

# Development of a Robust Pipeline for Mapping of Subcortical Structures

by

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# Approval

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## **Abstract**

This project focuses on developing a tool which can perform registration between subcortical surfaces. Current MATLAB-based 'Spherical Demons' algorithm, although very useful for most cases, fails to successfully complete surface registration in some cases. Therefore, FreeSurfer has been incorporated with 'spherical demons' algorithm to improve the existing surface registration algorithm by utilizing FreeSurfer's superior spherical parameterization algorithm to parameterize the surface. This significantly improved the quality (smoothness and uniformity) of the parameterization over the existing spherical mapping which led to successful surface registration between subcortical surfaces.

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# Chapter 1.

## Introduction

The Medical Image Analysis Lab (MIAL) was established by Dr. Mirza Faisal Beg and Dr. Ghassan Hamarneh in 2003. The primary focus of the lab is to create tools which can relate structural and functional aberrations of a brain to clinical disease within a precise anatomical framework for study purposes.

It is no exaggeration to say that the human brain is the most complex structure in the universe. No other brain in the animal kingdom is capable of generating the kind of higher consciousness associated with human ingenuity. Figure 1 provides an example of a human brain along with some of its regions. For brain analysis, these data are often useful and necessary. One of the most popular tools to visualize and interact with these data is FreeSurfer. It's a brain imaging software package for the analysis and visualization of structural and functional neuroimaging data from cross-sectional or longitudinal studies. It is developed by the Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging [1]. FreeSurfer includes tools for the reconstruction of topologically correct and geometrically accurate models of both the gray/white and pial surfaces, for measuring cortical thickness, surface area and folding, and for computing inter-subject registration based on the pattern of cortical folds [2].

Masters of Engineering (MEng) project in this report utilizes FreeSurfer's spherical parameterization algorithm to perform surface registration between subcortical surfaces of a brain by incorporating it with 'spherical demon' algorithm.

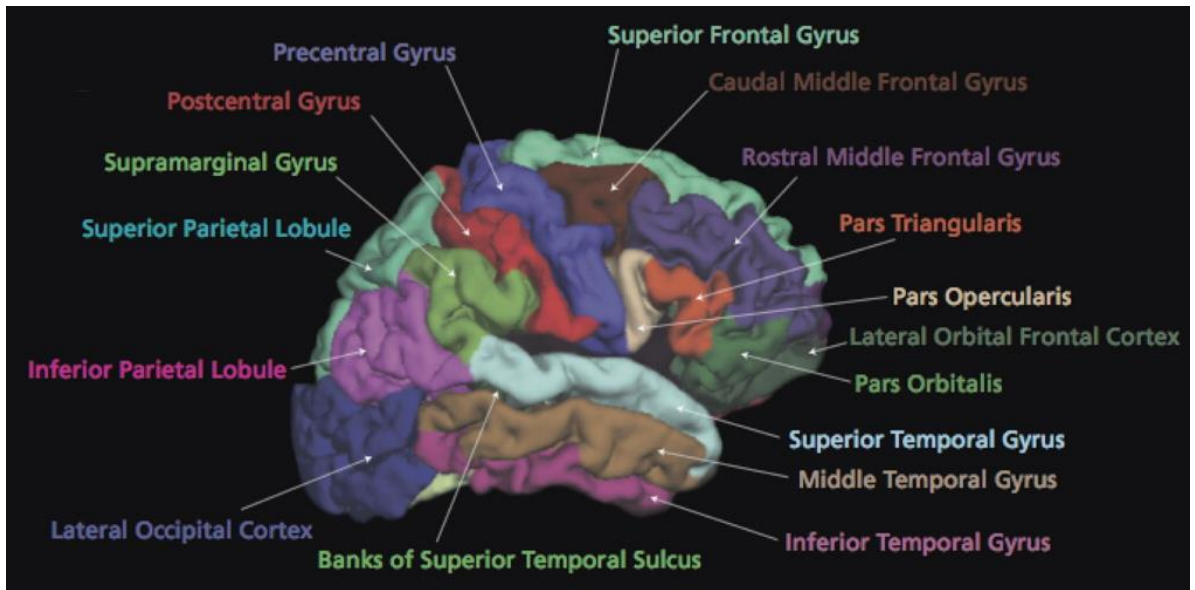
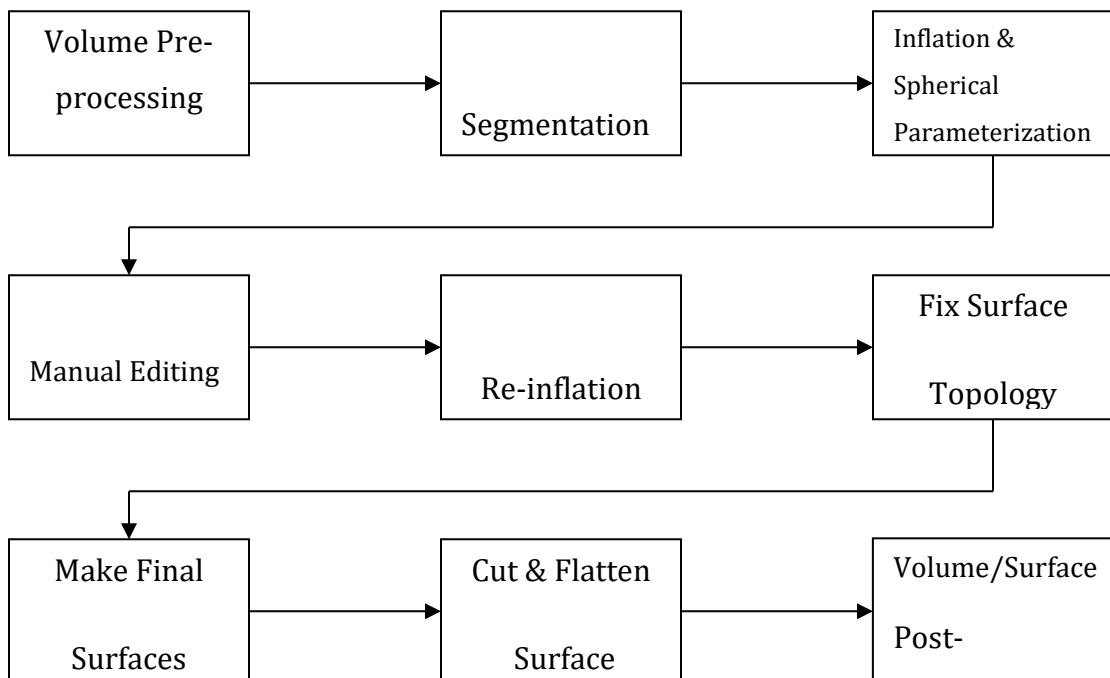


Figure 1: Regions of human brain [3]

## Chapter 2. Overview of FreeSurfer

FreeSurfer is one of the most robust medical image processing tool available. It takes MRI images of a brain as inputs and reconstructs brain's cortical surface and anatomical segmentation. The following flow chart represents the operations of FreeSurfer.



*Figure 2: Workflow of FreeSurfer*

The first step prepares the MRI data for processing. After it is ready for the FreeSurfer environment, it strips off the skull from the brain in the next step along with other segmentation operations. Once the surface is obtained, it is inflated into a 3-D object.



Spherical parameterization also takes place in the following process. Some tweaking might be required to validate the correctness of the surface. Therefore, after manual editing, it undergoes inflation process again. Before we get the final surface, an algorithm compares the obtained surface with a fixed surface to ensure the topology is correct. Finally, the desired surface is created followed by few modification and post-processing of the surface.

## Chapter 3. Surface Registration

Surface registration is performed between different brain surfaces in order to identify any brain abnormality. One healthy brain surface, set as a template, is aligned against different set of brain surface data. Figure 3 demonstrates this by having one template transforming to several different targets. By examining the transformation of one healthy brain to a brain with an unknown health condition, it is possible to analyze any abnormal deformation taken place in the output. Surface registrations can be either linear, which generally includes rotation, scaling, translation, and other affine transformations, or non-rigid/non-linear. For non-linear, transformation warps target brain surfaces to align with the reference brain surface. Complexity of registration also, of course, depends on the complexity of surfaces. Registration between two brain surfaces is, usually, much easier to perform than registration between two sub-cortical surfaces, for an example.

Incorporating FreeSurfer into spherical demon tool for surface registration involves several key steps. The major step is to use FreeSurfer's spherical parameterization algorithm. Initial white surface mesh is "inflated" to several other states, one of which is a sphere, typically **h.sphere**. Then the sphere is eventually mapped back into the target surface [4].

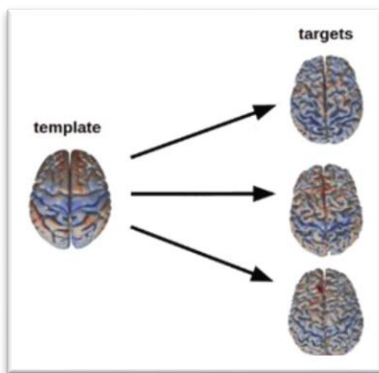


Figure 3: Surface Registration [5]

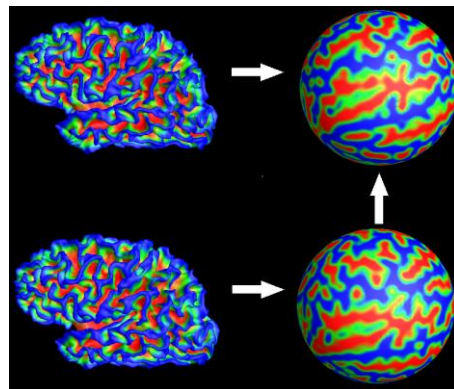


Figure 4: Spherical mapping of template and target surface [6]

## Chapter 4. Developing the tool

### 4.1. Existing tool

Registration between surfaces is not necessarily a new thing. There have been plenty of research and study conducted for this operation. However as mentioned previously, effectiveness of a surface registration algorithm also depends on the complexity of the surface along with other factors like whether the surface has been pre-registered (eg. LDDMM) etc. For registration between sub-cortical surfaces, one of the most well-known algorithm is known as “Spherical Demons”. It performs fast diffeomorphic landmark-free surface registration of 2D closed surfaces by assuming the 2D closed surfaces are spherically parameterized [7]. The following flowchart represents the algorithm.

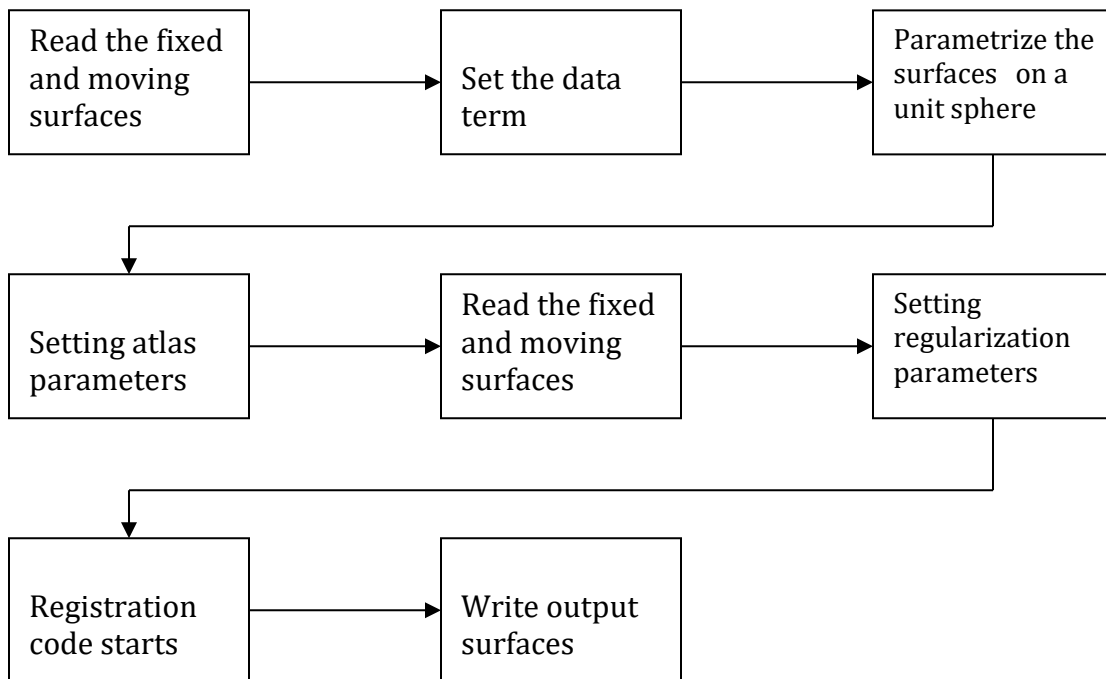
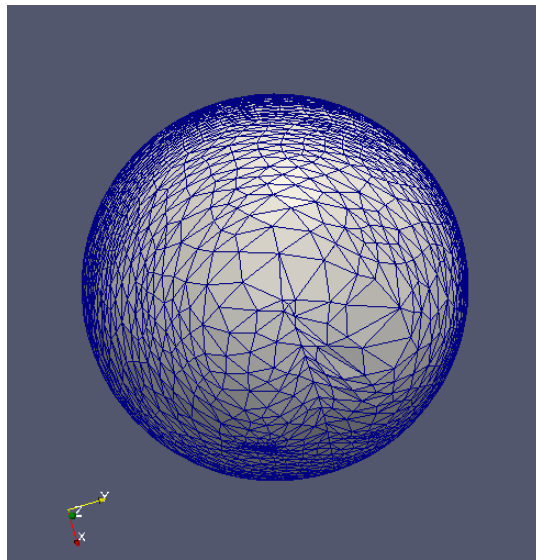
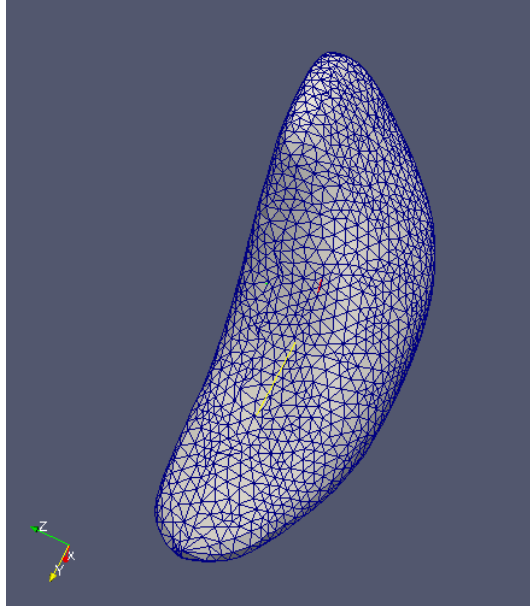


Figure 5: Workflow of Spherical Demons Algorithm

As can be seen in the flowchart, first it reads the 'target' and the 'template' surface files as **.byu** format. After setting up few parameters, the algorithm parametrizes the surfaces into a sphere. Few labelling parameters (atlas) are set in the next step, followed by forming mesh of the surfaces using the atlas and other parameters. Then the actual registration begins. The output files are written in **.byu** format.



*Figure 6: Spherical parameterization of a subcortical surface (rput) using existing MATLAB-based "Spherical Demons" tool*



*Figure 7: Output of the registration between a subcortical surface (rput - target) and a template (rput-LDDMM pre-registered)*

## **4.2. Limitation with the current tool**

Although the current tool worked well with few of the subcortical surfaces (rput, lhipp, lvent etc.), unfortunately, it fails for 'rthal' (from the ones we have tested).

While performing registration for 'rthal' subcortical surface, once it starts to form mesh structure, it struggles to compute face area and neighboring vertices, getting trapped into an infinite loop. The following snapshot is taken from MATLAB during operation.

```
Command Window
New to MATLAB? Watch this Video, see Demos, or read Getting Started.
j: 93000, Length of folded list is : 36
j: 94000, Length of folded list is : 63
j: 95000, Length of folded list is : 53
j: 96000, Length of folded list is : 96
j: 97000, Length of folded list is : 35
j: 98000, Length of folded list is : 32
j: 99000, Length of folded list is : 50
j: 100000, Length of folded list is : 127
j: 100000, Length of folded list is : 127
***** END UNFOLD *****
max vec: 35.0079, max warp bef smooth: 123.7392, median warp bef smooth: 75.1344, max warp after smooth: 118.0366, median warp after smooth: 74.417
1.3: Harm Energy: 27.9319, Error (before smooth): 715631, Error (after smooth): 738724.25, maxArea: 16.8866, minArea: 4.9573e-07
-----
Unfolding Mesh!!
***** UNFOLD *****
j: 0, Length of folded list is : 2860
j: 1, Length of folded list is : 2855
j: 2, Length of folded list is : 2853
j: 3, Length of folded list is : 2850
j: 4, Length of folded list is : 2847
j: 5, Length of folded list is : 2836
j: 6, Length of folded list is : 2838
j: 7, Length of folded list is : 2840
j: 8, Length of folded list is : 2829
j: 9, Length of folded list is : 2832
j: 10, Length of folded list is : 2822
j: 20, Length of folded list is : 2597
j: 30, Length of folded list is : 2330
j: 40, Length of folded list is : 2178
```

*Figure 8: Snapshot of the command window (performing registration between 'rthal' surfaces)*

This suggested a potential limitation of the tool. As it fails for this particular surface, it is possible it will fail for other surfaces as well. Hence the need to create a more robust tool for surface registration is imperative.

## Chapter 5. Potential FreeSurfer incorporation

### 5.1. Approach

FreeSurfer is one of the most robust tools available for visualization of surfaces. When the existing MATLAB-based “Spherical Demons” code failed to perform registration between ‘rthal’ the subcortical surfaces, incorporating FreeSurfer’s superior algorithm, if possible, is the first choice in order to make it work.

FreeSurfer has an elaborate pipeline it follows, as discussed previously. The approach is to use the power of FreeSurfer tool with MATLAB code at any stage of the algorithm. After a thorough study of the FreeSurfer pipeline and “Spherical Demons” code, it was evident that both spherically parameterize the surface into a sphere and gives an opportunity for a potential incorporation.

### 5.2. Implementation

Following the pipeline and command table provided by the developers [8], after getting the surface files (**?h.pial** and **?h.white**) from the image files, flag ‘mris\_smooth’ can be used to obtain **?h.smoothwm** file. This smooths very jagged original surface because of each triangle being on the edge of a voxel face and so are at right angles to each other [9].

The next step is to use the flag ‘mris\_sphere’ where **?h.smoothwm** is the input. This will, essentially, spherically parameterize the surface.

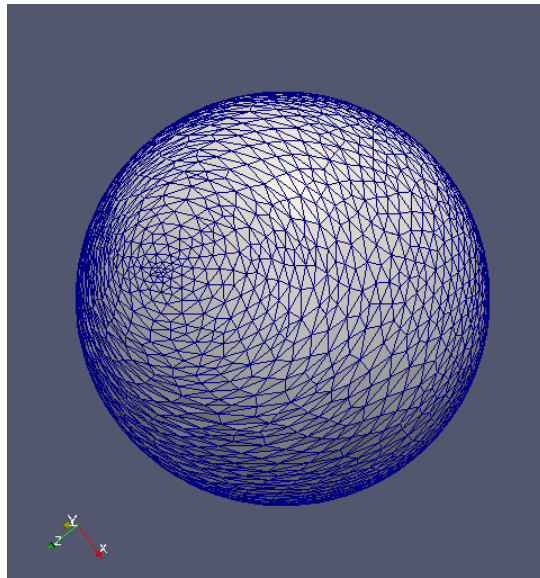
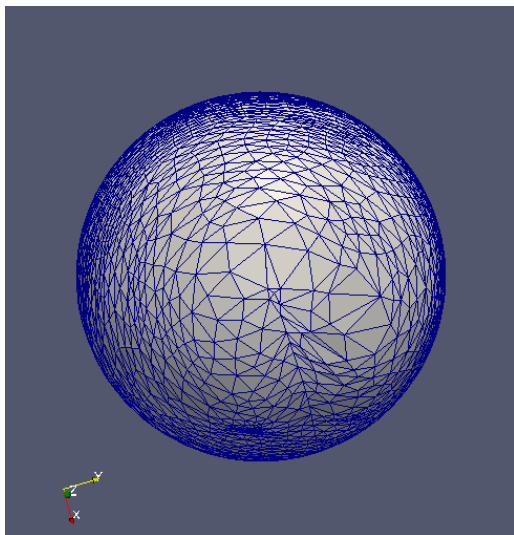
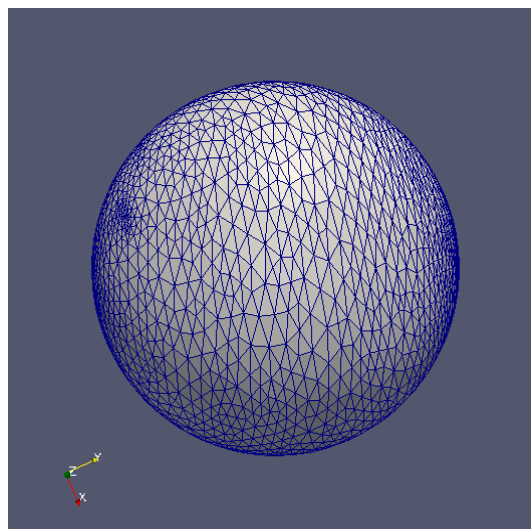


Figure 9: Spherical parameterization of a subcortical surface (*rcaud* – LDDMM pre-registered) using *FreeSurfer*



(a)



(b)

Figure 10: Comparison of spherical parameterization between subcortical surface '*rput*' using (a) *Spherical Demons* (b) *FreeSurfer*



As demonstrated in the figures above, parameterization using FreeSurfer creates much more smoother surface than using MATLAB-based [10] algorithm, to be specific, SPHARM-MAT toolbox in MATLAB [11]. It is expected that it is due the different mechanism both of the algorithm posses. FreeSurfer unfolds the surface by minimizing the metric distortions introduced by the inflation and projection procedures. These distortions are estimated based on an angularly spaced random sampling of distances in a 1-cm radius of each vertex [12]. Whereas 'spherical demons' aims to create an equal area mapping as well as minimize angle distortions by solving a constrained optimization problem [10]. However, further analysis is required to identify all the factors.

### **5.3. Incorporating with Spherical Demons Algorithm**

Looking back at the Spherical Demons algorithm workflow, at one stage it parameterizes the surface into a sphere. It uses it's own code written in MATLAB [10] for this operation. Replacing this with the flags mentioned above (for FreeSufer based spherical parameterization), a better resolved sphere is obtained. It is worth of mentioneing that as the code takes in **.byu** files as input, it's necessary to covert them into pial files (FreeSurfer environment friendly).

A separate script is written for the parameterization using FreeSurfer for **.byu** files. The script is called during the runtime of the program for the operation. Once the parameterization is finised successfully, the sphere needs to be centered for the code to retrieve data properly. It is done with a simple code in MATLAB. That's the last step before the code follows its regular routine and completes registration.

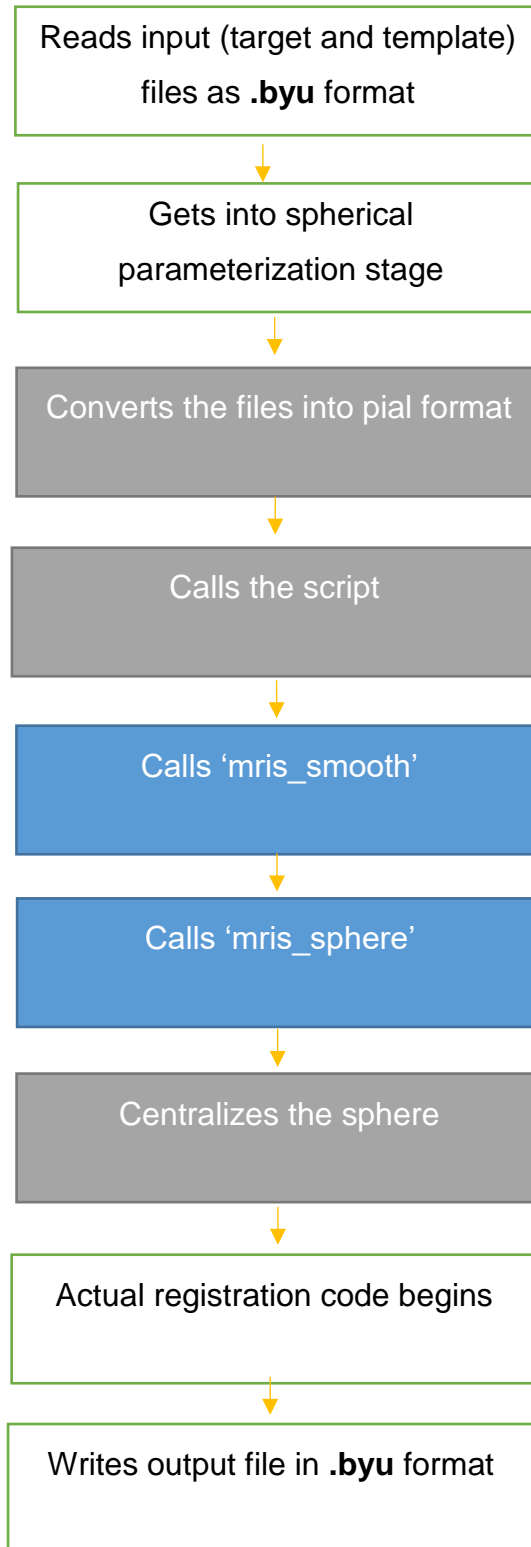
### **5.4. Scripting Languages and Programs**

BASH scripting is the main scripting used to write the scripts. MIAL group has been using it as its primary scripting language and, therefore, it was hassle free to use and easy to learn from peers as they have been using it for a while. It also has many

powerful features which were useful during writing the scripts, such as, reading or writing files, removing documents, running program, etc.

MATLAB (2012a), as mentioned before, is used to run the surface registration algorithm. It is also used to connect scripts on the background and run separate operations which were done with FreeSurfer.

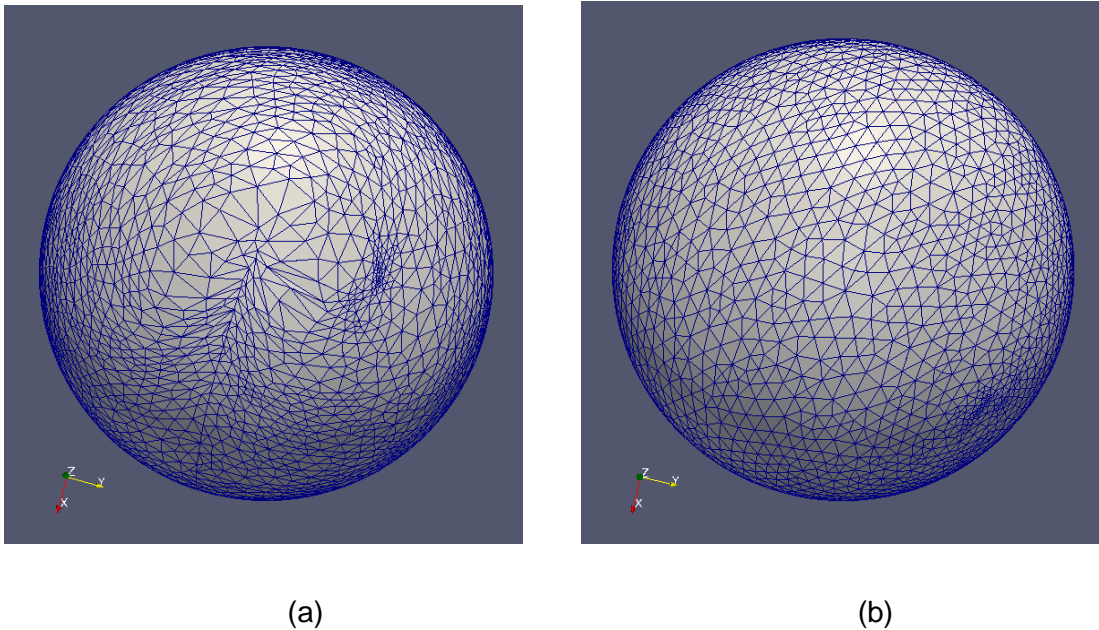
All the images of the sub-cortical surfaces have been visualized (in **.byu** format) using Paraview.



*Figure 11: Flow diagram of the incorporation of FreeSurfer based spherical parametrization into spherical demons algorithm.*

## Chapter 6. Verification and Results

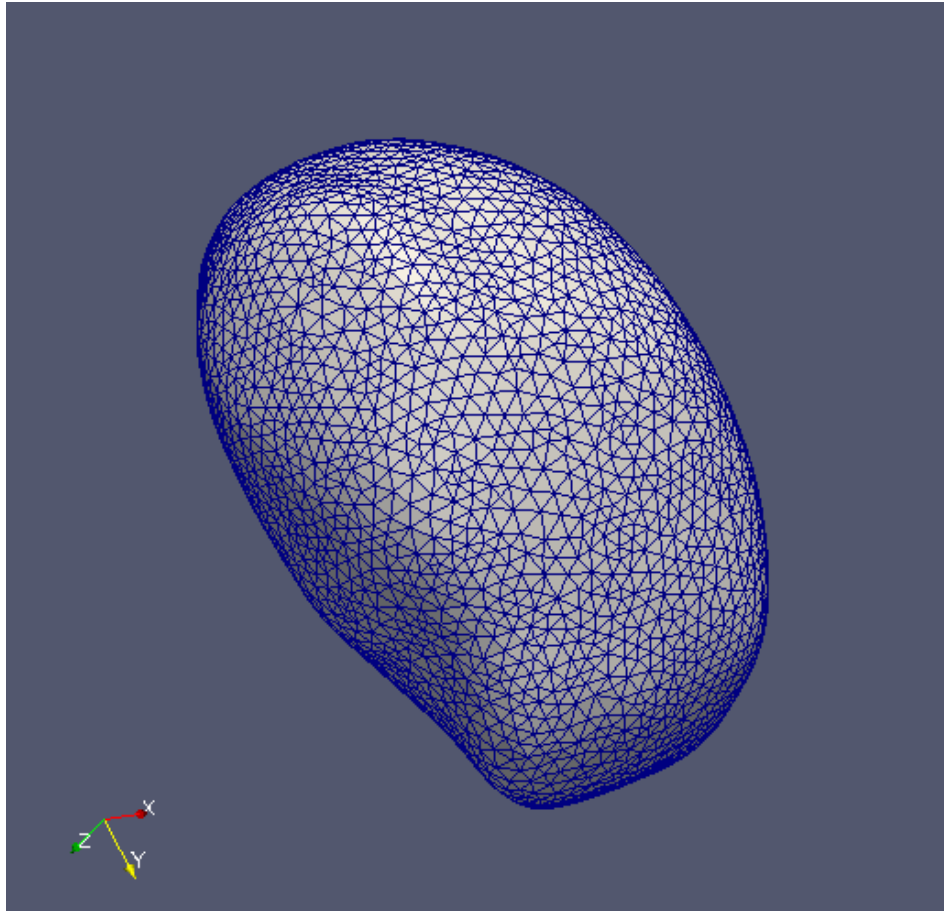
Modified spherical demons algorithm has more potential to operate successfully for variety of cases as incorporating such a robust tool as FreeSurfer should give more accurate data to work with. Running spherical parameterization on 'rthal' sub-cortical surface gives the following result.



*Figure 12: Comparison of spherical parameterization between subcortical surface 'rthal' using (a) Spherical Demons (b) FreeSurfer*

As expected, parameterization using FreeSurfer produces more uniform and smoother surface than spherical demon's algorithm.

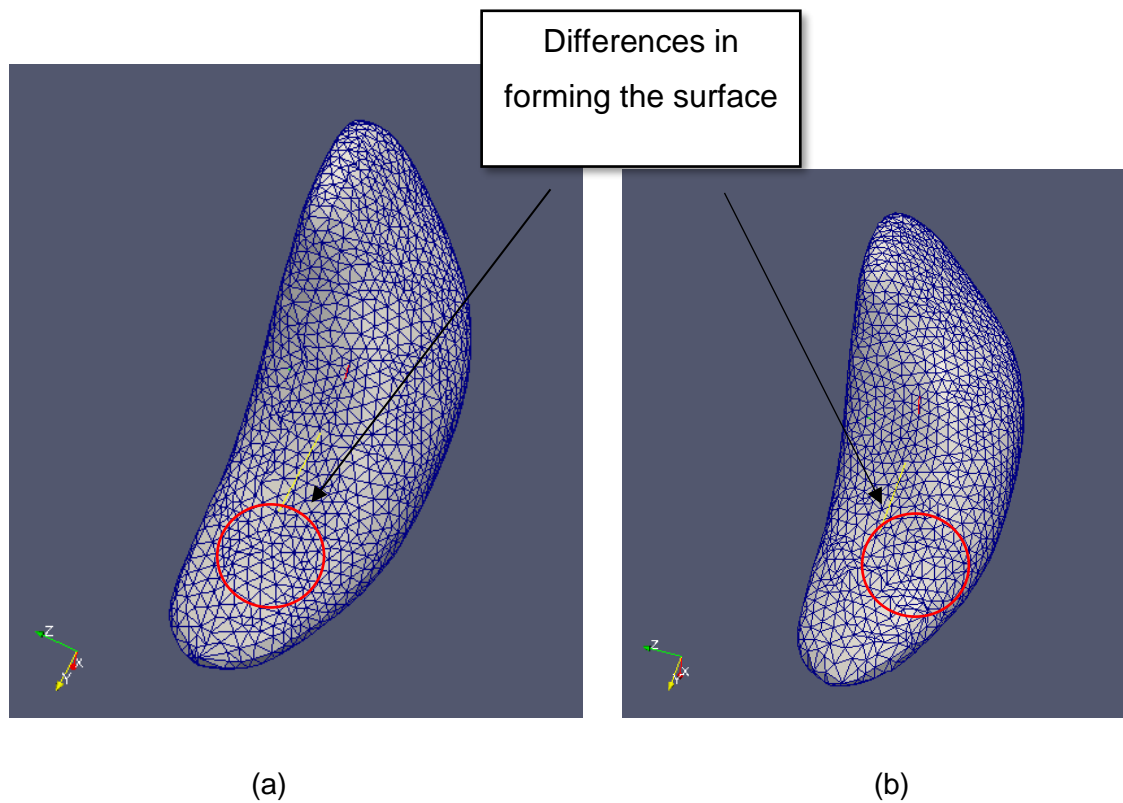
The next is to complete the spherical demons algorithm using FreeSurfer's spherical parameterization. The figure on the following page is the output result.



*Figure 13: Output of the registration between a subcortical surface (rthal - target) and a template (rthal-LDDMM pre-registered)*

Spherical demons algorithm successfully performed surface registration for 'rthal' sub-cortical surface which wasn't possible before. The whole process took less than 2 mins to complete and completed without any interruption or warnings.

For the surfaces the code was working successfully before, didn't have much visible changes on the output after incorporation. A comparison is provided below between registration performed with and without algorithm update.



*Figure 14: Comparison between surface registration of 'rput' sub-cortical surface (a) without FreeSurfer incorporation and (b) with FreeSurfer incorporation*

As can be seen from the diagram above, there is no significant difference in the actual shape of the output surface file. However, there are some minute differences on surface formation.

## Chapter 7. Application on Canids

One such example is performing surface registration between canids brain. The idea is to test significant differences between regions and species in cortical thickness at each of the comparable surface points (of different species). Comparing the different species brain with dog's brain can help to examine various evolutionary scenarios, such as, fox to dog transition or wolf to dog transition. Figures bellow demonstrate measurements of cortical thickness for different species.

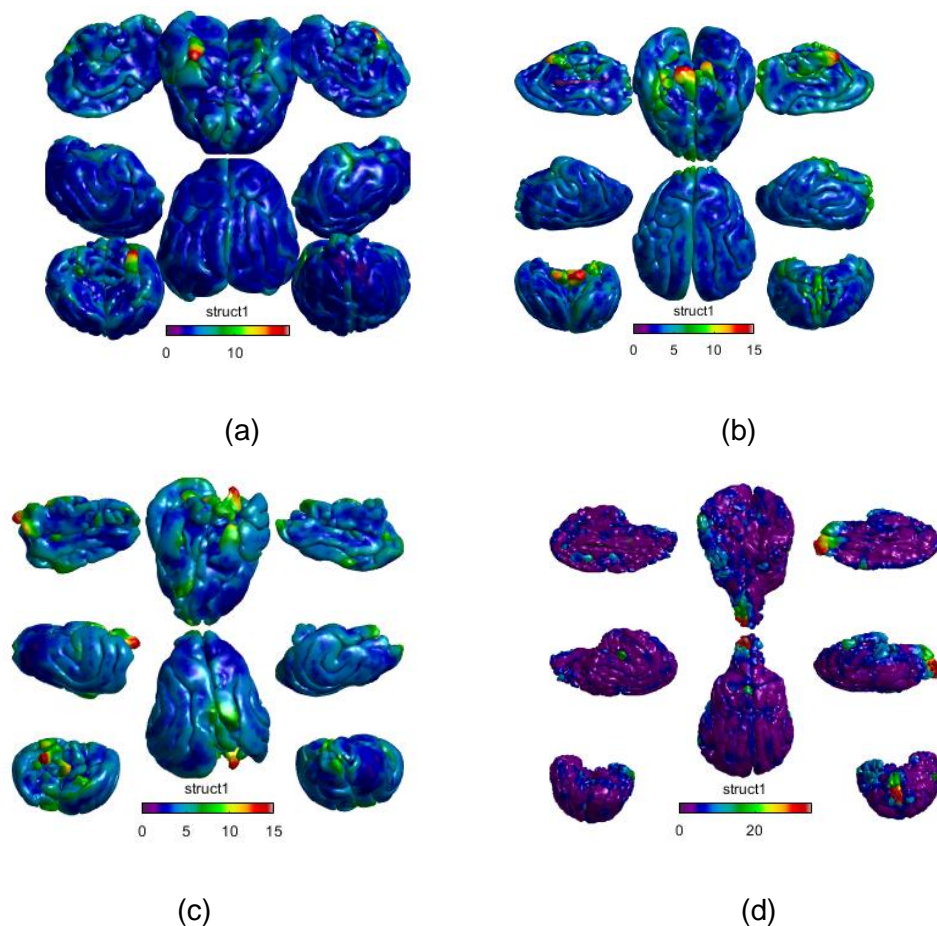
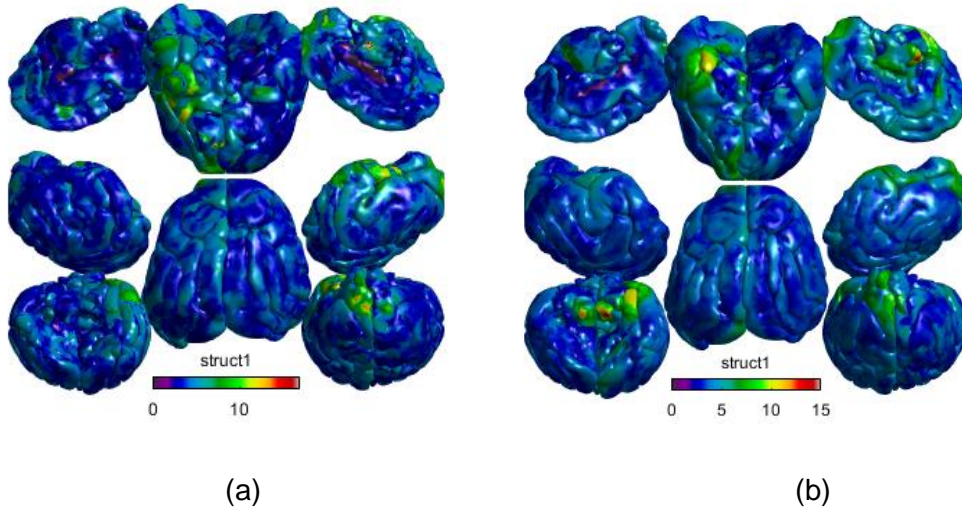


Figure 15: Measurements of cortical thickness (in  $\mu\text{m}$ ) for (a) dog's brain (b) maned wolf's brain (c) red fox's brain and (d) European wolf's brain



*Figure 16: Registration of brain surfaces between (a) dog and European wolf (b) dog and maned wolf*

Figure above showcases successful surface registration between different canids surfaces. It highlights underlying hotspots in cortical thickness between a dog, as a template, and, European wolf, maned wolf, as targets. This is another example where using MATLAB's SPHRAM toolbox for spherical parametrization fails to complete registration. All the surfaces have been pre-registered (affine alignment) before performing registration.

However, it is worth of mentioning that registration between other species (red fox, lycon) fails to perform with the updated tool. A better pre-registration (eg. LDDMM) might be needed to complete the registration.



## Chapter 8. **Limitations**

Although the usability of spherical demons has increased significantly, it still has a way to go. In some cases, where the surface is not LDDMM pre-registered, it fails to complete registration. Such example is while trying surface registration between a dog's brain with an another canids brain, where none of the surface is pre-registered, MATLAB crashes and exits the program. Algorithm in the spherical demons tool, perhaps, can be modified further to account such cases so that it can perform registration for any surfaces without any interruptions.

## Chapter 9. Conclusion

Running surface registration algorithm (spherical demons) without any modification is a competent tool by itself. However, it fails to perform registration for several cases. Incorporating FreeSurfer effectively boosts the capability of the tool. **Figure 13** showcases one such case where it performs surface registration between 'rthal' surfaces. The main reason for the performance improvement of the tool can be tracked down to improvement in spherical parameterization step of the algorithm. **Figure 10** demonstrates a comparison between two spheres which were produced with and without FreeSurfer's help and the differences are staggering.

Comparison between 'rput' sub-cortical surface registration is also carried out in **Figure 14**. As can be seen in the figure, it makes few different patterns while forming the triangles in the surface while retaining the actual shape of the object.

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## Appendix A.

### 9.1. Diffeomorphic mapping

A diffeomorphic mapping system is a system designed to map, manipulate, and transfer information which is stored in many types of spatially distributed medical imagery. It's a broad term which can refer to many different algorithms and methods of mapping. The acronym LDDMM, standing for large deformation diffeomorphic metric mapping is often used to refer to a specific suite of algorithms used for diffeomorphic mapping and manipulating dense imagery based on diffeomorphic metric mapping within the academic discipline of Computational anatomy, to be distinguished from its precursor based on diffeomorphic mapping. The distinction between the two is that diffeomorphic metric maps satisfy the property that the length associated to their flow away from the identity induces a metric on the group of diffeomorphisms, which in turn induces a metric on the orbit of Shapes and Forms within the field of Computational Anatomy. The study of shapes and forms with the metric of diffeomorphic metric mapping is called Diffeomorphometry [13].