Brain tissue temperature dynamics during functional activity and possibilities for optical measurement techniques

by

Greggory H. Rothmeier

Under the Direction of A. G. Unil Perera

Abstract

Regional tissue temperature dynamics in the brain is determined by the balance of the metabolic heat production rate and heat exchange with blood flowing through capillaries embedded in the tissue, the surrounding tissues and the environment. Local changes in blood flow and metabolism during functional activity can upset this balance and induce transient temperature changes. Invasive experimental studies in animal models have established that the brain temperature changes during functional activity are observable and a definitive relationship exists between temperature and brain activity. Here, we present a theoretical framework that links tissue temperature dynamics with hemodynamic activity allowing us to nonivasively estimate brain temperature changes from experimentally measured blood-oxygen level dependent (BOLD) signals. With this unified approach, we are able to pinpoint the mechanisms for hemodynamic activity-related temperature increases and decreases. In addition to this, the potential uses and limitations of optical measurements including functional near-infrared spectroscopy (fNIRS) and the thermal imaging are discussed.

INDEX WORDS: fMRI, BOLD, Temperature, etc.

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

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in the College of Arts and Sciences

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May 2012

Dedication

This is dedicated to my parents who made me go to college and to Brooke who inspired me to go to graduate school. If I wasn't lucky enough to have all of you I would probably be working for Geek Squad.

I also want to more specifically dedicate this to my mama. I miss you and I think about you every day.

Acknowledgements

I want to thank my advisors A. G. Unil Perera and Mukesh Dhamala for their guidance and leadership through my graduate school career. Likewise, I must thank everyone in Dr. Perera's and Dr. Dhamala's labs for always being helpful over the past couple of years. Thank you.

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List of Abbreviations

BOLD	Blood Oxygen Level Dependent
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
ROI	Region of Interest
CSF	Cerebral Spinal Fluid
OLM	Oxygen Limitation Model

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April 3, 2012

Date

Dick Miller
Department Chair

Chapter 1

Introduction

Since its invention in the 1950's [1] and later development in the 1970's [2], Magnetic Resonance Imaging (MRI) has allowed physicians and scientists a detailed view within the human body.

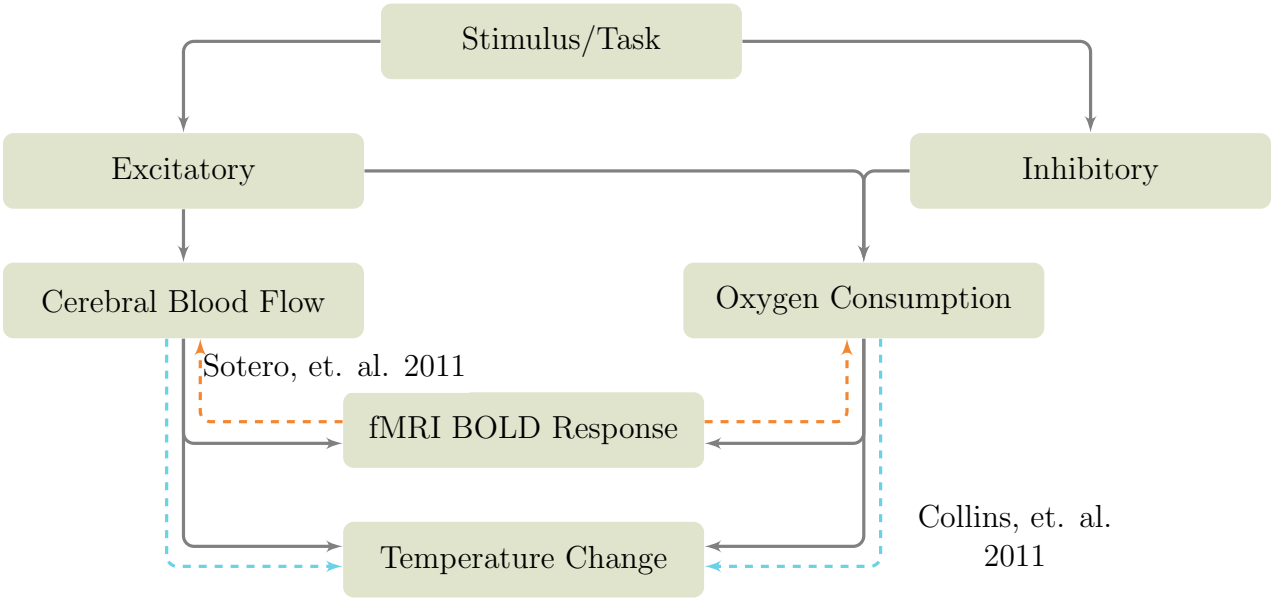


Figure 1.1: Generation of the fMRI BOLD response from changes in neuronal activity. Black arrows indicate a causal relationship while colored dashed-arrows indicate existing models for the relationship. The orange line (•) shows the model proposed by Sotero and Iturria-Medina [3] to calculate cerebral blood flow and metabolism and the blue line (•) shows how the model proposed by Collins et al. [4] is used to calculate temperature.

1.1 Models of the fMRI BOLD Response

Chapter 2

Calculating Temperature Changes using the fMRI BOLD Response

2.1 Introduction

Current efforts to model temperature changes be can categorized into two classes. The first class approaches the problem by considering a single voxel deep within the brain (single-voxel approach) while the second approach considers the brain and head as an entire system (multi-voxel approach). Each of these methods has their own pros and cons which will be discussed below.

2.1.1 Single-Voxel Approach

A single-voxel model of temperature was first proposed by SOMEONE, but has been refined over the past HOWLONG years CITEABUNCH to include more terms. Although different approaches consider different contributions to the temperature change, they all narrow the problem down to a single voxel which is usually 2mm x 2mm x 2mm. By simplifying the model, the heat equation can be simplified and the calculation is much easier to undertake. However, since the brain is not homogenous, the values used for parameters such as heat production and thermal conductivity are taken from an average of the tissues. As a result, this reduces the possible accuracy of such a model when applied to a subject.

The most recently published iteration of a single-voxel model was published by Sotero and Iturria-Medina

[3]. The basis of this model is a modification of the Penne's Bioheat Equation [5, 3].

$$C_t \frac{dT(t)}{dt} = (\Delta H^\circ - \Delta H_b) CMRO_2 \mid_0 m(t) - \rho_b C_b CBF \mid_0 f(t)(T(t) - T_a) - \frac{C_t}{\tau}(T(t) - T_0) \tag{2.1}$$

where C_t is the specific heat of the tissue, ΔH° is the enthalpy released in the oxidation of glucose, ΔH_b is the enthalpy used to release oxygen from hemoglobin, $COMRO_2 \mid_0$ is the metabolic rate at rest, ρ_b is the blood density, C_b is the specific heat of blood, $CBF \mid_0$ is the cerebral blood flow at rest, T_a is the arterial blood temperature, C_T is the specific heat for the tissue, and τ is a time constant for conductive heat loss. The values used are provided in table 2.2.

One advantage of using eq. (2.1) is that the resting state temperature can be analytically determined by substituting $\frac{dT(t)}{dt} = 0$ [3].

$$T_0 = T_a + \frac{(\Delta H \mid^\circ - \Delta H_b) CMRO_2 \mid_0}{\rho_B C_B CBF \mid_0} \tag{2.2}$$

If the values provided in table 2.2 are substitued into eq. (2.2), a resting temperature of 37.3057°C is found. Since the resting temperature is always greater than the arterial blood temperature, it limits the ability of the model to account for all experimental results.

While eq. (2.1) is appears complicated, conceptually the equation can be easily understood.

$$\textit{change in temperature} = \textit{heat generated by metabolism} - \textit{heat lost to convection} - \textit{heat lost to conduction} \tag{2.3}$$

The system is a balance between heat generation (metabolism) and heat transfer (conduction and convection). The direction of heat transfer by convection is determined by the difference between the voxel temperature and the arterial blood temperature $(T(t) - T_a)$. Similarly, the direction of heat transfer by conduction is determined by the difference between the voxel temperature and the temperature of the surrounding tissue $(T(t) - T_0)$. Since T_a is less than $T(0)$, an increase in blood flow $(f(t))$ will remove heat from the voxel thereby decreasing the temperature. Conversely, an increase in metabolism $(m(t))$ without a corresponding change in blood flow, will result in tissue warming.

2.1.2 Multi-Voxel Approach

The multi-voxel approach to calculating brain tissue temperature alleviates many of the issues that a single-voxel approach has. The most prominent advantage a multi-voxel approach has is the a result of it accounting

for a voxels location relative to the surface of the head and other voxels. By accounting for a voxel's location, the same BOLD response in two different locations can have vastly different effects on the local tissue temperature (more on this in section 2.3.1). At the heart of our method is a three-dimensional implementation of the Pennes bioheat equation (eq. (2.4))[4].

$$\rho c \frac{dT}{dt} = k\nabla^2 T - \rho_{blood} f(t) w c_{blood} (T - T_{blood}) + m(t) Q_m \tag{2.4}$$

where ρ is the tissue density, c is the specific heat of the voxel, k is the thermal conductivity, ρ_{blood} is the blood density, w is perfusion by blood, c_{blood} is the specific heat of blood, T_{blood} is the arterial blood temperature, and Q_m is the baseline metabolic heat production. $f(t)$ and $m(t)$ are the time-dependent changes in blood flow and metabolism. These two factors determine the short-term change in temperature and are calculated from the fMRI BOLD response (see section 2.2 for more on this).

2.2 Our Approach

The fundamental difference between our temperature modeling approach and the single-voxel models discussed in section 2.1 is that we consider the entire head. The Pennes bioheat equation (eq. (2.1)) [5, 3] includes three terms. The first and second terms describe heat generation by metabolism and heat exchange by convection to blood flow. On shorter time scales, these two terms dominate and are sufficient for determining the temperature change; however, the third term becomes important on longer time scales.

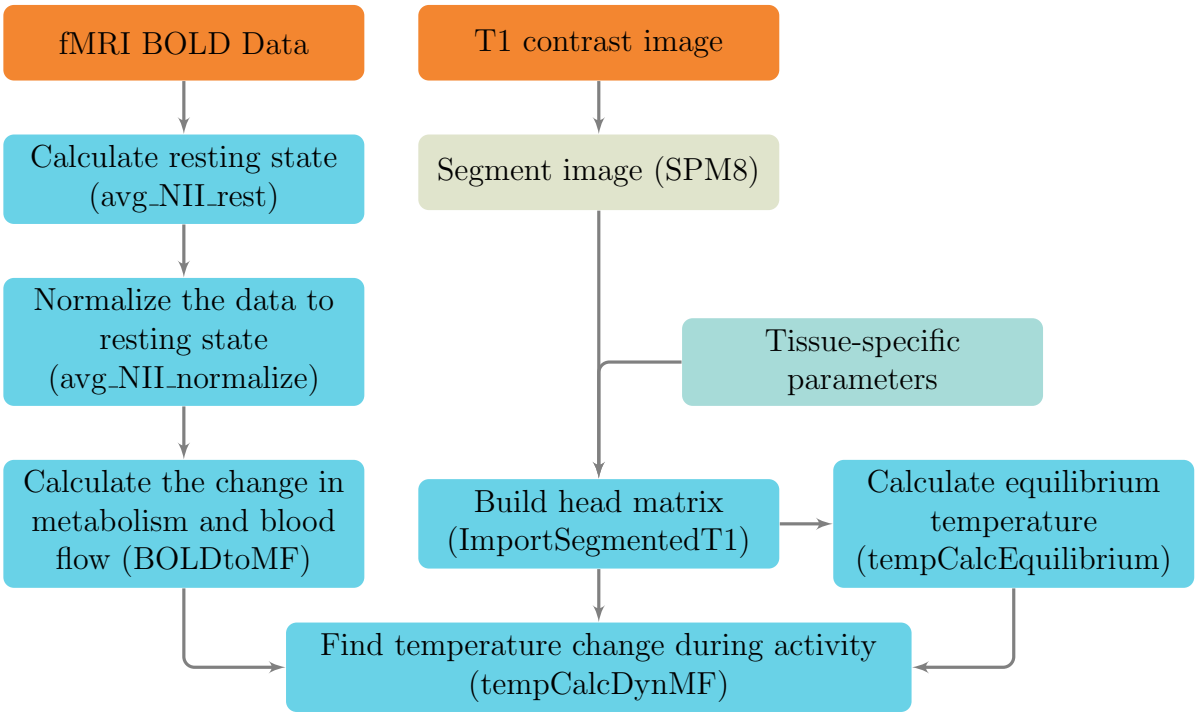
The third term describes the heat exchanged by conduction to surrounding tissues. This is a comparatively slow process, but on larger time scales determines the resting state temperature. When calculating the temperature change, it is important to first have an accurate resting state temperature. By considering the entire head, out model is able to accurately determine a resting state temperature for each voxel, enabling far more accurate temperature calculations than what is capable with single-voxel approaches. Figure 2.1 gives a schematic of the temperature calculation procedure.

[WRITE SOMETHING HERE]

2.2.1 Preparing the model of the head

In order to begin the temperature calculating procedure, a model of the head must first be created. Using SPM8 (`http://www.fil.ion.ucl.ac.uk/spm/`), we segmented a T1 contrast image of the head into five different tissue types: bone, cerebral spinal fluid, gray matter, white matter and soft tissue. It was assumed

Figure 2.1: The procedure used to calculate temperature from BOLD data. Orange blocks (●) represent data, the sandy-colored block (●) is a step done using SPM8 and the teal blocks (●) are steps done using a function provided within temptools (appendix A).



that soft tissue voxels that are in contact with air are more appropriately labeled as skin, so in total we are left with a model of the head separated in to six tissue types (fig. 2.2). The advantage this has is that we are able to use tissue specific parameters when doing the calculations, thereby improving the accuracy of the results. The parameters used are available in table 2.1. The code used to create the head matrix is discussed in appendix A.1.

2.2.2 Calculating the equilibrium temperature

The first step in calculating the temperature change is to first know what the resting state temperature is for each voxel within the head. Our approach was to have the initial temperature for all tissue voxels to be equal to 37°C and air voxels are kept at 24°C. The starting temperature of the tissue doesn't affect the final resting state temperature; however, starting off at drastically different values could greatly increase the calculating time required before the temperature stabilizes. The finite difference implementation of the Pennes bioheat equation (eq. (2.4)) is used to update the temperature. The temperature is updated until the temperature for every voxel has stabilized ($\frac{dT}{dt} < 10^{-6}$ °C/s). Since temperature changes due to changes in neuronal activity are typically greater than 10^{-2} °C, a change in temperature less than 10^{-6} °C/s is sufficiently small

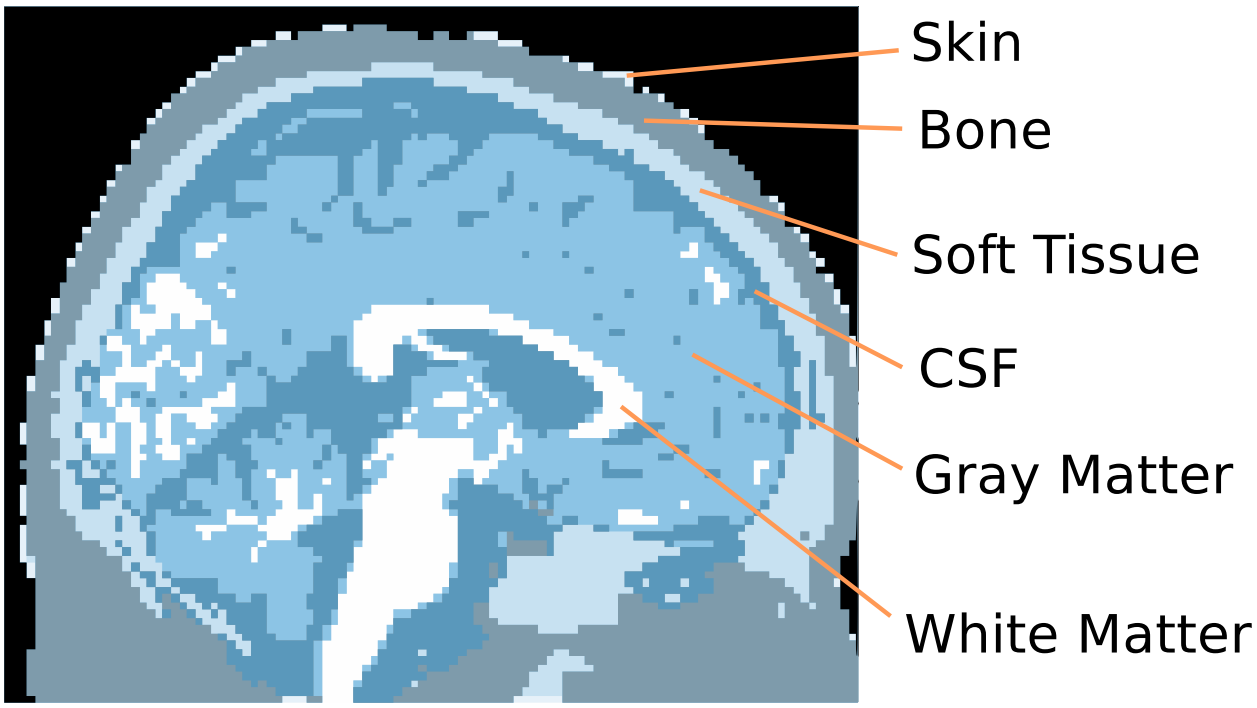


Figure 2.2: Slice of the segmented head. Each color represents a different tissue type.

that transient temperature changes are negligible and temperature can be considered stabilized. The code used to calculate the equilibrium temperature is detailed in appendix A.3.

Table 2.1: Tissue-specific parameters used to calculate the temperature change (from Collins et al. [4]).

Tissue	f_0 $100\ ml/(g\ min)$	ρ kg/m^3	c $J\ kg^{-1}\ ^\circ C^{-1}$	k $W\ m^{-1}\ ^\circ C^{-1}$	Q_m W/m^3
Bone	3	1,080	2,110	0.65	26.1
Cerebrospinal Fluid	0	1,007	3,800	0.50	0
Gray Matter	67.1	1,035.5	3,680	0.565	15,575
White Matter	23.7	1,027.4	3,600	0.503	5,192
Muscle	3.8	1,041	3,720	0.4975	687
Skin	12	1,100	3,150	0.342	1,100

Table 2.2: Parameters used to solve the single-voxel Penne's Bioheat Equation. (modified from Sotero and Iturria-Medina [3])

Parameter	Meaning	Value
T_a	Arterial blood temperature	37°C
C_{tissue}	Tissue Heat Capacity	3.664 J/(gK)
ΔH°	Enthalpy released by oxidation of glucose	4.710^5 J
ΔH_b	Enthalpy used to release O_2 from hemoglobin	2.810^4 J
$CMRO_2 \mid_0$	Cerebral metabolic rate of O_2 consumption at rest	0.026310^{-6} mol/(gs)
$CBF\mid_0$	Cerebral blood flow at rest	0.0093 cm^3/(gs)
ρ_b	Blood density	1.05 g/cm^3
C_B	Blood heat capacity	3.894 J/(gK)
τ	Time constant for conductive heat loss from the ROI to the surrounding tissue	190.52 s
a, b, c	Parameters of the gamma function fitted from E(f) vs. f	0.4492, 0.2216, −0.9872
A	Maximum BOLD signal change	0.22
α	Steady state flow-volume relation	0.4
β	Field-strength dependent parameter	1.5
Variable	**Meaning**	
m(t)	$CMRO_2$ normalized to baseline	
f(t)	CBF normalized to baseline	
T(t)	Temperature	
W(t)	Lambert W Function	
$\frac{\Delta S(t)}{S_0}$	Change in BOLD signal normalized to rest	

2.2.3 Calculating Metabolism and Blood Flow Changes from fMRI BOLD

This is the critical step where we use fMRI BOLD data to calculate the normalized change in metabolism and blood flow. The method used [3] is an assemblage of a couple other works [CITATION NEEDED]. It starts by using the relation between metabolism and blood flow proposed by Buxton et al. [6]:

$$m(t) = f(t)\frac{E(t)}{E_0} \tag{2.5}$$

where E_0 is the oxygen extraction at rest and $E(f)$ is

$$E(f) = 1 - (1 - E_0)^{\frac{1}{f(t)}} \tag{2.6}$$

in accordance with the oxygen limitation model [7]. Combining eq. (2.5) with eq. (2.6) yields

$$m(t) = \frac{f(t)}{E_0}\left[1 - (1 - E_0)^{\frac{1}{f(t)}}\right] \tag{2.7}$$

Sotero and Iturria-Medina [3] goes about solving eq. (2.7) by adjusting $E(t)$ data generated by eq. (2.6) and fitting it to the gamma function for the f range (0.7–2.0) that is within experimentally reported values [8, 9, 10]:

$$\frac{E(f)}{E_0} = af^c(t)e^{-bf(t)} \tag{2.8}$$

where values for a, b and c are provided in table 2.2. From this approximation we have the final form of metabolism:

$$m(t) = af^{c+1}(t)e^{-bf(t)}. \tag{2.9}$$

As proposed by Davis et al. [11], the BOLD signal changes ($\frac{\Delta S(t)}{S_0}$) can be described in terms of $m(t)$ and $f(t)$:

$$\frac{\Delta S(t)}{S_0} = \frac{S(t) - S_0}{S_0} = A(1 - f^{\alpha-\beta}(t)m^{\beta}(t)) \tag{2.10}$$

Substituting eq. (2.9) into eq. (2.10) yields

$$f(t)e^{-\frac{b\beta}{\alpha+\beta c}f(t)} = \left(\frac{\left(A - \frac{\Delta S(t)}{S_0}\right)}{Aa^{\beta}}\right)^{\frac{1}{\alpha+\beta c}} \tag{2.11}$$

where A is the maximum change in BOLD signal. Multiplying each side by $-\frac{b\beta}{\alpha+\beta c}$ gives

$$-\frac{b\beta}{\alpha+\beta c}f(t)e^{-\frac{b\beta}{\alpha+\beta c}f(t)} = -\frac{b\beta}{\alpha+\beta c}\left(\frac{\left(A - \frac{\Delta S(t)}{S_0}\right)}{Aa^{\beta}}\right)^{\frac{1}{\alpha+\beta c}} \tag{2.12}$$

which can be solved by using the Lambert W function

$$z = W(x) \tag{2.13}$$

where z is given by

$$ze^z = x \tag{2.14}$$

Finally, $f(t)$ is obtained from eq. (2.12)

$$f(t) = \frac{\alpha+\beta c}{b\beta}W(y(t)) \tag{2.15}$$

where

$$y(t) = -\frac{b\beta}{\alpha + \beta c}\left[\frac{(A - \frac{S(t)}{S_0} - 1)}{Aa^{\beta}}\right]^{\left(\frac{1}{\alpha+\beta c}\right)} \tag{2.16}$$

is a function of the BOLD signal. Using eqs. (2.9), (2.15) and (2.16) allows for the metabolism and blood flow to be calculated from the BOLD signal (values used are provided in table 2.2).

In order to process the files, the input BOLD data is stored in folder as a separate file for each time step. The first step in processing the data for temperature calculations is to determine a resting state BOLD signal (S_0). The resting state is calculated by taking the element-wise mean of the data when the subject is at rest (i.e. the first and last 20 seconds). This results in one data set where each voxel is a mean of all of the voxels at the location over time (S_0). In order to calculate the metabolism and blood flow, the BOLD dataset needs to be normalized to this resting state ($\frac{\Delta S(t)}{S_0}$).

Once $\frac{\Delta S(t)}{S_0}$ is known for each time step, eqs. (2.9), (2.15) and (2.16) can be used to calculate the metabolism and blood flow. The implementation of these functions is available in appendix A.2.

2.2.4 Calculating the change in temperature in the active brain

2.3 Results

2.3.1 Using Theoretical BOLD Data

2.3.2 Using Experimental BOLD Data

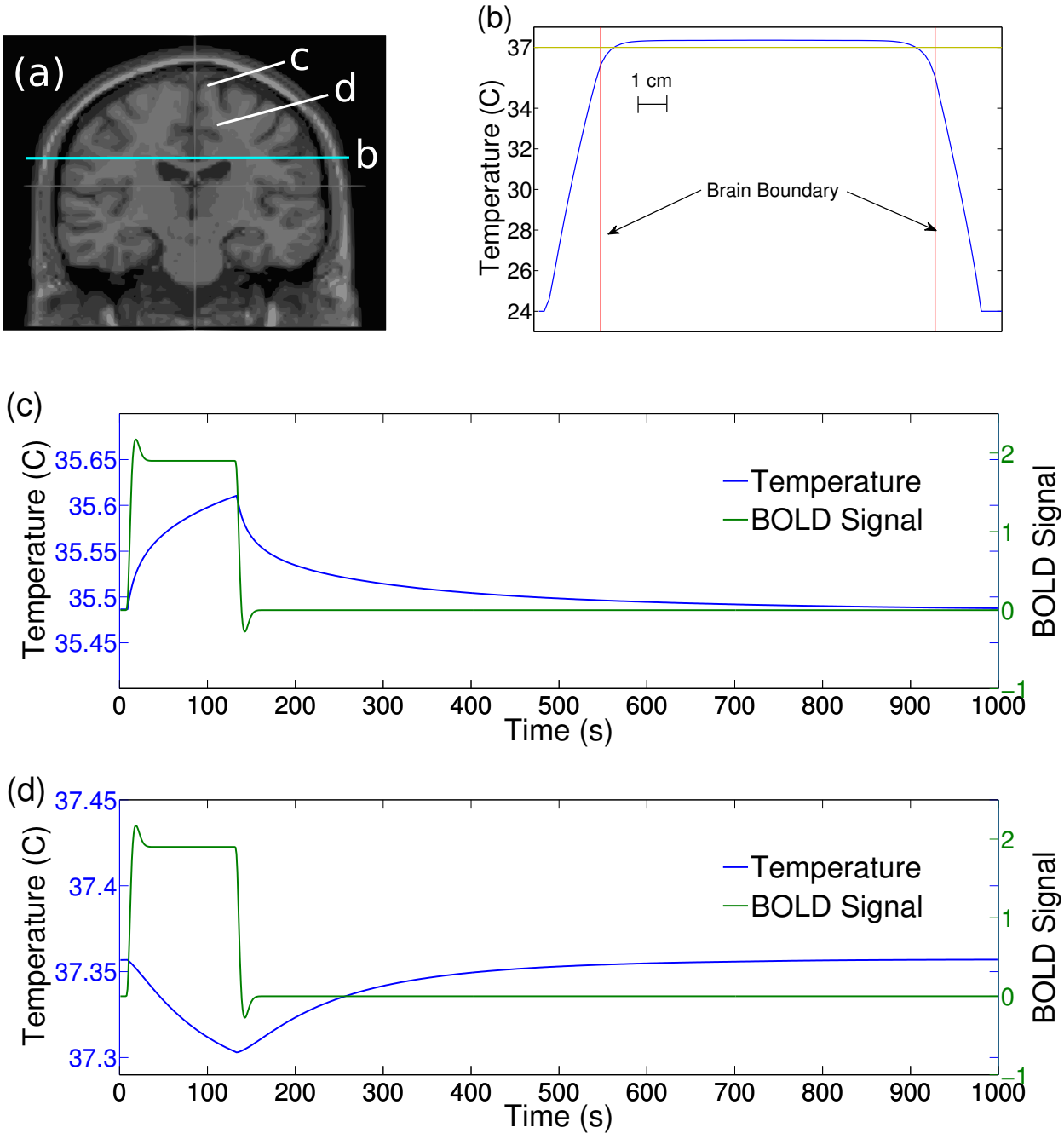


Figure 2.3: Temperature changes using simulated BOLD signals. (a) Slice of the head (y = -12) with indicators of the locations for parts (b)-(d). (b) Equilibrium temperature along a line through the head. Red lines indicate the brain boundary and the gold line indicates the blood temperature (37°C) used for calculations. Inside the brain, a 4-6 mm thick shell is created where the equilibrium temperature is less than the blood temperature. Within this shell, (c) the temperature rises with increased brain activity while (d) tissue deeper in the brain experiences the opposite effect.

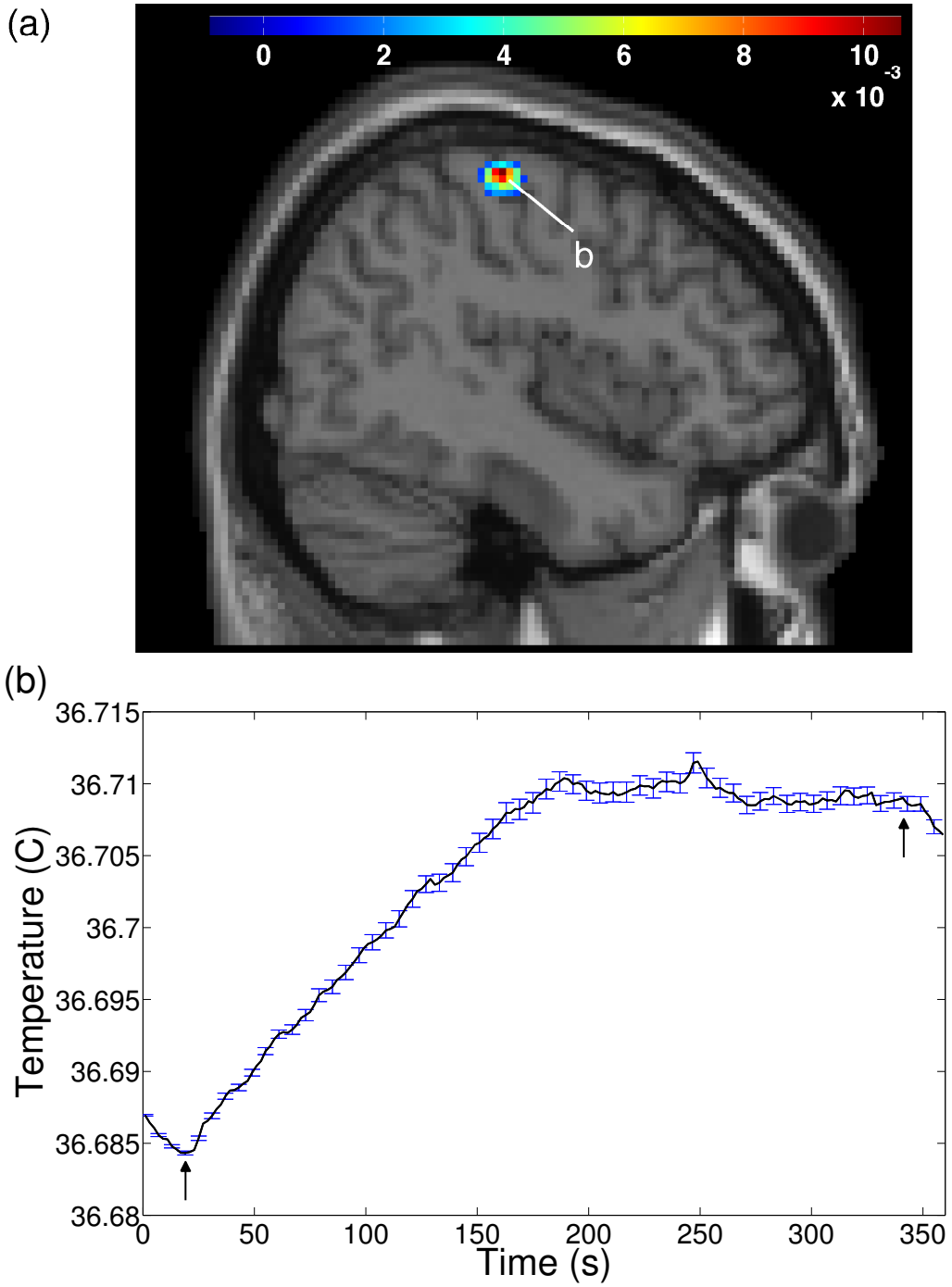


Figure 2.4: Temperature calculated from a voxel within the motor cortex. (a) A slice (x = -44) showing the motor cortex warming during a finger-tapping task. (b) Temperature at a voxel within the motor cortex (-44, -24, 60) with standard error indicated by blue error bars (Arrows indicate task onset and conclusion, N=24).

Chapter 3

Detector Applications to measuring the active brain

3.1 Functional Near-Infrared fNIR Imaging

$$I = I_0 e^{-\alpha x} \tag{3.1}$$

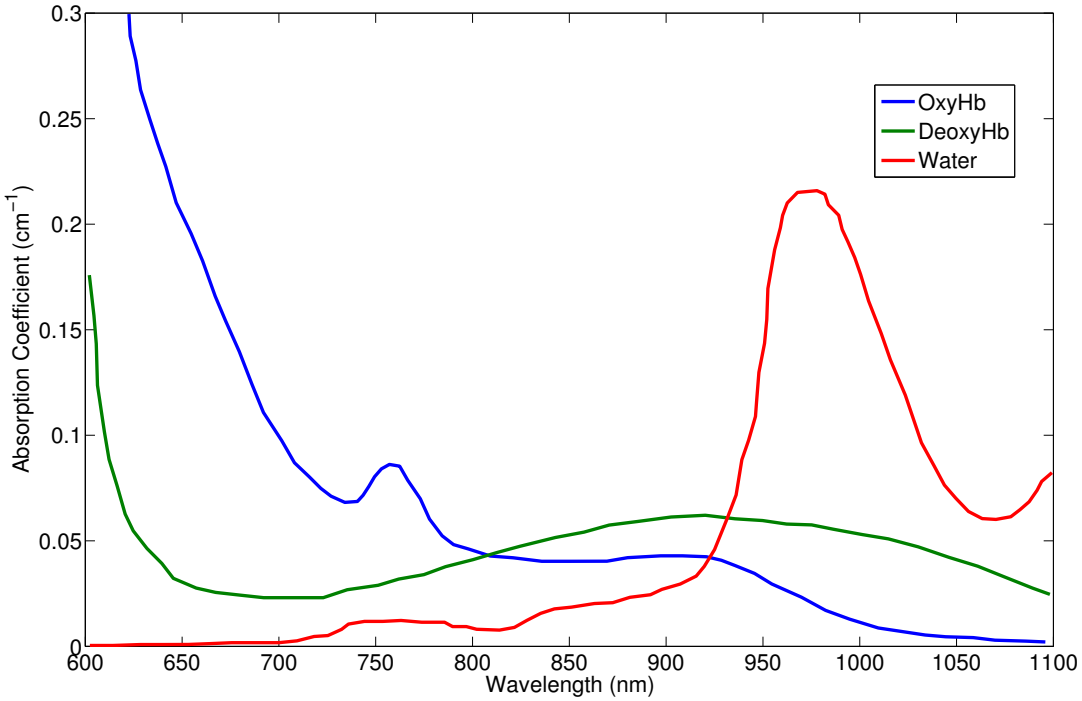


Figure 3.1: Absorption spectra of water, Hb and Dhb. From Cope [12] and HB stuff from Horecker [13]

3.2 Temperature Measurements

From the Beer-Lambert law eq. (3.1), the penetration depth, δ_p can be expressed as

$$\delta = \frac{1}{\alpha} \tag{3.2}$$

where α is the absorption coefficient. At body temperature (37°) the peak wavelength in the blackbody spectrum is approximately BLA. For water at this wavelength, α is approximately HUGE, so δ is VERY SMALL.

Chapter 4

Conclusion

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Appendix A

Code

The following sections include the code used. It was written for Matlab R2011b and requires SPM8 to run. Additionally, it is recommended that you have at least 4 GB of RAM in order to work with the large datasets that are produced. For information about how to visualize the data produced, see appendix B. All of the code is available through the temptools github page (`https://github.com/greggroth/temptools`). Additionally, many of the tasks can be completed using the temptools gui (figs. A.1 to A.4) which can be invoked by running

```
temptools
```

at the Matlab command prompt (make sure the temptools directory and subdirectories have been added to the Matlab path). The procedure used is explained in section 2.2 and a graphical representation is available in fig. 2.1.

Figure A.1: The main window of temptools. From here, you can go through the calculation steps and launch the visualization tool.

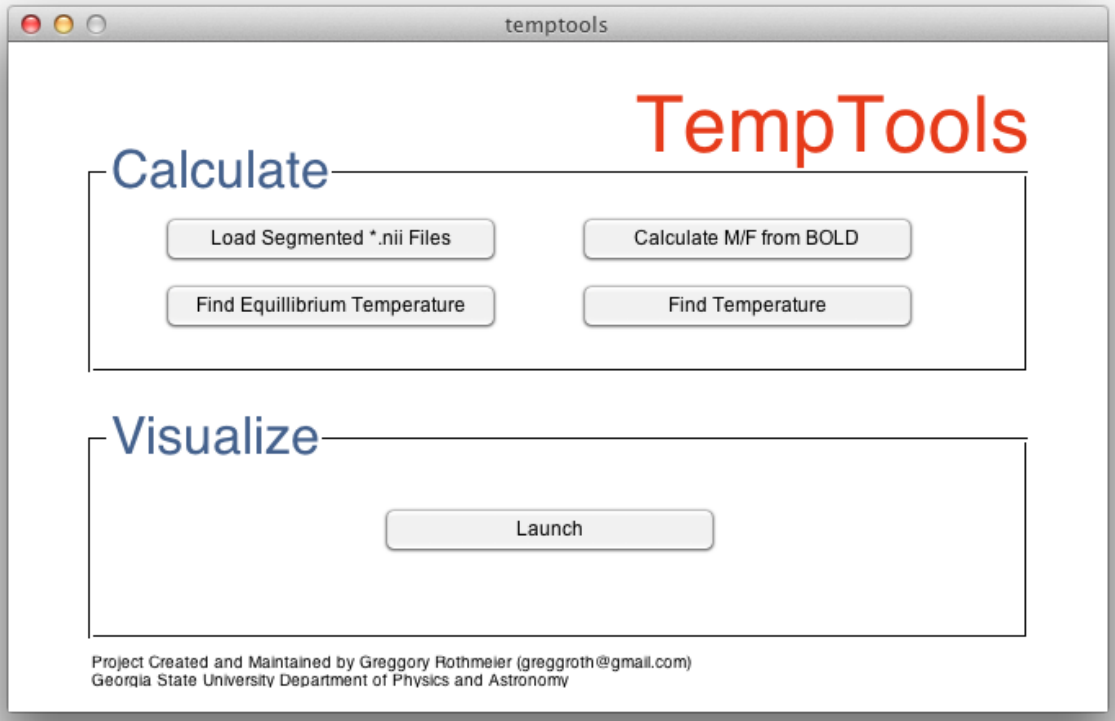


Figure A.2: This is the interface for calculating the equilibrium temperature (method explained in appendix A.3) under certain conditions.

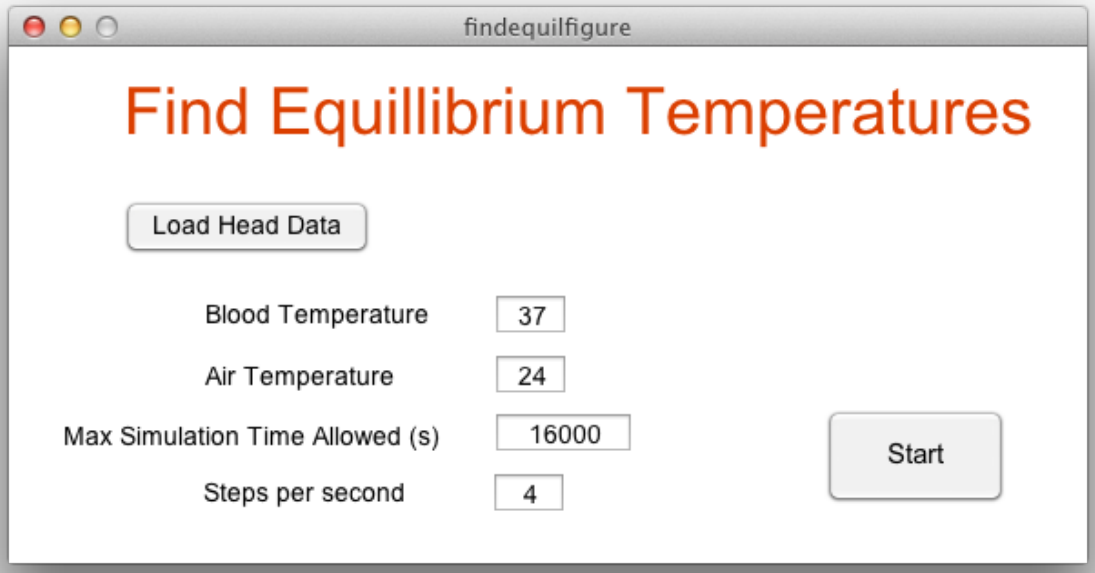


Figure A.3: The interface for calculating temperature changes when blood flow and metabolism are time dependent. This can be achieved by either loading metabolism and blood flow datasets or by using generated activity.

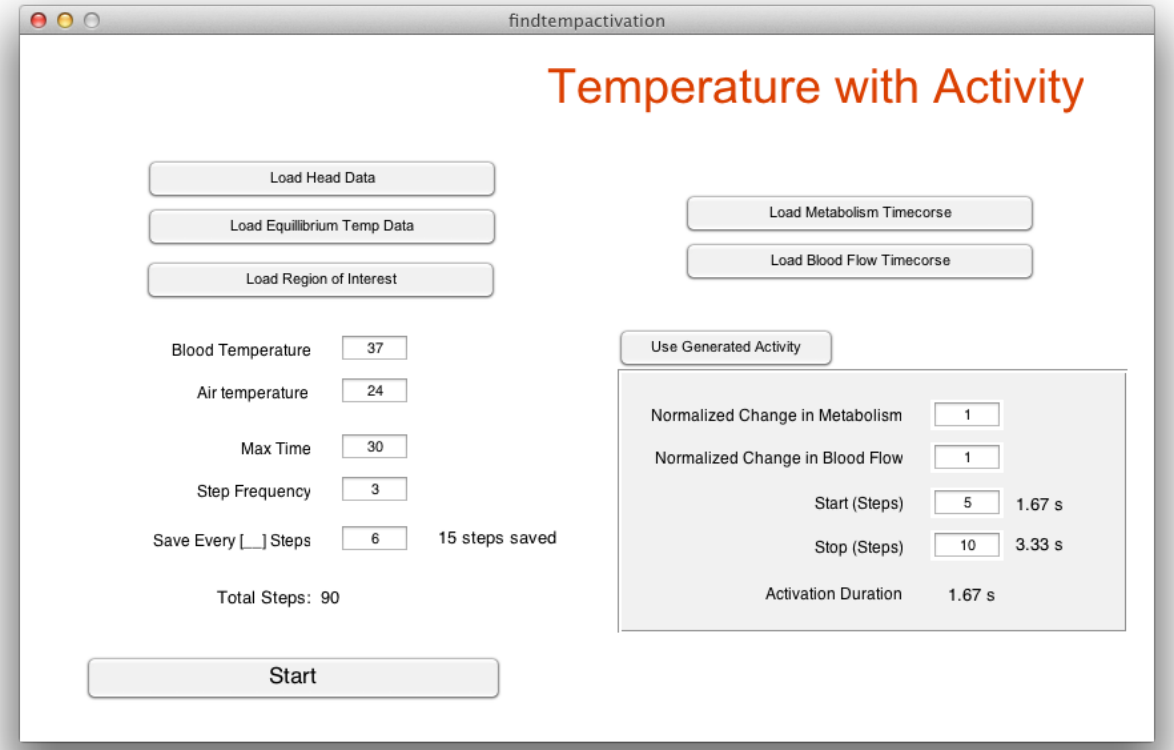
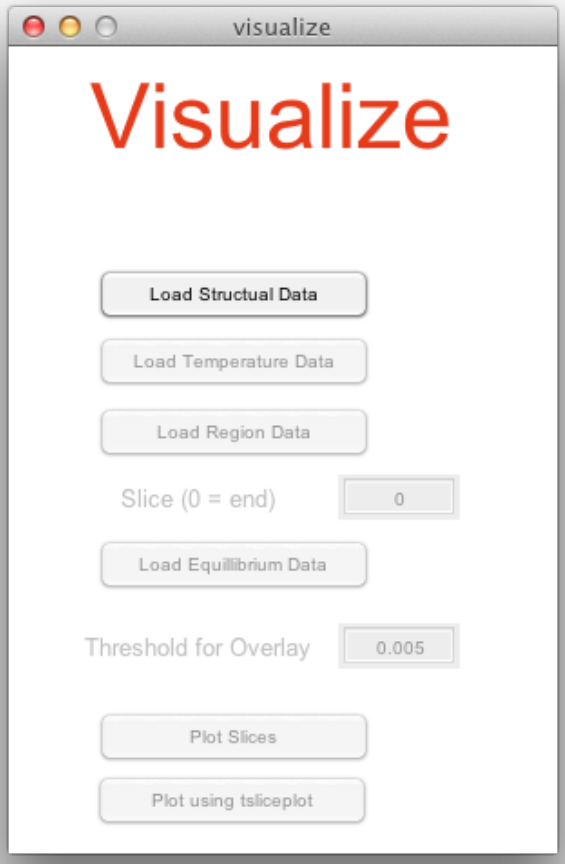


Figure A.4: Visualize your data using the temptools visualization window. This loads all of the required data and launches a slice browser or tsliceplot (see appendix B for more details).



A.1 Creating the Head Matrix

Before any calculations can be done, a matrix containing tissue-specific parameters must be created. First, a T1 contrast image should be segmented using SPM8 (`http://www.fil.ion.ucl.ac.uk/spm/software/spm8/`). For ease of consistency, the one provided by SPM8 in ./canonical/ is best to use. Using SPM's "New Segmentation" algorithim will segment the image into five different tissue types (gray matter, white matter, cerebral spinal fluid, soft tissue and bone). Once this is complete, run ImportSegmentedT1() within this directory and it will return a matrix that has been populated with the tissue-specific parameters required for accurate temperature calculations. The functions fillAir() (A.1.2), fillHoles() (A.1.3), build_skin() (A.1.4) and repair_headdata() (A.1.5) are functions required by BulkImportNII(). More information about this procedure is in section 2.2.1.

A.1.1 ImportSegmentedT1()

```
1  function [ total ] = ImportSegmentedT1(varargin)
2  %  ImportSegmentedT1 Import NII files from a directory
3  %   Must be run within the directory containing the files
4  %
5  %   Output: head data as single with variables stored in the 4th
6  %   dimension.
7  %
8  %   Author:  Greggory Rothmeier (greggroth@gmail.com)
9  %   Georgia State University
10 %   Created:  5/31/11
11
12 statusbar = waitbar(0,'Initializing');
13
14 if size(varargin) == 1
15     oldFolder = cd(varargin{1});
16 end
17
18
19 % =====================
```

```
% = Tissue Parameters =
% ======================
% Each tissue type is assigned an integer index (i.e. gray matter -> 11)
% such that tissue-specific parameters can be found by looking at that
% element within the corresponding storage matrix
% (i.e. QmSTORE(11) -> gray matter Qm)

% Parameters taken from Colins, 2004

tisorder = [11 15 5 13 3];  %  Using:  [GM WM CSF Muscle Bone]

QmSTORE = [0 0 26.1 11600 0 26.1 697 0 0 302 15575 0 697 1100 5192];
cSTORE = [1006 4600 2110 3640 3800 1300 3720 3000 4200 2300 3680 3500
   3720 3150 3600];
rhoSTORE = [1.3 1057 1080 1035.5 1007 1850 1126 1076 1009 916 1035.5 1151
    1041 1100 1027.4];
kSTORE = [0.026 0.51 0.65 0.534 0.5 0.65 0.527 0.4 0.594 0.25 0.565
   0.4975 0.4975 .342 .503];
wSTORE = [0 1000 3 45.2 0 1.35 40 0 0 2.8 67.1 3.8 3.8 12 23.7];

% ====================================
% = Import the pre-segmented T1 files =
% ====================================
%  The T1 contrast image sould be segmented using SPM8.
%  This loop needs to complete before the next one can begin
%  Import all of the datat and store as 'cdat1','cdat2', etc.
for i = 1:5
    eval(strcat('dat',num2str(i),' = loadNII(''rc', num2str(i), '
       single_subj_T1.nii'');'))
    %  Preallocate
    eval(strcat('out', num2str(i),' = zeros(cat(2,size(dat', num2str(i),'
       ),7));'))
end
```

```
48
49  % ============================
50  % = Populate the head matrix =
51  % ============================
52  %  For each data file, it fills in the data from the data storage arrays
53  %  for that particular type of tissue.  It picks which ever tissue is
54  %  the most likely candidate for that voxel based on the segmented data
55
56  %   PROBLEM:  It returns 0 (later filled with air) if there is equal
57  %   probability of a voxel being two or more different types of tissue.
58  %   SOLVED BY fillHoles()
59
60
61  for i = 1:5
62      %  Preallocate
63      holder = zeros(cat(2,size(dat1),7),'single');
64      mask = zeros(size(dat1));
65      final = zeros(size(holder),'single');
66
67      %  Create a mask that indicates whether it is the mostly likely
          tissue type
68      guide = [1 2 3 4 5 1 2 3 4 5];  %  This guides it through the data
          correctly
69      eval(strcat('mask = (dat',num2str(i),'>dat',num2str(guide(i+1)),') &
          (dat',num2str(i),'>dat',num2str(guide(i+2)),') & (dat',num2str(i),'
          >dat',num2str(guide(i+3)),') & (dat',num2str(i),'>dat',num2str(
          guide(i+4)),') & (dat',num2str(i),'~=0);'))
70      %  move structure data to new matrix
71      holder(:,:,:,1) = mask;
72      %  get indicies of tissues
73      a = find(holder(:,:,:,1) == 1);
74      %  gets coordinates from index
75      [x y z t] = ind2sub(size(holder),a);
```

```
76
77      %  go to each tissue point and store the info
78      for j = 1:length(a)
79          final(x(j),y(j),z(j),:) = [tisorder(i) 0 QmSTORE(tisorder(i))
                cSTORE(tisorder(i)) rhoSTORE(tisorder(i)) kSTORE(tisorder(i))
                wSTORE(tisorder(i))];
80      end
81
82      %  Saves the result to a unique output variable (out1, out2, etc)
83      eval(strcat('out',num2str(i),'= final;'))
84
85      clearvars a x y z t holder final;
86      waitbar(i/6,statusbar,sprintf(['File ',num2str(i),' Import Compete'])
          );
87  end
88
89  % The filleAir() function checks for any voxels which were not assigned a
90  % tissue type and fills them in with air
91  almostthere = fillAir(out1+out2+out3+out4+out5);
92  % The fillHoles() function corrects for a voxel having two
93  % equally-probable tissue types
94  total = single(buildskin(fillHoles(dat1,dat2,dat3,dat4,dat5,almostthere))
      );
95  waitbar(1,statusbar,'Saving Data')
96
97  cd(oldFolder);
98  close(statusbar);
99
100 end
```

A.1.2 fillAir()

```
1  function [ output ] = fillAir( tissue )
```

```
% fillAir() fills gaps in data with air
%   Once you import all of the data using loadNII(), run it thought this
    to
%   fill in the remaining spaces with air.

airdata = [1 0 0 1006 1.3 0.026 0];

%  Picks out air spots
a = find(tissue(:,:,:,1) == 0);
[x y z t] = ind2sub(size(tissue),a);

for i = 1:length(a)
    tissue(x(i),y(i),z(i),:) = airdata;
end

output = tissue;

end
```

A.1.3 fillHoles()

```
function [ out_head ] = fillHoles( in1,in2,in3,in4,in5,headin)
% fillHoles() checks for misassigned voxels
%
% Solves an issue where a voxel with two equally probable tissue
% types resulted in being assigned as air.  This checks for air
% voxels that are surrounded by tissue and decides a tissue it
% it would be best suited as

head = squeeze(headin(:,:,:,1));  %  I only need the tissue indices so
    this makes things easier down the line

%%  Data Storage
```

```
QmSTORE = [0 0 26.1 11600 0 26.1 697 0 0 302 15575 0 697 1100 5192];
cSTORE = [1006 4600 2110 3640 3800 1300 3720 3000 4200 2300 3680 3500
  3720 3150 3600];
rhoSTORE = [1.3 1057 1080 1035.5 1007 1850 1126 1076 1009 916 1035.5 1151
   1041 1100 1027.4];
kSTORE = [0.026 0.51 0.65 0.534 0.5 0.65 0.527 0.4 0.594 0.25 0.565
  0.4975 0.4975 .342 .503];
wSTORE = [0 1000 3 45.2 0 1.35 40 0 0 2.8 67.1 3.8 3.8 12 23.7];

%%  Get locations of holes
%   Where two tissue types have the same probability

idx1 = (in1==in2 | in1 == in3 | in1==in4 | in1==in5) & logical(in1);
idx2 = (in1==in2 | in2 == in3 | in2==in4 | in2==in5) & logical(in2);
idx3 = (in1==in3 | in2 == in3 | in3==in4 | in3==in5) & logical(in3);
idx4 = (in1==in4 | in2 == in4 | in3==in4 | in4==in5) & logical(in4);
idx5 = (in1==in5 | in2 == in5 | in3==in5 | in4==in5) & logical(in5);
%  This array will have a zero anywhere there were two or more common
%  elements between any of the five arrays.
idx = idx1|idx2|idx3|idx4|idx5;

[xmax ymax zmax] = size(in1)
[x y z] = ind2sub(size(in1),find(idx));  %  get x, y and z coordinates of
   the holes

for i = 1:length(x)  %  go to each hole and do work
    if (x(i)~=1)&&(y(i)~=1)&&(z(i)~=1)&&(x(i)~=xmax)&&(y(i)~=ymax)&&(z(i)
      ~=zmax)&&(headin(x(i),y(i),z(i),1)==1)  %  keeps away from the edge
       and only looks at voxels that were assigned air
        [commonesttissue nouse secondbest] = mode([head(x(i)+1,y(i),z(i))
           head(x(i)-1,y(i),z(i)) head(x(i),y(i)+1,z(i)) head(x(i),y(i)
          -1,z(i)) head(x(i),y(i),z(i)+1) head(x(i),y(i),z(i)-1)]);
```

```
36          if commonesttissue == 1 && length(secondbest{1})>=2  % if air and
                something else are equally common, it'll choose air.  This
              forces it to pick the tissue if possible.
37              commonesttissue = secondbest{1}(2);
38          end
39          headin(x(i),y(i),z(i),:) = [commonesttissue 0 QmSTORE(
              commonesttissue) cSTORE(commonesttissue) rhoSTORE(
              commonesttissue) kSTORE(commonesttissue) wSTORE(commonesttissue
              )];
40      end
41  end
42
43  out_head = headin;
44
45  end
```

A.1.4 build_skin()

```
1   function [ head_out ] = build_skin( head_in )
2   % build_skin() Creates a layer of skin around the head
3   %
4   % This will check all voxels that were previously labeled
5   % as soft tissue and checks if it has a neighbor which is air.
6   % If so, then it is reassigned as skin.
7
8   if ndims(head_in)==4
9       head_in = head_in(:,:,:,1);
10  end
11
12  % Git a list of all voxels labeled as muscle
13  muscle_voxels = find(head_in==13);
14
15  % Go through each of them and check for neighboring air voxels
```

```
for i=1:length(muscle_voxels)
    [x y z] = ind2sub(size(head_in), muscle_voxels(i));
    % makes sure we're not at a voxel at the boundry of the dataset
    if (x~=1) && (x~=size(head_in,1)) && (y~=1) && (y~=size(head_in,2)) &&
        (z~=1) && (z~=size(head_in,3))
      % Looks for neighboring voxels that are air
      if ((head_in(x+1,y,z)==1) || (head_in(x-1,y,z)==1) || (head_in(x,y
        +1,z)==1) || (head_in(x,y-1,z)==1) || (head_in(x,y,z+1)==1) || (
        head_in(x,y,z-1)==1))
          head_in(x,y,z) = 14;
      end
    end
end

head_out = repair_headdata(head_in);

end
```

A.1.5 repair_headdata()

This function will go through the dataset and make sure the tissue-specific parameters are correct for the tissue type assigned for that voxel. fillAir(), fillHoles() and build_skin() all correct mislabeled voxels, but they only correct the tissue assignment. After using any of these functions, the data must be passed through repair_headdata to update the stored parameters.

```
function [ head_out ] = repair_headdata( head_in )
% repaid_headdata repopulates the headdata matrix
%   If any changes are made to the index column in the headdata matrix,
   use
%   this function to repopulate and correct the parameter values before
   running
% any other functions.
%  head_in can be either 3 or 4 dimenisions

```

```
8
9  % ======================
10 % = Parameter Storage =
11 % ======================
12
13 QmSTORE = [0 0 26.1 11600 0 26.1 697 0 0 302 15575 0 500 1100 5192];
14 cSTORE = [1006 4600 2110 3640 3800 1300 3720 3000 4200 2300 3680 3500
     3010 3150 3600];
15 rhoSTORE = [1.3 1057 1080 1035.5 1007 1850 1126 1076 1009 916 1035.5 1151
      978.5 1100 1027.4];
16 kSTORE = [0.026 0.51 0.65 0.534 0.5 0.65 0.527 0.4 0.594 0.25 0.565
     0.4975 0.3738 .342 .503];
17 wSTORE = [0 1000 3 45.2 0 1.35 40 0 0 2.8 67.1 3.8 3.3 12 23.7];
18
19 if ndims(head_in)==4
20     head_in = head_in(:,:,:,1);
21 end
22
23 % Reassign the parameter values
24 head_out = cat(4,head_in, zeros(size(head_in)), QmSTORE(head_in), cSTORE(
     head_in), rhoSTORE(head_in), kSTORE(head_in), wSTORE(head_in));
25
26 end
```

A.2 Loading the fMRI Data

The following sections details the processing required to convert the BOLD data (in NIFTI format) to metabolism and blood flow time-courses that can then be used to calculate temperature.

A.2.1 sample_bold_import()

The following code automates the procedure of processing and doing all the calculations on the dataset reported in Dhamala et al. [14]. It's is written for my data on my machine, but it can be used to gain a better understanding of the procedure. For a conceptual explanation, see section 2.2.3.

```
%%=====================================================================
%%     How to process preprocessed BOLD data to calculate temperature
%%=====================================================================

% This Matlab script was used to automate the the process of using BOLD
   data
% stored in NIFTI (*.nii) format to calculate temperature changes.  The
% particulars of the code may be specific to this case, but the procedure
% should be the same when doing these calculations on other datasets.
   All
% required functions are included as an attachment to my thesis and are
% available on my github (https://github.com/greggroth/tempcalc)

cd('/Users/Greggory/Documents/Data/fmri_rhythmic_tapping01/NIFTI')

directories = dir('*01');

%%  Move coregistered files to new Directory
for i = 1:length(directories)
    dir_name = directories(i).name;
    main_path = cd( [dir_name filesep dir_name '_NIFTI_1'] );
    mkdir 'Coregistered'
    movefile('r*.nii','Coregistered')
```

```
22      main_path = cd( [dir_name filesep dir_name '_NIFTI_2'] );
23      mkdir 'Coregistered'
24      movefile('r*.nii','Coregistered')
25      cd(main_path)
26  end
27
28  %%  Calculate Rest State
29  disp('Calculating Rest State')
30  for i = 1:length(directories)
31      dir_name = directories(i).name;
32      avg_NII_rest([dir_name filesep dir_name '_NIFTI_1' filesep '
          Coregistered']);
33      avg_NII_rest([dir_name filesep dir_name '_NIFTI_2' filesep '
          Coregistered']);
34  end
35
36
37  %%  Normalize to Rest and Mask
38  disp('Normalize to Rest and Mask')
39  for i = 1:length(directories)
40      dir_name = directories(i).name;
41      avg_NII_normalize([dir_name filesep dir_name '_NIFTI_1' filesep '
          Coregistered'], fullfile(dir_name, [dir_name '_NIFTI_1'], '
          Coregistered', 'RestState', 'RestStateAvg.nii'), 'fullBrainMask.nii
          ');
42      avg_NII_normalize([dir_name filesep dir_name '_NIFTI_2' filesep '
          Coregistered'], fullfile(dir_name, [dir_name '_NIFTI_2'], '
          Coregistered', 'RestState', 'RestStateAvg.nii'), 'fullBrainMask.nii
          ');
43  end
44
45
46  %%  Calculate metabolism and blood flow change
```

```
47 disp('Calculate metabolism and blood flow change')
48 for i = 1:length(directories)
49     dir_1 = [ directories(i).name filesep  directories(i).name '_NIFTI_1'
           filesep 'Coregistered' filesep 'Normalized_to_rest'];
50     dir_2 = [ directories(i).name filesep  directories(i).name '_NIFTI_2'
           filesep 'Coregistered' filesep 'Normalized_to_rest'];
51     BOLDtoMF(dir_1);
52     BOLDtoMF(dir_2);
53 end
54
55
56 %%  Calculate the change in temperature based on metabolism and blood
     flow
57
58 % load('equil.mat');  % equillibriumT
59 % load('tt_headdata.mat');  % headdata
60 mask = loadNII('fullBrainMask.nii');
61
62 for i = 1:length(directories)
63     disp([int2str(i) '-1 started'])
64     tic
65     % Part I
66     actResult.dat = tempCalcDynMF(headdata, 37, 24, 720, 360,
         equillibriumT, ...
67         fullfile(directories(i).name,[directories(i).name '_NIFTI_1'],'
             Coregistered', 'Normalized_to_rest', 'Output_18-Sep-2011', 'm.
             mat'), ...
68         fullfile(directories(i).name,[directories(i).name '_NIFTI_1'],'
             Coregistered', 'Normalized_to_rest', 'Output_18-Sep-2011', 'f.
             mat'), ...
69         4, mask);
70     % Store the parameters used for the calculations for reference in the
         future
```

```
71      [c lmax] = max(actResult.dat(:));
72      [likelymax x y z] = ind2sub(size(actResult.dat),lmax);
73      actResult.likelymaxslice = round(likelymax/2);
74      actResult.bloodT = 37;
75      actResult.airT = 24;
76      actResult.tmax = 360;
77      actResult.stepf = 2;
78      actResult.savestepf = 4;
79      actResult.metabandflowdata = 'From Dataset';
80      save(fullfile(directories(i).name,[directories(i).name '_NIFTI_1'],'
          Coregistered', 'Normalized_to_rest', 'Output_18-Sep-2011','
          tt_act_res.mat'), 'actResult');
81      old = cd([directories(i).name,filesep,[directories(i).name '_NIFTI_1'
          ],filesep,'Coregistered', filesep,'Normalized_to_rest', filesep,'
          Output_18-Sep-2011']);
82      writeT_to_nii(actResult, equillibriumT, exp_nii);
83      cd(old)
84      clear actResult
85      % Part II
86      disp([int2str(i) '-2 started'])
87      actResult.dat = tempCalcDynMF(headdata, 37, 24, 720, 360,
          equillibriumT, ...
88          fullfile(directories(i).name,[directories(i).name '_NIFTI_2'],'
              Coregistered', 'Normalized_to_rest', 'Output_18-Sep-2011', 'm.
              mat'), ...
89          fullfile(directories(i).name,[directories(i).name '_NIFTI_2'],'
              Coregistered', 'Normalized_to_rest', 'Output_18-Sep-2011', 'f.
              mat'), ...
90          4, mask);
91      [c lmax] = max(actResult.dat(:));
92      [likelymax x y z] = ind2sub(size(actResult.dat),lmax);
93      actResult.likelymaxslice = round(likelymax/2);
94      actResult.bloodT = 37;
```

```
95      actResult.airT = 24;
96      actResult.tmax = 360;
97      actResult.stepf = 2;
98      actResult.savestepf = 4;
99      actResult.metabandflowdata = 'From Dataset';
100     save(fullfile(directories(i).name,[directories(i).name '_NIFTI_2'],'
          Coregistered', 'Normalized_to_rest', 'Output_18-Sep-2011','
          tt_act_res.mat'), 'actResult');
101     old = cd([directories(i).name,filesep,[directories(i).name '_NIFTI_2'
          ],filesep,'Coregistered', filesep,'Normalized_to_rest', filesep,'
          Output_18-Sep-2011']);
102     writeT_to_nii(actResult, equillibriumT, exp_nii);
103     cd(old)
104     clear actResult
105     disp([int2str(i) ' finished in ' num2str(toc)])
106 end
```

A.2.2 avg_NII_rest()

```
1  function [ ] = avg_NII_rest( varargin )
2  %UNTITLED4 Summary of this function goes here
3  %   Detailed explanation goes here
4
5  %% Setup
6  switch length(varargin)
7      case 0
8          fold_name = uigetdir;
9          if ~fold_name  % Cancel Button
10             return
11         end
12     case 1
13         fold_name = varargin{1};
14     otherwise
```

```
15 end
16
17 %  Go to the folder containing the files
18 oldfold = cd(fold_name);
19 file_list = dir('*.nii');
20
21 %  We're only interested in the rest period
22 %  (first and last 10 steps in this case)
23 file_list = file_list([1:10 170:180]);
24 file_count = length(file_list);
25
26 %  Cell array to store all of the datasets in.
27 datHolder = cell(file_count,1);
28
29 statusbar = waitbar(0,'Initializing');
30
31 for j=1:file_count
32     try
33         waitbar(j/file_count,statusbar,sprintf('%d%%',round((j/file_count
              )*100)));
34     catch err
35         return
36     end
37     fi = load_nii(file_list(j).name);
38     datHolder{j} = fi.img;
39 end
40
41 %%  Calculate the mean
42 ymax = size(datHolder{1},2);
43 zmax = size(datHolder{1},3);
44 output = zeros(size(datHolder{1}));
45
46 for i=1:ymax
```

```
47      try
48          waitbar(i/ymax,statusbar,sprintf('%d%%',round((i/ymax)*100)));
49      catch err
50          return
51      end
52      for k=1:zmax
53          excStr = cell(length(datHolder),1);
54          for l=1:length(datHolder)
55              excStr{l} = [',datHolder{' int2str(l) '}(:,' int2str(i) ','
                    int2str(k) ')''''];
56          end
57          comb = eval(['cat(1' cell2mat(excStr') ')']);
58          output(:,i,k) = mean(comb);
59      end
60  end
61
62  close(statusbar)
63
64  fi.img = output;
65  mkdir('RestState')
66  save_nii(fi,fullfile('RestState','RestStateAvg.nii'));
67
68  cd(oldfold)
69
70  end
```

A.2.3 avg_NII_normalize()

```
1   function [  ] = avg_NII_normalize( varargin )
2   %UNTITLED6 Normalize to rest state
3   %   Detailed explanation goes here
4
5   %% Setup
```

```
switch length(varargin)
    case 0
        fold_name = uigetdir('Directory Containing Data');
        if ~fold_name  % Cancel Button
            return
        end

        [rest_file rest_path rest_index]= uigetfile('*.nii','Resting
          State NIFTI File');
        switch rest_index
            case 0
                return
            case 1
                rest_dat = load_nii(fullfile(rest_path,rest_file));
                rest_dat = double(rest_dat.img);
            otherwise
                error('An error has occured loading the resting state
                  data')
        end

        [mask_file mask_path mask_index] = uigetfile('*.nii','Mask');
        switch mask_index
            case 0
                return
            case 1
                mask_dat = load_nii(fullfile(mask_path, mask_file));
                mask_dat = logical(mask_dat.img);
                if max(size(mask_dat) ~= size(rest_dat))
                    error('The Mask and Resting State files must have the
                        same size')
                end
            otherwise
```

```
35                  error('An error has occured loading the resting state
                      data')
36              end
37          case 1
38              fold_name = varargin{1};
39              [rest_file rest_path rest_index]= uigetfile('*.nii','Resting
                  State NIFTI File');
40              switch rest_index
41                  case 0
42                      return
43                  case 1
44                      rest_dat = load_nii(fullfile(rest_path,rest_file));
45                      rest_dat = double(rest_dat.img);
46                  otherwise
47                      error('An error has occured loading the resting state
                          data')
48              end
49          case 2
50              fold_name = varargin{1};
51              rest_dat = loadNII(varargin{2});
52              [mask_file mask_path mask_index] = uigetfile('*.nii','Mask');
53              switch mask_index
54                  case 0
55                      return
56                  case 1
57                      mask_dat = load_nii(fullfile(mask_path, mask_file));
58                      mask_dat = logical(mask_dat.img);
59                      if max(size(mask_dat) ~= size(rest_dat))
60                          error('The Mask and Resting State files must have the
                              same size')
61                      end
62                  otherwise
```

```
63                  error('An error has occured loading the resting state
                      data')
64          end
65      case 3
66          fold_name = varargin{1};
67          rest_dat = loadNII(varargin{2});
68          mask_dat = loadNII(varargin{3});
69      otherwise
70          return
71  end
72
73  %  Go to the folder containing the files
74  oldfold = cd(fold_name);
75  file_list = dir('*.nii');
76  file_count = length(file_list);
77
78  %  Make a directoy to save the normalized data to
79  saveDir = 'Normalized_to_rest';
80  if ~isdir(saveDir)
81      mkdir(saveDir);
82  end
83
84  statusbar = waitbar(0,'Initializing');
85
86  % for each file: load it, devide by the rest state and save it
87  for i=1:file_count
88      try
89          waitbar(i/file_count,statusbar,[fold_name sprintf('%d%%',round((i
                /file_count)*100))]);
90      catch err
91          return
92      end
93      [file_path file_name file_ext] = fileparts(file_list(i).name);
```

```
94      file_hold = load_nii(file_list(i).name);
95      file_hold.img = double(file_hold.img)./rest_dat - 1;
96      file_hold.img(~mask_dat) = 0;              % set everything outside
          the mask to 0
97      file_hold.img(isnan(file_hold.img)) = 0;  % set all NaN's to 0
98      file_hold.img(isinf(file_hold.img)) = 0;  % set all inf's to 0
99      file_hold.img(file_hold.img == -1) = 0;   % correct these for voxels
          that are giving me problems
100     file_hold.hdr.dime.datatype = 16;  % set the datatype to single
101     file_hold.hdr.dime.bitpix = 16;
102     save_nii(file_hold,fullfile(saveDir,[file_name '_rn' file_ext]))
103 end
104
105 close(statusbar)
106 cd(oldfold)
107
108 end
```

A.2.4 BOLDtoMF()

```
1  function [ ] = BOLDtoMF( varargin)
2  %BOLDtoMF Calculate metabolism and blood from from BOLD reponse
3  %
4  %   Input: Directory containing a series of *.nii files of the BOLD
5  %   response.
6  %
7  %   Output: Two new files will be created in a new subdirectory with a
8  %   variable for each time step.
9  %
10 %   Usage:
11 %       BOLDtoMF
12 %       BOLDtoMF(directory)
13 %
```

```
14 %   If a directory is not provided, one will be requested.
15 %
16 %   Method from Sotero, et. al. 2010
17
18 % =========
19 % = Setup =
20 % =========
21
22 % if a folder isn't an argument, it'll prompt for one
23 switch length(varargin)
24     case 0
25         fold_name = uigetdir;
26         if ~fold_name  % Cancel Button pressed
27             return
28         end
29     case 1
30         fold_name = varargin{1};
31     otherwise
32         error('Input is not understood')
33 end
34
35 %  Go to the folder containing the files
36 oldfold = cd(fold_name);
37 file_list = dir('*.nii');
38 file_count = length(file_list);
39
40 %  Set up a directory for the outputs
41 newFolder = ['Output_',datestr(clock,1)];
42 mkdir(newFolder)
43
44 %  Make *.mat files to append the data to
45 m0001 = 0; f0001 = 0;
46 save(['./' newFolder '/m.mat'],'m0001');
```

```
47  save(['./' newFolder '/f.mat'],'f0001');
48
49  s = loadNII(file_list(1).name);
50  norm = ones(size(s));
51
52  % ===========
53  % = Do Work =
54  % ===========
55  % This will calculate the metabolism and blood flow.  The output is
56  % appended to 'm.mat' and 'f.mat' within a new folder created
57  % within the directory containing the data.
58
59  statusbar = waitbar(0,'Initializing');
60
61  maxBOLD = 0.22;
62
63  % Required Parameters
64  %   [alpha beta a      b      c      A    ]
65  p = [0.4 1.5 0.1870 0.1572 -0.6041 maxBOLD];
66
67  % Calc flow and metabolism for when BOLD = 1
68  s = 0;
69  y = -((p(4)*p(2))/(p(1)+p(2)*p(5)))*((p(6)-s)/(p(6)*p(3)^p(2)))^(1/(p(1)+
      p(2)*p(5)));
70  fNOACT = -((p(1)+p(2)*p(5))/(p(4)*p(2)))*lambertw(y);
71  mNOACT = p(3)*fNOACT^(p(5)+1)*exp(-p(4)*fNOACT);
72
73
74  %%  Calc flow and metabolism
75  disp(fold_name)
76  for j=1:file_count
77      try
```

```
78          waitbar(j/file_count, statusbar, sprintf('%d%%', round((j/
                file_count)*100)));
79      catch err
80          return
81      end
82      s = loadNII(file_list(j).name);  %  Load up the file
83      s(isnan(s)) = 1;
84      s(isinf(s)) = 1;
85      y = -((p(4)*p(2))/(p(1)+p(2)*p(5))).*((p(6)-s)./(p(6)*p(3)^p(2)))
            .^(1/(p(1)+p(2)*p(5)));
86      if (size(y,1)==91)&&(size(y,2)==109)&&(size(y,3)==91)
87          f = -((p(1)+p(2)*p(5))/(p(4)*p(2))).*lambw_mex(real(y));
88      else
89          f = -((p(1)+p(2)*p(5))/(p(4)*p(2))).*lambw(y);
90      end
91      m = p(3)*f.^(p(5)+1).*exp(-p(4)*f);
92      % Clean up NaNs that may have popped up
93      m(isnan(m))=1;
94      f(isnan(f))=1;
95      % Normalize to resting m and f
96      m = m./mNOACT;
97      f = f./fNOACT;
98
99      % Rename and save the data
100     eval(['m' sprintf('%04d',j) ' = m;']);
101     eval(['f' sprintf('%04d',j) ' = f;']);
102     eval(['save(''./' newFolder '/m.mat'', ''m' sprintf('%04d',j) ''','''-
            append'');']);
103     eval(['save(''./' newFolder '/f.mat'', ''f' sprintf('%04d',j) ''','''-
            append'');']);
104     clear m0* f0*
105 end
106
```

```
107 close(statusbar)
108 cd(oldfold)
109
110 end
```

A.2.5 lambw() and lambw_mex()

The lambw() function is a wrapper for the wapr() function available on Matlab FileExchange (`http://www.mathworks.com/matlabcentral/fileexchange/3644-real-values-of-the-lambert-w-function/content/Lambert/wapr.m`). A compiled version of this function (lambw_mex()) runs much faster and is recommended. This function is used over Matlab's built-in Lambert-W function for the sake of performance.

```
1  function [ array_out ] = lambw( array_in )
2  % lambw Wrapper for wapr()
3  % Available:  http://www.mathworks.com/matlabcentral/fileexchange/3644-
     real-values-of-the-lambert-w-function/content/Lambert/wapr.m
4  %   Dwapr() doesn't work any arrays over Nx1, so this steps through the
5  %   full matrix and gives the rows to wapr.  Works pretty fast.
6
7  %#codegen
8
9  if ndims(array_in) ~= 3
10     error('This only works (for now) with a three dimensional array.')
11 end
12
13 xmax = size(array_in,1);
14 ymax = size(array_in,2);
15
16 array_out = zeros(size(array_in));
17 for ix=1:xmax
18     for iy=1:ymax
19         array_out(ix,iy,:) = wapr(array_in(ix,iy,:));
20     end
21 end
```

```
22
23 end
```

A.3 Calculating the Equilibrium Temperature

In order to determine the temperature fluctuations due to changes in activity, the baseline temperature must first be established for each voxel. The function tempCalcEquilibrium() will update the temperature using the Penne's bioheat equation (eq. (2.4)) until the change in temperature for each voxel falls below a certain threshold. Details about this procedure are available in section 2.2.2.

A.3.1 tempCalcEquilibrium()

```
1  function temperature_Out = tempCalcEquillibrium(tissue,bloodT,airT,nt,
     tmax,pastCalc,printprogress)
2  % tempCalcEquillibrium  Find the equillibrium values
3  %   tissue: holds all of the strucual information
4  %   bloodT: Temperature of the blood
5  %   airT:   Temperature of the surrounding ait
6  %   nt:     Max number of time steps
7  %   tmax:   Total amount of time the simulation should run over
8  %
9  %   This is based off of tempCalc() but loops until the rate of change of
10 %   a each voxel is sufficiently small then outputs what's
11 %   calculated.  If if takes too long to do all at once, split it up into
12 %   smaller time chunks and use the last step from the previous dataset
     as
13 %   pastCalc in order to resume.
14 %
15 %   Note: This does not save the time corse because it can take a lot of
     step to
16 %   find the equillibrium.  It outputs the last time step.
17 %
18 %   Writen by Greggory Rothmeier (greggroth@gmail.com)
19 %   Georgia State University Dept. Physics and Astronomy
20 %   May, 2011
21 tic
```

```
%%   Default Values
if nargin<2, bloodT = 37;        end
if nargin<3, airT = 24;          end
if nargin<4, nt = 100;           end
if nargin<5, tmax = 50;          end
if nargin<6, pastCalc = 0;       end
if nargin<7, printprogress = 1; end

% These rescue the data if the calculation is interrupted.
global temperature
global dirty

c = onCleanup(@InterCatch);
dirty = 1;

dx = 2*10^-3;         %  Voxel size (m)

if nt<(2*tmax),
   warning('Time step size is not large enough.  Results will be
     unreliable.  Consider increasing the number of steps or reducing
     tmax.')
end


% Constants used that aren't already stored in tissue
[xmax ymax zmax t] = size(tissue);
clear t;
dt = tmax/(nt-1);
% rhoBlood = 1057;
% wBlood = 1000;
% cBlood = 3600;

% =========
```

```
53 % = Setup =
54 % =========
55 %   Starts all tissue voxels at bloodT (default 37) and maintains air at
     airT (default 24)
56 %   The condition squeeze(tissue(:,:,:,)~=airIndex picks out the elements
      that are
57 %   tissue
58
59 temperature = ones(3,xmax,ymax,zmax,'single')*airT;
60 if pastCalc == 0
61     temperature(1,squeeze(tissue(:,:,:,1))~=1) = bloodT;
62 else
63     temperature(1,:,:,:) = pastCalc;
64 end
65 numElements = numel(temperature(1,:,:,:));
66
67 % ===========
68 % = Do Work =
69 % ===========
70 %   This is a vectorized version of the next section.  For the love of
     god
71 %   don't make any changes to this without first looking below to make
     sure
72 %   you know what you're changing.  This is [nearly] impossible to
73 %   understand, so take your time and don't break it.
74 %   data is stored in 'tissue' as such :
75 %   [tissuetype 0 Qm c rho k w];  <--  second element is blank for all.
76 %   [    1      2  3 4  5  6 7
77
78 %  This makes an array that has smoothed out variations in k by averaging
      all
79 %  of the k's around each voxel (including itself).  This is a hap-hazard
```

```
80  %  solution to the problem that if you only take the value of k for the
      voxel
81  %  without considering what surrounds it, it doesn't matter whether the
      head
82  %  is surrounded by air, water or anything else.  Since water is a better
83  %  thermal conductor than air, we need a way of accounting for this.
      This is
84  %  one way:
85  averagedk = (circshift(tissue(:,:,:,6),[1 0 0])+circshift(tissue(:,:,:,6)
      ,[-1 0 0])+circshift(tissue(:,:,:,6),[0 1 0])+circshift(tissue(:,:,:,6)
      ,[0 -1 0])+circshift(tissue(:,:,:,6),[0 0 1])+circshift(tissue(:,:,:,6)
      ,[0 0 -1])+tissue(:,:,:,6))/7;
86  rhoblood = 1057;
87  cblood = 3600;
88
89  %%  Specify Percision Goal
90  tolerence = 1;     % fraction of voxels have a slope less than 'zeropoint
      '
91  zeropoint = 2.5e-7;  % point at which the slope between two *steps* is
      considered essentially zero
92
93
94  goal = numElements - tolerence*numElements;
95  goon = numElements; %  Forces the while loop to run the first time
96  format shortG;
97  % temperature(1,:,:,:) = Current Temperature
98  % temperature(2,:,:,:) = Next Temperature
99  % Resets after each update
100 if printprogress
101     disp(['Goal:  ', num2str(goal),' remaining voxels'])
102 end
103 t2 = 1;
```

```
104 while goon(1)>goal && t2<=nt  % runs until either 'goal' elements have a
      slope greater than 'zeropoint' or it exceeds nt
105     if printprogress
106      disp([t2 goon(1) ((numElements-goon(1))/numElements)*100]) % progress
107     end
108     temperature(2,:,:,:) = squeeze(temperature(1,:,:,:)) + ...
109          dt/(tissue(:,:,:,5).*tissue(:,:,:,4)).* ...
110          ((averagedk/dx^2).*...
111          (circshift(squeeze(temperature(1,:,:,:)),[1 0 0])-2*squeeze(
               temperature(1,:,:,:))+circshift(squeeze(temperature(1,:,:,:))
               ,[-1 0 0])+...  % shift along x
112           circshift(squeeze(temperature(1,:,:,:)),[0 1 0])-2*squeeze(
                temperature(1,:,:,:))+circshift(squeeze(temperature(1,:,:,:))
                ,[0 -1 0])+...  % shift along y
113           circshift(squeeze(temperature(1,:,:,:)),[0 0 1])-2*squeeze(
                temperature(1,:,:,:))+circshift(squeeze(temperature(1,:,:,:))
                ,[0 0 -1]))...  % shift along z
114              -(1/6000)*rhoblood*tissue(:,:,:,7)*cblood.*(squeeze(
                   temperature(1,:,:,:))-bloodT)+tissue(:,:,:,3));
115     %   resets the air temperature back since it's also modified above,
          but
116     %   it needs to be kept constant throughout the calculations
117     temperature(2,squeeze(tissue(:,:,:,1))==1) = airT;
118     %   checks how quickly the temperature is changing and if it is close
119     %   enough to zero to be considered stopped ('zeropoint')
120     goon = size(temperature(abs(squeeze(temperature(2,:,:,:)-temperature
          (1,:,:,:)))>zeropoint));
121     temperature(1,:,:,:) = temperature(2,:,:,:);  % moves 2 back to 1
122     t2 = t2 + 1;
123 end
124
125 temperature_Out = temperature(2,:,:,:);  % Only outputs the last time
      step
```

```
126 dirty = 0;
127
128 % equilTemperature = temperature_Out;
129 % save('equil.mat','equilTemperature');
130
131 %% To Combine Datasets
132 %  use this technique if there are seperate datasets that need combining
133 %    vertcat(squeeze(res1(:,:,:,:)),squeeze(res2(2:end,:,:,:)))
134 %  Where for all by the first dataset, you need to do the time from 2:end
135 %  so that there are no repeats (remember that the last timestep from the
136 %  previous dataset serves as the first for the new one)
137
138
139 time = toc;
140 end
141
142 function InterCatch
143 global dirty
144 if dirty
145     disp('Interupt Intercepted.  Inprepretating Interworkspace Data.')
146     global temperature
147     % equillibriumT = zeros([1 size(temperature(1,:,:,:))]);
148     % equillibriumT(1,:,:,:) = temperature(1,:,:,:);   %might be better
        to swtich equilT to be 3d rather than 4d
149     equillibriumT = temperature;
150     save('equiltempAbortDump.mat','equillibriumT');
151     % setappdata(0,'InterpOut',temperature);
152 end
153 end
```

A.4 Calculating the Temperature Change

The following function takes as inputs the head data matrix (appendix A.1), the metabolism and blood flow time courses (appendix A.2) and the equilibrium temperatures (appendix A.3) and calculates the temperature time-course. More details about this algorithm can be found in section 2.2.4.

A.4.1 tempCalcDynMF

```
function temperatureOut = tempCalcDynMF(tissue,bloodT,airT,nt,tmax,
  pastCalc,metab,flow,savesteps,region)
% tempCalcChaning Metabolism  How does changin metabolism
% affect things?
%
%   tissue: holds all of the strucual information
%   bloodT: Temperature of the blood
%   airT:   Temperature of the surrounding ait
%   nt:     Number of time steps
%   tmax:   Total amount of time the simulation should run over
%
%   region: logical matrix same size as head
%
%   Writen by Greggory Rothmeier (greggroth@gmail.com)
%   Georgia State University Dept. Physics and Astronomy
%   May, 2011

statusbar = waitbar(0,'Initializing');

%%   Default Values
if nargin<2,  bloodT = 37;          end
if nargin<3,  airT = 24;            end
if nargin<4,  nt = 3;               end
if nargin<5,  tmax = 1;             end
if nargin<6,  pastCalc = 0;         end
```

```
25
26
27  % Length of one side of a voxel (m)
28  dx = 2*10^-3;
29
30  if nt<(2*tmax),
31     warning('Time step size is not large enough.  Results will be
          unreliable.  Consider increasing the number of steps or reducing
          tmax.')
32  end
33
34
35  % Constants used that aren't already stored in tissue
36  [xmax ymax zmax t] = size(tissue);
37  clear t;
38  dt = ones([xmax ymax zmax])*(tmax/(nt-1));
39  % rhoBlood = 1057;
40  % wBlood = 1000;
41  % cBlood = 3600;
42
43  %%  Determine Metab/Flow Data Storage System
44  if ischar(metab)&&ischar(flow)
45    % if file locations are given rather than data
46       option = 1;
47  else
48    % Preallocate matrices for holding metabolism and blood flow data
49       metabMulti = ones([xmax ymax zmax],'single');
50       flowMulti = ones([xmax ymax zmax],'single');
51       option = 0;
52  end
53
54  %%  Maps
55  % Creates a map that identifies where there is tissue
```

```
% the condition squeeze(tissue(:,:,:,)~=airIndex picks out the
% elements that are tissue

tmax = ceil((nt-1)/savesteps);
temperatureOut = ones(tmax,xmax,ymax,zmax,'single');
temperature = ones(2,xmax,ymax,zmax,'single')*airT;
if pastCalc == 0
    temperature(1,squeeze(tissue(:,:,:,1))~=1) = bloodT;
else
  % Starts everything off at the pre-determined equilibium temperatures
    temperature(1,:,:,:) = pastCalc(end,:,:,:);
end
temperatureOut(1,:,:,:) = temperature(1,:,:,:);


% ===========
% = Do Work =
% ===========
%   This is a vectorized version of the next section.  For the love of
%   god don't make any changes to this without first looking below to
%   make sure you know what you're changing.  This is [nearly]
%   impossible to understand, so take your time and don't break it.
%   data is stored in 'tissue' as such :
%  [tissuetype 0 Qm c rho k w] <--  second element is blank for all.
%  [    1      2  3 4  5  6 7]

% This makes an array that has smoothed out variations in k by
% averaging all of the k's around each voxel (including itself). This
% is a hap-hazard solution to the problem that if you only take the
% value of k for the voxel without considering what surrounds it, it
% doesn't matter whether the head is surrounded by air, water or
% anything else. Since water is a better thermal conductor than air, we
% need a way of accounting for this. This is one way:
```

```
89
90  averagedk = (circshift(tissue(:,:,:,6),[1 0 0])+circshift(tissue(:,:,:,6)
       ,[-1 0 0])+circshift(tissue(:,:,:,6),[0 1 0])+circshift(tissue(:,:,:,6)
       ,[0 -1 0])+circshift(tissue(:,:,:,6),[0 0 1])+circshift(tissue(:,:,:,6)
       ,[0 0 -1])+tissue(:,:,:,6))/7;
91  rhoblood = 1057;
92  cblood = 3600;
93
94  %%  Only saves every 4 steps to reduce the final matrix size
95  for t2 = 1:nt-1
96      waitbar(t2/(nt-1),statusbar,sprintf('%d%%',round(t2/(nt-1)*100)));
97
98  % if a variable needs to be used multiple times for the same time step.
99      t3 = floor((t2-1)/4)+1;  % 1 1 1 1 2 2 2 2 3 3 . . .
100
101     % if a file is specified, pulls the data from the file for each step
102     if option
103         eval(strcat('load(fullfile(metab),''-mat'',''m',sprintf('%04d',t3)
              ,''');'));
104         eval(strcat('load(fullfile(flow),''-mat'',''f',sprintf('%04d',t3),
              ''');'));
105         eval(strcat('metabMulti = m',sprintf('%04d',t3),';'));
106         eval(strcat('flowMulti = f',sprintf('%04d',t3),';'));
107         eval(strcat('clear f', sprintf('%04d',t3),' m',sprintf('%04d',t3))
              )
108     else
109         metabMulti(region) = metab(t2);   %  region is hardcoded here
110         flowMulti(region) = flow(t2);
111     end
112
113     temperature(2,:,:,:) = squeeze(temperature(1,:,:,:)) + ...
114          dt./(tissue(:,:,:,5).*tissue(:,:,:,4)).* ...
115          ((averagedk/dx^2).*...
```

```
116           (circshift(squeeze(temperature(1,:,:,:)),[1 0 0])-2*squeeze(
                temperature(1,:,:,:))+circshift(squeeze(temperature(1,:,:,:))
                ,[-1 0 0])+...  % shift along x
117            circshift(squeeze(temperature(1,:,:,:)),[0 1 0])-2*squeeze(
                 temperature(1,:,:,:))+circshift(squeeze(temperature(1,:,:,:))
                 ,[0 -1 0])+...  % shift along y
118            circshift(squeeze(temperature(1,:,:,:)),[0 0 1])-2*squeeze(
                 temperature(1,:,:,:))+circshift(squeeze(temperature(1,:,:,:))
                 ,[0 0 -1]))...  % shift along z
119              -(1/6000)*rhoblood*flowMulti.*tissue(:,:,:,7)*cblood.*(
                   squeeze(temperature(1,:,:,:))-bloodT)+metabMulti.*tissue
                   (:,:,:,3));
120       % resets the air temperature back since it's also modified above,
121       % but it needs to be kept constant throughout the calculations
122       temperature(2,squeeze(tissue(:,:,:,1))==1) = airT;
123       temperatureOut(ceil(t2/savesteps),:,:,:) = temperature(2,:,:,:);
124       temperature(1,:,:,:) = temperature(2,:,:,:);  % moves 2 back to 1
125       clear metabMulti flowMulti
126   end
127   close(statusbar);
128
129   % ============
130   % = Old Code =
131   % ============
132   % This is what used to be used. It's much slower (~60 times slower),
133   % but it's much easier to understand compared to the above code. If any
134   % changes need to be made above, first look through this code to ensure
135   % you understand what's happening before making changes. It's really
136   % easy to mess up the code above and nearly impossible to figure out
137   % where.
138   %
139   %  good luck.
140
```

```
% for t2 = 1:nt-1
%     for x2 = 2:xmax-1
%         for y2 = 2:ymax-1
%             for z2 = 2:zmax-1
%                 if tissue(x2,y2,z2,1) ~= 1,
%                     temperature(t2+1,x2,y2,z2) = temperature(t2,x2,y2,z2) + (dt/(tissue(x2,y2,z2,5)*tissue(x2,y2,z2,4)))*((tissue(x2,y2,z2,6)/dx^2)*...
%                         (temperature(t2,x2+1,y2,z2)-2*temperature(t2,x2,y2,z2)+temperature(t2,x2-1,y2,z2)+...
%                         temperature(t2,x2,y2+1,z2)-2*temperature(t2,x2,y2,z2)+temperature(t2,x2,y2-1,z2)+...
%                         temperature(t2,x2,y2,z2+1)-2*temperature(t2,x2,y2,z2)+temperature(t2,x2,y2,z2-1))...
%                         -(1/6000)*rhoBlood*wBlood*cBlood*(temperature(t2,x2,y2,z2)-bloodT)+tissue(x2,y2,z2,3));
%                 end
%             end
%         end
%     end
% end

end
```

Appendix B

Visualization Tools

The temperature data is a four dimensional dataset (time, x, y and z), so good visualizations tools are necessary to analyzing the results. The primary tool I use is a modification of SliceBrowser (`http://www.mathworks.com/matlabcentral/fileexchange/20604`) and is provided as part of temptools (`https://github.com/greggroth/temptools/tree/master/lib/SliceBrowser`). In working with this, I also created a function (TempPlot()) to act as a wrapper and handle possible plotting situations depending on the number of inputs.

B.0.2 TempPlot()

```
1  function [ ] = TempPlot( head, tempdata, highlightRegion, slice, equil,
     threshold,point)
2  %TempPlot Plot data from tempCalc() or BulkImportNII()
3  %   INPUT TempPlot(structuredata)
4  %         TempPlot(structuredata,temperaturedata)
5  %         TempPlot(structuredata,temperaturedata,highlightRegion)
6  %         TempPlot(structuredata,temperaturedata,highlightRegion,slice)
7  %         TempPlot(structuredata,temperaturedata,highlightRegion,slice,
     EquillibriumData)
8  %
9  %   This function with determine which type of data it is and then plot
     it
```

```
10 %   appropiately.
11 %
12 %   equil - Equillibrium state data
13 %   threshold - threshold value for being displayed as an overlay
14 %   REQUIRES:  SliceBrowser (http://www.mathworks.com/matlabcentral/
     fileexchange/20604)
15 %%  Error checking and data restructuring where necessary
16 if ndims(head) == 4
17     head = head(:,:,:,1);
18 elseif ndims(head) ~= 3
19     error('Input ''head'' must have either 3 or 4 dimensions');
20 end
21
22 if nargin > 1
23     if ndims(tempdata) == 3  % should only happen when comparing two
         equilibrium datasets
24     temp = tempdata;
25     tempdata = zeros([1 size(temp)]);
26     tempdata(1,:,:,:) = temp;
27     elseif ndims(tempdata) ~= 4
28     error('Input ''tempdata'' must have either 3 or 4 dimensions');
29     end
30     tempdataShort = squeeze(tempdata(end,:,:,:));
31 end
32
33 if nargin > 2
34     if ndims(highlightRegion) ~= 3
35     error('Input ''highlightRegion'' must have 3 dimensions');
36     end
37     if size(highlightRegion) ~= size(head)
38     error('Input ''highlightRegion'' must be of the same size as ''head''
         ');
39     end
```

```
40      tempdataShort = squeeze(tempdata(end,:,:,:));
41  end
42
43  if nargin > 3
44      if slice > size(tempdata,1)
45      error('Input ''slice'' must be less or equal to the length of the
            first dimension of ''tempdata''');
46      end
47      tempdataShort = squeeze(tempdata(slice,:,:,:));
48  end
49
50  if nargin > 4
51      if ndims(equil) == 3
52          eq = equil;
53      elseif ndims(equil) == 4
54          eq = squeeze(equil(1,:,:,:));
55      else
56          error('Input ''equil'' must have either 3 or 4 dimensions');
57      end
58      clear 'equil';
59  end
60
61  %%  Pick how to format the call of SliceBrowser()
62  switch nargin
63      case 1
64      SliceBrowser(head,1,head);
65      colormap(gray);
66      case 2
67      %SliceBrowser(squeeze(tempdata(size(tempdata,1),:,:,:)),tempdata,head
            );
68      SliceBrowser(tempdataShort,tempdata,head);
69      case 3
70      SliceBrowser(tempdataShort,tempdata,head,highlightRegion);
```

```
71      case 4
72      SliceBrowser(tempdataShort,tempdata,head,highlightRegion);
73      case 5
74      SliceBrowser(tempdataShort-eq,tempdata,head,highlightRegion);
75      case 6
76      SliceBrowserOverlay(tempdataShort-eq,tempdata,head,highlightRegion,
          threshold);
77      case 7
78      imgoverlay(head,tempdataShort-eq,point,threshold)
79  end
80
81  end
```

B.0.3 tsliceplot

This is a visualization tool I wrote that allows you to view the change in temperature versus time for a line passing through the head. Screenshots of the tool can be seen in figs. B.1 and B.2.

Usage:

```
tsliceplot(temperature_data, equilibrium_temperature_data)
```

The script is available as part of temptools (`https://github.com/greggroth/temptools/tree/master/lib/tsliceplot`).

Figure B.1: Experimental data for activity in the motor cortex visualized with tsliceplot.

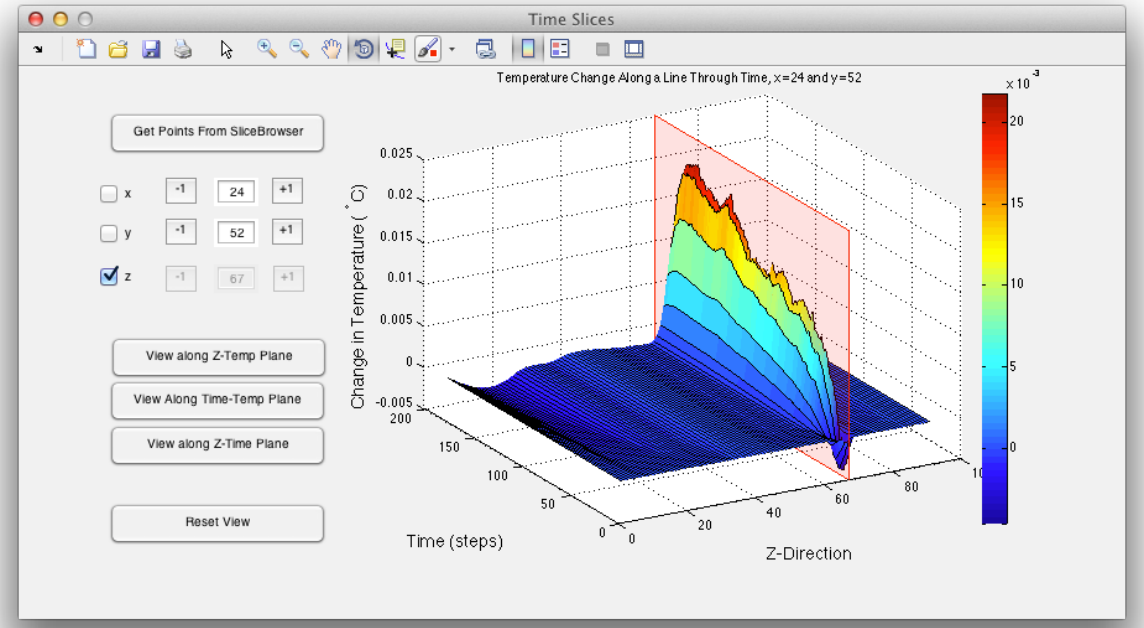


Figure B.2: The same data as is presented in fig. B.1, but viewed flat-on along the z vs. time plane.