AP was renamed as DWI\_up and DWI\_AP was renamed to DWI\_down. The b-values and b-vectors were renamed to dwi.bval and dwi.bvec, respectively. After all of these files are in place, run the following command line commands.

```
fslroi DWI\_up b0\_up 0 1
fslroi DWI\_down b0\_down 0 1

fslmerge -t both\b0 b0\_up b0\_down

topup --imain=both\b0 --datain=acq_params.txt --config=mine.cnf --out=topup\_results
applytopup --imain=b0\_up,b0\_down --inindex=1,2 --datain=acq_params.txt --topup=topup\_results
--out=b0\_hifi

bet b0\_hifi b0\_hifi\_brain -m -f 0.2
eddy --imain=DWI\_up --mask=b0\_hifi\_brain\_mask --index=index.txt --acqp=acq_params.txt --
bvecs=dwi.bvec --bvals=dwi.bval --fwhm=0 --topup=topup\_results --flm=quadratic --out=eddy\_unwarped
```

These commands first obtain the b0 image, which is the baseline image used for calculating field maps, for both encoding directions. Then the two b0's are merged together into one file. Topup and eddy are applied for distortion correction. Bet is applied for brain extraction. The distortion corrected file is named "eddy\_unwarped.nii."

### 2.2.3 Diffusion Tensor Images

After the DWI images have been corrected, diffusion tensor images (DTI) are calculated using FSL's DTIFIT. Upon opening FSL choose "FDT Diffusion." Then choose "DTIFIT Reconstruct diffusion tensors" in the drop down menu, select to input files manually, and put in the following files. (reference and figure of DTIFIT)

Diffusion weighted data:	eddy_unwarped.nii
BET binary brain mask:	b0_hifi_brain_mask.nii
Output basename:	desired output location
Gradient directions:	dwi.bvec
b values:	dwi.bval

DTIFIT will output the eigenvalues (named L1, L2, and L3) and the eigenvectors (named V1, V2, and V3) for the diffusion tensor field. The files were converted from NiFTI format to nrrd format using ITK-SNAP (reference and figure) although there is a loss of precision. The files were then input into SCIRun to build the tensor field using the eigenvalue and eigenvectors. The SCIRun CalculateFieldData module only requires two eigenvectors as input because it calculates the third eigenvector automatically since it should be orthogonal to the first two. This process can be done in either SCIRun 4 or SCIRun 5 and the same results are produced.

(SCIRun figures of building DTI)

The tensor field was built in SCIRun rather than in 3D Slicer (reference if haven't seen yet) or FSL DTIFIT because the output data would be "backwards" and couldn't be registered with the mesh.

### 2.2.4 fMRI

fMRI data was preprocessed using the 1000 Functional Connectomes Project pipeline scripts (reference) which do anatomical preprocessing, functional preprocessing, registration to the  $T_1$  MRI,

segmentation, and nuisance signal regress. The outline pipeline used on this fMRI dataset, specific to the University of Utah, can be found at [https://bitbucket.org/UtahBrainNetworks/base\\_prep](https://bitbucket.org/UtahBrainNetworks/base_prep) and includes specific instructions for installation, compilation, and usage.

After running fMRI data through the pipeline “rest.nii”, the preprocessed fMRI file, was opened in Matlab using the “load\_nii(‘rest.nii’)” function within the NiFTI toolbox. The 4D “img” variable ( $x, y, z, t$ ) is then resized to a 2D variable ( $x*y*z,t$ ) and saved to use in SCIRun. (reference for NiFTI toolbox?)

### 2.2.5 EEG

The filetype of the EEG recordings in an .edf file after it had a 60Hz notch filter and its harmonics. The EEG signal matrix was obtained using a Matlab script called “edfRead.m.” To run this script use the following command “[hdr, record] = edfread(fname).” The variable ‘record’ will contain the signals. The last two rows of the matrix were removed because they did not correspond to EEG electrodes. Also the beginning and end of the experiment were cut out of the matrix when the EEG net is being put on and taken off.

### 2.2.6 Registration

Since the subject did not move in between the  $T_1$  and  $T_2$  MRI, no registration was necessary before segmentation and meshing. The tetrahedral mesh was generated in its own coordinate space from the segmentation, and was registered to the DTI coordinate space with a rigid registration using SCIRun. (figure of registration network – explain more?) The fMRI data was registered to the mesh coordinate space with a rigid registration using SCIRun. (figure registration network – explain more?) The fMRI data can use same transform to register to DTI later if desired.

## 2.3 MRI Segmentation of Tissues

Segmentation of the head tissues proved to be the most time consuming section of the pipeline. The head volume was segmented into air, cerebral spinal fluid (CSF), white matter, grey matter, skull, sinus, eyes, and scalp. Segmentation of the brain can be difficult due to the similar intensities of the different tissues, making merely applying a median filter and thresholding the image not enough. (show a figure of this happening?)

The brain was initially segmented by inputting a skull stripped  $T_1$  MRI into FSL FAST Segmentation. This outputs CSF, white matter, and grey matter layers as well as a bias-corrected  $T_1$  MRI. This method, compared with Freesurfer, Statistical Parametric Mapping through Matlab (SPM), Atlas Based Classification through 3D Slicer, and Seg3D methods alone, produced the best initial brain segmentation results for this data due to how well it filled in each tissue. (??) (three panel figure of FSL FAST results)

Although the FSL Fast results were a great improvement compared to the other segmentation trials, manual segmentation still needed to be done on those layers to add more detail and take out any cross over between the layers. Since white matter is the innermost layer, it was worked on first. All manual editing was done using Seg3D software. (ref) First a threshold layer was created from the FSL Fast output. Every slice in every direction was inspected and manually edited whether that was adding more detail that could be seen with the naked eye or cleaning up noise from FSL Fast. This manual editing of the white matter took roughly 40 hours of work. (Figure of before and after editing – hook detail!)

After the white matter was completed, a threshold layer for grey matter was created from the FSL Fast output. Each slice in every direction of the grey matter was inspected as well. The white matter layer was removed from the grey matter using a boolean remove mask filter. Any holes between the two layers were decided manually. More detail was added to the grey matter folds to add to the CSF layer as well. The last part of editing the grey matter was decided to add a grey matter nucleus to the layer. The thresholding algorithms generated a lot of noise around these nuclei so they were segmented by hand, using the paintbrush tool, and added to the grey matter layer with a boolean or mask filter. The nuclei were also removed from the white matter layer using a boolean remove mask filter. The manual editing of the grey matter took roughly 20 hours of work. (figures of grey matter and nuclei)

After the grey and white matter layers were completed, the CSF layer was made by creating a solid threshold layer for the entire brain and removing the white and grey matter layers using a boolean remove mask filter. The white matter, grey matter, and CSF layers were then checked for holes, whether on the surface or the inside of the segmentation. Also a quality check on the layers was performed to ensure that the layers were at least two pixels wide. This is an important note for creating a hole-less tetrahedral mesh. The creation of the CSF layer and the manual editing and hole checking took roughly 4 hours of work. (??) (Figures of CSF? Figures of all three brain layers together?)

The skull and the sinus layers are the most difficult to segment using only an MRI because they both appear black in the image, and the volunteer did not have a CT scan. (define CT-scan) The first attempt to create a bone layer was first to use FSL's skull stripping using the BET2 tool to create a skull. Then to threshold the remainder of the bones in Seg3D from the  $T_1$  MRI and connect it to the skull from FSL. (figure and compare the two skull layers) Although this gave a decent skull for only having an MRI layer, the method to segment sinus layer was still to be determined. As a second method, the skull was estimated from an MR-based synthetic pseudo-CT. An improved iterative version of the patch-based method was used described by Torrado-Carvajal et al. [ref] that takes the  $T_1$  and  $T_2$  images as input, and synthesize the pseudo-CT based on both images providing more refined and accurate bone boundaries. MR input images were preprocessed to correct for MRI bias inhomogeneities (N4 bias correction tool in the Insight Toolkit)(ref?) prior to computing the pseudo-CT. (figure of the pseudo-CT output) This method gave a good starting place for skull segmentation, but still needed manual editing. After using a median filter (pixel radius?) and thresholding, each slice in each direction was manually edited by hand. (figure of segmentation) Since the volunteer has a permanent retainer in their mouth, the mouth was segmented as solid bone for now. This is not concerning because the EEG cap used did not cover the volunteer's mouth. (picture? explain EEG caps) The psedu-CT image also provided a segmentation of the sinuses and esophagus by thresholding the black pixels. After the thresholding, the sinus layer was also manually edited. Quality checks were done on both layers to ensure that there were no holes and that the layers were at least two pixels thick. (figure) Manually editing the second skull and the sinuses took roughly 30-40 hours of work.

The eyes, skin, and air layers were simple, in comparison, to segment. The eyes were easily segmented by thresholding the  $T_2$  MRI. (figure of T2 axially) The skin layer was segmented by thresholding the entire volume and removing all of the previous layers using a boolean remove mask filter. A quality check was performed on the skin layer to ensure that it was at least two pixels thick. The important places to check for this is at the bridge of the nose and the bottom of the chin. (sagittal figure) Last, the air was segmented by thresholding the entire image and removing

the solid skin layer. (how much time?) There was a check to ensure that the segmentation did not contain any holes between layers after they were removed. (should I explain this procedure?) To create these three layers took roughly 8 hours of work, most of which was ensuring there were no holes in the segmentation. This is imperative to creating a quality mesh.

Segmented Tissue	Amount of Work (hrs)
White Matter	40
Grey Matter	20
CSF	4
Skull & Sinus	35
Eyes, Scalp, & Air	8

## 2.4 Finite Element Mesh Generation

Segmentations were used to generate realistic 3D geometries for use in subsequent finite element simulations. A smooth, linear, subject-specific, boundary-conforming, tetrahedral finite element mesh was generated using Cleaver software (ref and figure) on a Late 2013 Mac Pro with a 2.7 Ghz 12 Core Intel Xeon E5 processor, 64 GB of RAM, and an AMD FirePro graphics card. Cleaver is a multimaterial meshing package that produces structured meshes of tetrahedral elements with guaranteed minimum element angles, resulting in quality meshes that require fewer computational resources. To make a very high resolution mesh with no holes the following parameters were used: scaling factor: 0.6, size multiplier: 1.0, lipschitz: 0.2, padding: 0, element sizing method: apdative. Along with these parameters, indicator functions must be input to Cleaver. These are made by creating distance maps in Seg3D. Ensure the map is inverted before making the distance map. This produced a mesh with 60.2 million elements and 10.3 million nodes. (figure[s]) This mesh was so large due to the complexity of the segmentation. To reduce the size of the mesh, a mesh was made with a scaling factor of 1.0 with the remainder of the parameters as described before. The computing sizing field was exported from Cleaver and manipulated using SCIRun4 (ref and figure of network) by changing how quickly the elements increase in size. This was done by multiplying the scaling by a factor of 27. The changed sizing field was then input into Cleaver with the same indicator functions and cleaved a new mesh. This produced a mesh with 15.7 million elements and 2.7 million nodes with no holes. However, this mesh does contain one flat tetrahedra. It is later removed in a SCIRun network, and is currently being investigated by Cleaver software developers.

## 2.5 Mathematical Modeling

The head mesh, with associated inhomogeneous and anisotropic regions, was used as a volume conductor to solve the following boundary value problem:

$$\nabla \cdot \sigma \nabla \Phi = -I_V \quad \text{in } \Omega, \tag{1}$$

where  $\Phi$  is the electrostatic potential,  $\sigma$  is the electrical conductivity tensor, and  $I_V$  is the current per unit volume defined within the solution domain,  $\Omega$ . Equation (1) is solved for  $\Phi$  with a known description of  $I_V$  and the Neumann boundary condition:

$$\sigma \nabla \Phi \cdot \mathbf{n} = 0 \quad \text{on } \Gamma_T, \tag{2}$$

which says that the normal component of the electric field is zero on the surface interfacing with air (here denoted by  $\Gamma_T$ ). The brain and surrounding tissue and skull were discretized, and using dipoles for current source the electrical field was calculated within the brain and then projected onto the surface of the scalp.

### 2.5.1 Electrical Conductivity Preparation

All electrical conductivities were homogeneous for each tissue with the exception of white matter when using tensor data. The isotropic conductivities are as follows (Rullman):

Tissue Type	Isotropic Conductivity ( $S/m$ )
White Matter	0.1429
Grey Matter	0.3333
Cerebrospinal Fluid (CSF)	1.79
Skull	0.001
Skin	0.4346
Sinus	1e-6
Eyes	0.5051

When DTI tensor data is added, there are two approaches to converting the tensor data to conductivities. The first is scaling the data (ref), and the second is giving the white matter a fixed ratio of conductivity.

$$\sigma_{aniso} = \frac{\sigma_{iso}}{\sqrt[3]{d_1 d_2 d_3}} D \quad (3)$$

where  $D$  is the diffusion data,  $d_i$  is the  $i$ th eigenvalue of  $D$ , and  $\sigma_{iso}$  is the white matter isotropic conductivity.

$$\sigma_{aniso} = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ W \end{bmatrix}, W = \begin{bmatrix} \sigma_{iso} \\ \frac{\sigma_{iso}}{10} \\ \frac{\sigma_{iso}}{10} \end{bmatrix} \quad (4)$$

where  $v_i$  is the  $i$ th eigenvector of  $D$  and  $W$  is the white matter ratio vector and the ratio is 10 : 1.

### 2.5.2 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

$$\int ((\bar{\sigma}_e + \bar{\sigma}_i) \nabla \phi_e) \cdot \nabla \psi(\bar{x}) d\bar{x} = - \int (\bar{\sigma}_i \nabla V_m) \cdot \nabla \psi(\bar{x}) d\bar{x}, \quad \forall \psi \in \Omega \quad (5)$$

where,  $\Omega$  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 5 to a system of linear equations

$$A\phi_e = -RV_m \quad (6)$$

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  $R_{j,k} = \langle \nabla \psi_j, \bar{\sigma}_i \nabla \psi_k \rangle_\Omega$ , while  $\phi_e$  and  $V_m$  represent extracellular and transmembrane potentials, respectively.<sup>?</sup>

We used SCIRun, the open-source problem solving environment, to apply parameters and to solve Equation 6 numerically. Within the SCIRun environment, isotropic and anisotropic conductivity tensors were applied to the mesh as well as inhomogeneous regions, initial and boundary conditions were defined, and border regions were generated in order to compute potentials by way of a conjugate gradient method with a Jacobi preconditioner.

## 3 Results

### 3.1 Segmentation

### 3.2 Finite Element Meshes

### 3.3 Forward Problem

#### 3.3.1 Isotropic

#### 3.3.2 Anisotropic

### 3.4 fMRI Visualization

### 3.5 EEG Visualization

## 4 Conclusion

In this paper we have outlined a comprehensive pipeline to build an inhomogeneous, anisotropic head and brain model based on human data of all image modalities for use in electroencephalography with an emphasis in forward and inverse problem research as well as visualizations of function MRI data and EEG data. Along with the pipeline, the human data will be released as open-source to enable other scientists to have a starting point to continue further research. Building a model can be time consuming and hinder further important research. This model will allow scientists to have a straight-forward path to building their own model and/or using the model that I have built.

Further investigations from building this pipeline include finding better decimation algorithms for 3D tetrahedral finite element meshes. Due to the number of materials included in the mesh, current decimation algorithms have not been able to further simplify the mesh. More exact registration techniques that will provide a better transformation matrix for moving images to DTI space, especially fMRI data. More inclusive methods for functional MRI data into a source localization head model. More specific processing of EEG data for different applications which will make for better visualization.

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## References

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