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Detection and Quantification of Small Changes in MRI Volumes

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Abstract

Please use no more than 300 words and avoid mathematics or complex script.

*Dedicated to all hard-working
doctoral students at Uppsala University*

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1. Introduction

1.1 Description of the problem

When a person suffers an accident that produces trauma to the head, one of the first things that should be performed is an MRI of the brain region in order to spot possible brain injuries. If the damage is large, a medical specialist can usually recognize which parts of the brain have been affected without automated help. However, if the damage is minor, it is generally much harder for the doctor to figure out what could be the consequences of the injury.

For this particular project we have the following conditions: A patient's brain is scanned, producing a first MRI just after receiving trauma to the head. The patient has not received extensive damage, and so the MRI comes out as expected from a medical specialist. After a period of three to twelve months later, a new MRI of the same patient is taken and is compared with the initial MRI.

It is assumed that if there are symptoms produced as a consequence of the accident, then there must be differences in the brain of the patient, even when the differences might be too small to see with the naked eye.

The goal of this project is to analyse and test different registration and morphometry methods, in order to compare this type of brain MRIs and produce information on the differences between them.

The final result of the project should be a tool that allows the medical specialist to do the comparison on his or her own.

1.2 Importance

Manual examination of MRI studies suffers from many problems. The study can be affected specially by acquisition related factors such as:

- One cannot assume a one-to-one correspondence between slices from one acquisition to the next in order to make side-by-side comparisons.
- A different scanner may be used in every examination, producing a scan which will have different signal characteristics.
- Often, scanning parameters are not the same from one acquisition to the next.

- Change can present itself in many ways. The radiologist is required to assimilate all this data before making a decision, which often is quite difficult.

A very important part of change detection is therefore not simply the detection of change but the separation of acquisition-related change from disease-related change. Also, methods that produce objective, reproducible and accurate metrics of disease course are of great interest since the change in appearance over time is essential to understanding disease course [9].

Also, it is not enough to be able to determine if there are differences, since from a clinical standpoint, knowing where and how changes have occurred is as important as knowing that they have occurred [9].

From a practical point of view, it is also very important for the patients to be able to obtain a correct diagnosis, specially if the symptoms they are suffering are hard to explain or subjective, as it is common with non-extensive brain injuries.

1.3 Related Works

Many related works focus on inter-subject studies, which means that they compare images acquired from different individuals in order to diagnose diseases or identify abnormalities. This generally implies that the first step in the analysis process is one of *spatial normalization* or *inter-subject registration*, in which the aim is to reduce the anatomical variability in the volumetric brain scans.

The works of [20, 12] use this technique combined with voxelwise group analysis of functional magnetic resonance imaging (fMRI), and the works of [1, 6] also use spatial normalization combined with diffusion tensor imaging in order to study brain white matter.

More similar works, related to the quantification of small changes in volume observed over time can be observed in [5, 11]. The results of these works are used to diagnose and evaluate disease progression and treatment.

Some other works that also use the specific techniques described later in this project are:

- Hajnal et al. in [4] and Lemieux et al. in [8] utilize subtraction after applying rigid registration on the volumes.
- Rey et al. in [11] introduce the Jacobian operator of the deformation field resulting from the registration as a measure of local volume variation.
- Pohl et al. in [10] describe a semiautomatic procedure targeted toward identifying difficult-to-detect changes in brain tumor imaging. The result of this study is also a module for *3D Slicer*, and was very useful for this project since its source code is open for other researchers to view.

More information about the module can be found on its webpage:

[http://www.slicer.org/slicerWiki/index.php/Documentation/
4.1/Modules/ChangeTracker](http://www.slicer.org/slicerWiki/index.php/Documentation/4.1/Modules/ChangeTracker)

2. Methods

2.1 Registration

“Image registration is the process of overlaying two or more images of the same scene taken at different times, from different viewpoints, and/or by different sensors. It geometrically align two images –the reference and sensed images.”[21]

“Image registration is a crucial step in all image analysis tasks in which the final information is gained from the combination of various data sources like in image fusion, change detection, and multichannel image restoration.”[21]

The following images show a checkerboard comparison of two volumes taken of the same patient at different times. Figure 2.1 shows the image comparison before performing affine registration. Figure 2.2 shows the comparison of images after the registration has been done.

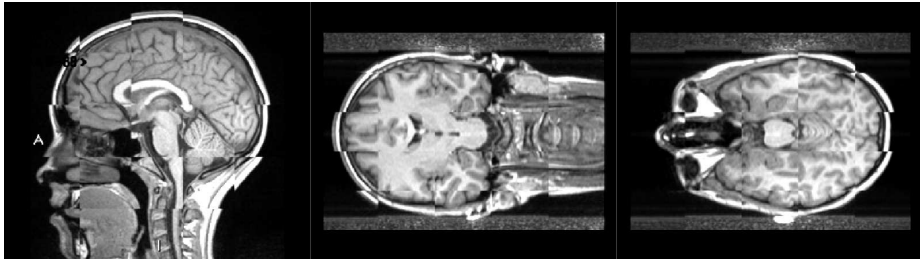


Figure 2.1. Comparison of volumes before registration

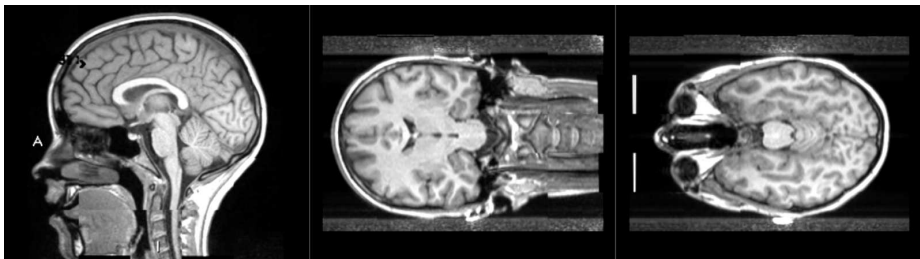


Figure 2.2. Comparison of volumes after registration

The second volume has been modified using affine registration so that the comparison between both volumes becomes much easier.

According to [21], the majority of the registration methods consist of the following steps:

1. *Feature detection*: Salient and distinctive objects are detected.
2. *Feature matching*: The correspondence between the features detected in the sensed image and those detected in the reference image is established.
3. *Transform model estimation*: The type and parameters of the mapping functions are estimated. These functions align the sensed image with the reference image.
4. *Image resampling and transformation*: The sensed image is transformed by means of the mapping functions.

2.1.1 Registration Methods used

There are many different methods to accomplish registration between images or volumes. In this project only a few of these methods were used based on experiments performed with some of the available methods. The chosen procedures were the ones that behaved better under the specific conditions of this work.

Affine Registration

In geometry, an *affine transformation* or an *affinity* is a transformation which preserves straight lines (i.e., all points lying on a line initially still lie on a line after the transformation) and ratios of distances between points lying on a straight line. It does not necessarily preserve angles or lengths, but does have the property that sets of parallel lines will remain parallel to each other after an affine transformation [15].

The implementation of affine registration used during this project is the one included in *3D Slicer* version 4.1.

The application is able to register two images together using an affine transform and mutual information, and it allows the user to modify quite a few parameters in order to obtain the expected result.

If you would like to know more about this implementation of affine registration please refer to the module webpage:

<http://wiki.slicer.org/slicerWiki/index.php/Documentation/4.1/Modules/AffineRegistration>

B-Spline Registration

In the mathematical subfield of numerical analysis, a *B-spline* is a spline function that has minimal support with respect to a given degree, smoothness, and domain partition.

However, in computer graphics, the term *B-spline* frequently refers to a spline curve parametrized by spline functions that are expressed as linear combinations of *B-splines* (in the mathematical sense explained above) [16].

Just like in the case of affine registration, the implementation of B-Spline registration used during this project is the one included in *3D Slicer* version 4.1.

The application divides the volumes into a grid of user-defined size in which each line is a B-spline that will be modified by the registration to create a transform that aligns the two volumes.

If you would like to know more about this implementation of B-spline registration please refer to the module webpage:

<http://wiki.slicer.org/slicerWiki/index.php/Documentation/4.1/Modules/BSplineDeformableRegistration>

BRAINS Demon Warp Registration

As with the registration methods explained before, *BRAINS Demon Warp* registration is implemented as a module in *3D Slicer* version 4.1.

The module works by using the ITK filter based on Thirion's Demons algorithm, in which the main idea is to consider the objects boundaries in one image as semi-permeable membranes and to let the other image, considered as a deformable grid model, diffuse through these interfaces, by the action of effectors situated within the membranes. [13].

An important characteristic of this implementation, that was particularly useful for this project, is that it can produce a *deformation field* as the output of the registration. A deformation field is a vector image in which each point is a vector that indicates the amount of deformation necessary at that point in order to align the volumes.

If you would like to know more about the implementation of *BRAINS Demon Warp* registration please refer to the module webpage:

<http://wiki.slicer.org/slicerWiki/index.php/Documentation/4.1/Modules/BRAINSDemonWarp>

2.2 Morphometry

Morphometry refers to the measurement of external form. More specifically, *brain morphometry* is concerned with the measurement of brain structures and changes thereof during development, aging, learning, disease and evolution. Its goal is to derive specific information from noninvasive neuroimaging data of live brains, typically obtained from magnetic resonance imaging (MRI); and to quantify the anatomical features of the brain in terms of shape, mass and volume [17].

In general, brain morphometry can be divided into three different methods: *deformation-based*, *tensor-based* and *voxel-based* morphometry. Defined briefly as:

- *Deformation-based*: Uses deformation fields to identify differences in the relative positions of structures.
- *Tensor-based*: Uses deformation fields to identify differences in the local shape of brain structures.
- *Voxel-based*: Uses voxel-wise comparison of the local concentration of grey matter.

2.2.1 Morphometry methods used

Only *tensor-based* and *voxel-based* morphometry methods were used during this project, since their outputs were easier to adapt to our requirements.

Voxel-based Morphometry

A useful measure of structural difference among populations is derived from a comparison of the local composition of different brain tissue types (e.g., grey matter, white matter, etc). Voxel-based morphometry (VBM) has been designed to be sensitive to these differences, while discounting positional and other large scale volumetric differences in gross anatomy.

Since its inception, VBM has become an established tool in morphometry being used to detect cortical atrophy and differences in slender white matter tracts [3].

An objection to VBM is that it is sensitive to systematic shape differences attributable to misregistration. Many potential differences can arise as a result of movement or different positioning of the subject in the scanner, and also there can be systematic differences in the relative intensity of grey matter voxels compared to white matter [3].

All these differences can be detected by VBM since they are all real differences among the data, even when they may not imply an increase or reduction in grey matter density.

When VBM is used to compare MRI data of many different subjects, as is the case many times, the process involves spatially normalizing all the images to the same stereotactic space, extracting the gray matter from the normalized images, smoothing, and finally performing a statistical analysis to localize, and make inferences about, group differences. The output from the method is a statistical parametric map showing regions where gray matter concentration differs significantly between groups [2].

For a detailed step-by-step description of VBM, please refer to [2].

Tensor-based Morphometry

The goal of tensor-based morphometry (TBM) is to determine regional shape differences.

A deformation field that maps one image to another can be considered a discrete vector field. By taking the gradients at each element of the field, a *Jacobian matrix* field is obtained, in which each element is a tensor describing the relative positions of the neighboring elements. Morphometric measures derived from this tensor field can be used to locate regions with different shapes. The field obtained by taking the determinants at each point gives a map of the structure volumes relative to those of a reference image [2].

In principle, the *Jacobian matrices* of the deformations (a 2nd order tensor field relating to the spatial derivatives of the transformation) should be more reliable indicators of brain shape than absolute deformations. Absolute deformations represent positions of brain structures, rather than local shape, and need to be quantified relative to some arbitrary reference position [3].

A *Jacobian matrix* contains information about the local stretching, shearing and rotation involved in the deformation, and is defined at each point by:

$$J = \begin{bmatrix} \frac{\partial y_1}{\partial x_1} & \frac{\partial y_1}{\partial x_2} & \frac{\partial y_1}{\partial x_3} \\ \frac{\partial y_2}{\partial x_1} & \frac{\partial y_2}{\partial x_2} & \frac{\partial y_2}{\partial x_3} \\ \frac{\partial y_3}{\partial x_1} & \frac{\partial y_3}{\partial x_2} & \frac{\partial y_3}{\partial x_3} \end{bmatrix}$$

The form of TBM that was used in this project involves comparing relative volumes of different brain structures, where the volumes are derived from *Jacobian determinants* at each point. According to [3], this type of morphometry is useful for studies that have specific questions about whether growth or volume loss has occurred, and so is appropriate for our problem.

The *Jacobian determinant* is the determinant of the *Jacobian matrix* and is sometimes simply called “the Jacobian”.

For a differentiable function f (a function whose derivative exists at each point in its domain), the *Jacobian determinant* of f 's *Jacobian matrix* at a given point gives important information about the behavior of f near that point.

For instance, if the *Jacobian determinant* at a point p is positive, then f preserves orientation near p ; if it is negative, f reverses orientation. The absolute value of the *Jacobian determinant* at p gives us the factor by which the function f expands or shrinks volumes near p [18].

3. Proposed Solutions

3.1 Tools used

3.1.1 3D Slicer

Slicer, or **3D Slicer**, is a free, open source software package for visualization and image analysis. It is natively designed to be available on multiple platforms, including Windows, Linux and Mac Os X.

3D Slicer provides image registration, processing of DTI (diffusion tractography), an interface to external devices for image guidance support, and GPU-enabled volume rendering, among other capabilities. 3D Slicer has a modular organization that allows the easy addition of new functionality and provides a number of generic features not available in competing tools.

3D Slicer is built on VTK, a pipeline-based graphical library that is widely used in scientific visualization. In version 4, the core application is implemented in C++, and the API is available through a Python wrapper to facilitate rapid, iterative development and visualization in the included Python console. The user interface is implemented in Qt, and may be extended using either C++ or Python.

Slicer supports several types of modular development. Fully interactive, custom interfaces may be written in C++ or Python. Command-line programs in any language may be wrapped using a light-weight XML specification, from which a graphical interface is automatically generated [14].

For more information on this tool please refer to its official webpage:

<http://www.slicer.org/>

3.1.2 ITK

ITK stands for **Insight Segmentation and Registration Toolkit**, it's a cross-platform, open-source application development framework widely used for the development of image segmentation and image registration programs.

ITK is implemented in C++ and it is wrapped for Tcl, Python and Java. This enables developers to create software using a variety of programming languages.

ITK's code is highly efficient, which means that many software problems are discovered at compile-time, rather than at run-time during program execution. It also enables ITK to work on two, three, four or more dimensions.

For more information on this tool please refer to its official webpage:

<http://www.itk.org/>

3.1.3 Other Tools

Programming Languages

The programming languages chosen during this project are **C++** and **Python**, mainly because they are main languages in which 3D Slicer is written, which means that it was easier to communicate with 3D Slicer by using them.

MATLAB

MATLAB is a numerical computing environment and programming language. It allows matrix manipulations, plotting of functions and data, implementation of algorithms, creation of user interfaces, and interfacing with programs written in other languages, including C, C++, Java, and Fortran [19].

MATLAB was used during this project specifically to create and quickly manipulate MRI volume files.

Official website for this tool: <http://www.mathworks.com/>

ParaView

ParaView is an open-source, multi-platform data analysis and visualization application. ParaView users can quickly build visualizations to analyze their data using qualitative and quantitative techniques.

ParaView was used during this project to visualize the deformation fields produced after the registration of two volumes.

Official website for this tool: <http://www.paraview.org/>

3.2 Implemented Methods

During the course of this project two different methods were implemented, both taking into account previous works about morphometry and quantification of small changes in volumes.

3.2.1 Voxel-based method

This method was implemented as a *3D Slicer* module with the following steps:

1. The user selects the base and follow-up volumes to be compared.
2. The user selects the registration method to be used and applies it on the volumes.
3. The module subtracts the base volume and the volume resulting from the registration and shows the resulting differences as colored layer on top of the base volume.

The registration methods available are: *Affine registration* (default), *B-Spline deformable registration* and *BRAINS Demon Warp registration*; all of them available as already existing modules in *3D Slicer*.

For more information on the registration methods, please refer to section 2.1.1.

The subtraction is done pixel-by-pixel and the result produces a label volume that shows the differences in color over the original base volume. The chosen color table for the label volume is “PET-Heat”, directly available in *3D Slicer*, since it seemed to produce a volume that was brighter and with easier to spot differences.

Strengths and Weaknesses

This method performs especially well in cases of volume loss, since this condition implies larger differences in intensity between both volumes. According to the experiments performed, the size of this differences can be really small and the method may still produce useful results.

The method depends a lot on the registration results obtained in the second step. If the registration result is poor, the program will produce “ghosts” or false differences that may confuse the user.

Note that a poor registration result might not necessarily be a direct consequence of the registration method chosen, it may also be due to problems with the volumes; for example, if the patient’s position changes a lot from one volume to the next, or if the MRI machine has very distinct settings in each examination.

Since in our specific case we deal with differences that are quite small, sometimes it is still hard to see them in the results; specially if we are looking at a screenshot of the application, rather than the actual application where we can see all of the frames in the volume.

Example

The following is an example of a volume without mayor differences that has been modified in order to add some obvious differences in the shape of circles in both of the original volumes.

1. The user selects the *MRIChangeDetectorModule* in *3D Slicer*.

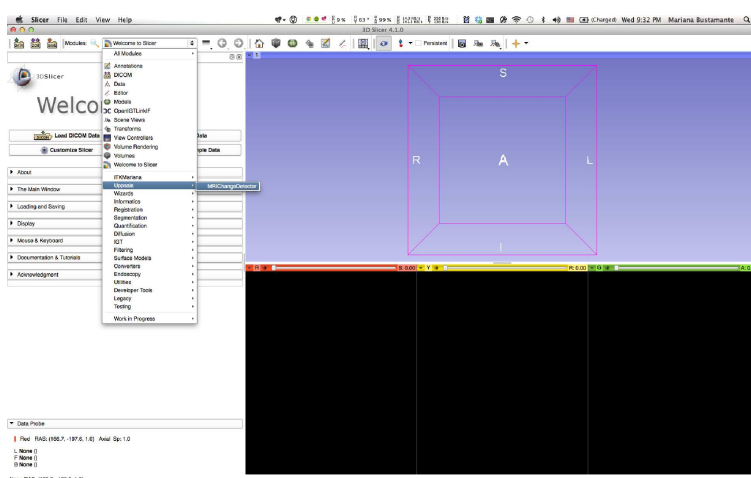


Figure 3.1. Step 0: Module selection

2. The user adds the volumes to be analysed.

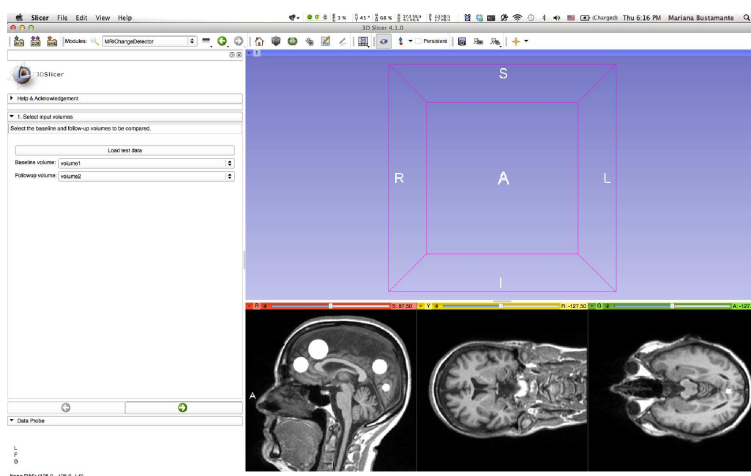


Figure 3.2. Step 1: Adding volumes

3. The user chooses the registration method to be applied.

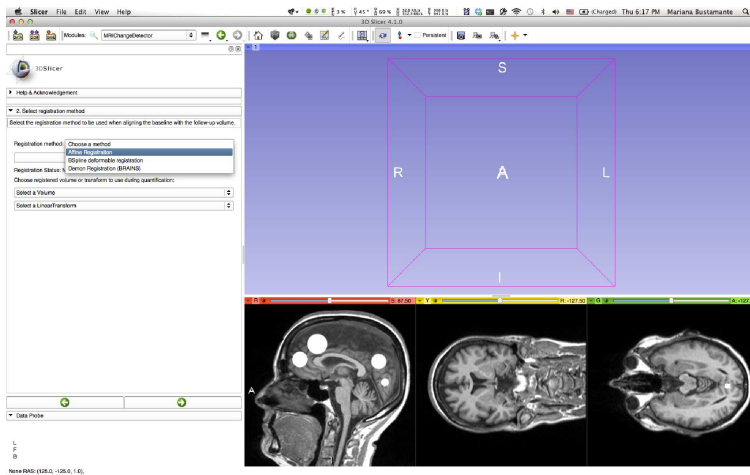


Figure 3.3. Step 2: Registration method

4. The user clicks the button “Run Quantification” and the program runs the subtraction and creation of label volume.

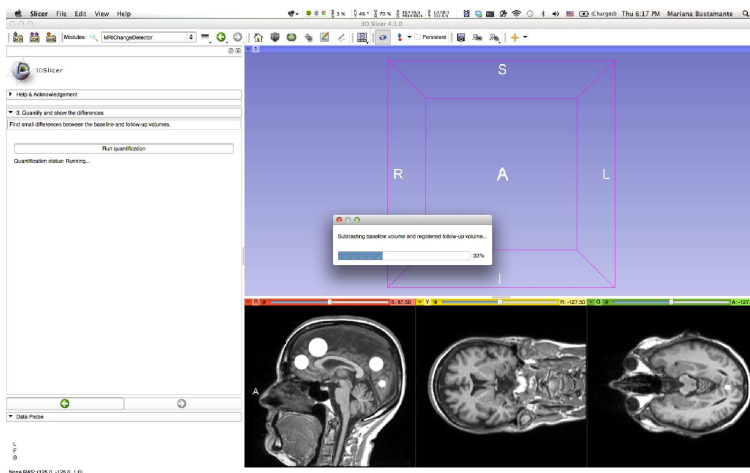


Figure 3.4. Step 3: Running quantification

5. The program shows the resulting label volume.

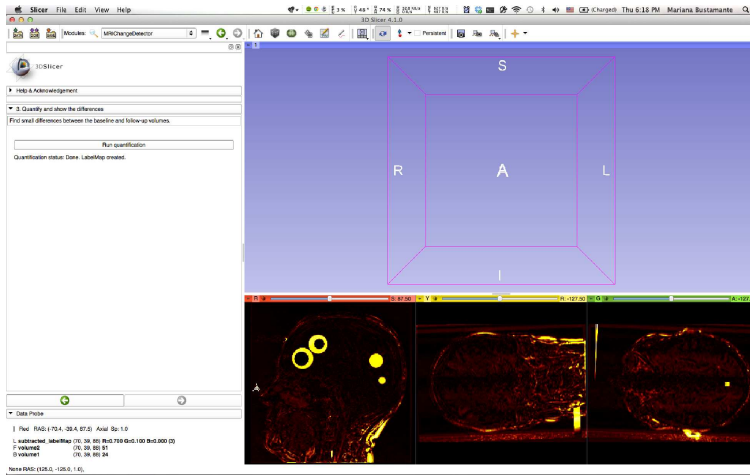


Figure 3.5. Step 4: Quantification result

Note that the resulting differences look like rings. This is the expected result because both of the original volumes were modified by adding circles of distinct sizes.

6. The user can now watch the label volume on top of the original volume and move the planes as he wishes.

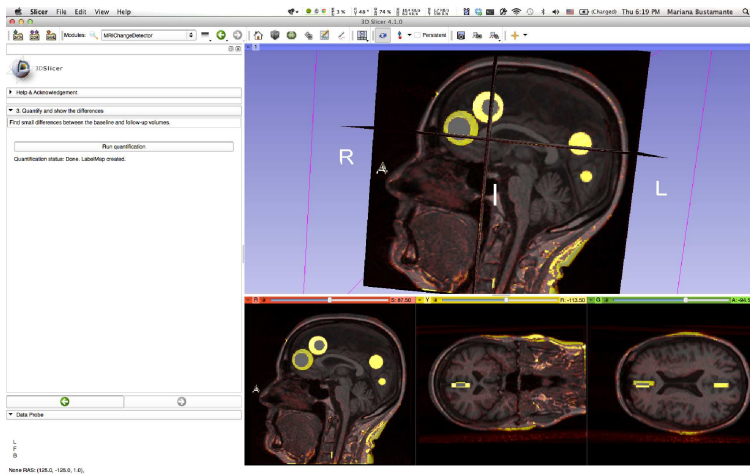


Figure 3.6. Step 5: User visualization

Technical Details

The user interface of the module is written in *Python* using some libraries from *Qt* and *CTK*, being *ctkWorkflowWidgetStep* from *CTK* the most important since it allows the creation of a “step-by-step” wizard.

The part of the module in charge of the subtraction of volumes is written in C++ using *ITK*.

The subtraction is done using the ITK filter *AbsoluteValueDifferenceImageFilter*, which computes the difference between each two pixels and then calculates the absolute value of the result. This allows the module to detect all the possible differences between the volumes, regardless of the sign of the resulting value.

3.2.2 Tensor-based method

- Method theory
 - Why is the method good/works?
 - Strengths and weaknesses
 - Example
 - Technical details

4. Experiments

4.1 Organization(better title)

4.2 Voxel-based method Results

4.3 Tensor-based method Results

5. Applications

5.1 Raili's study

5.2 other projects

6. Conclusions

6.1 Future works

- Improve Tensor-based method - Make it public to Slicer people

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