Quantification of intraventricular blood clot in MR-guided focused ultrasound surgery

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ABSTRACT

Purpose: Intraventricular hemorrhage (IVH) affects nearly 15% of preterm infants. It can lead to ventricular dilation and cognitive impairment. To ablate IVH clots, MR-guided focused ultrasound surgery (MRgFUS) is investigated. This procedure requires accurate, fast and consistent quantification of ventricle and clot volumes.
Methods: We developed a semi-autonomous segmentation (SAS) algorithm for measuring changes in the ventricle and clot volumes. Images are normalized, and then ventricle and clot masks are registered to the images. Voxels of the registered masks and voxels obtained by thresholding the normalized images are used as seed points for competitive region growing, which provides the final segmentation. The user selects the areas of interest for correspondence after thresholding and these selections are the final seeds for region growing. SAS was evaluated on an IVH porcine model.
Results: SAS was compared to ground truth manual segmentation (MS) for accuracy, efficiency, and consistency. Accuracy was determined by comparing clot and ventricle volumes produced by SAS and MS, and comparing contours by calculating 95% Hausdorff distances between the two labels. In Two-One-Sided Test, SAS and MS were found to be significantly equivalent ($p < 0.01$). SAS on average was found to be 15 times faster than MS ($p < 0.01$). Consistency was determined by repeated segmentation of the same image by both SAS and manual methods, SAS being significantly more consistent than MS ($p < 0.05$).
Conclusion: SAS is a viable method to quantify the IVH clot and the lateral brain ventricles and it is serving in a large-scale porcine study of MRgFUS treatment of IVH clot lysis.

Keywords: Image-Guided Therapy, Segmentation, Intraventricular hemorrhage (IVH), Neurosurgery, MR-guided focused ultrasound surgery (MRgFUS).

1. MOTIVATIONS AND BACKGROUND

One of the most frequent complications in pregnancy is premature birth. During the second and third trimester, preterm infants are at risk of severe neurological disruption. At this time infants are highly vulnerable to hemorrhaging[1]. Hemorrhaging is such a prevalent problem that infants born before 32 weeks gestation are screened using a diagnostic cranial ultrasound. The mechanism contributing to this high sensitivity is not fully disconcerted, but has been attributed to the developing brain's periods of instability, causing reduced cerebral perfusion pressure regulation[2].

Intraventricular hemorrhaging (IVH) affects nearly 15% of preterm infants[3]. IVH is bleeding within the ventricular system of the brain. An IVH clot can block the flow cerebrospinal fluid (CSF), but CSF continues to be produced, leading to ventricular dilation increased intracranial pressure. This pathological state is termed hydrocephalus. 40-50% of IVHs lead to hydrocephalus[4]. Hydrocephalus can cause cognitive and motor impairments that are carried on into adult life, and if left untreated can result in death[5].

The existing technique to manage the ventricular dilation is the temporary insertion of a catheter through the fontanelle, or the surgical insertion of a permanent ventriculoperitoneal (VP) shunt to drain the built-up CSF and alleviate pressure[6]. These treatments do not assist in the removal of the clot causing the blockage, and they have high morbidity and low success rate, with approximately 2/3 of shunt insertions having complications, and 1/3 requiring revisions[7]. A non-invasive approach targeting the IVH clots could potentially prevent hydrocephalus and minimalize risks associated with invasive therapies.

MR-guided focused ultrasound surgery (MRgFUS) is currently being investigated to ablate the clot on a porcine model[8]. The procedure involves a series of treatments of high intensity and high frequency ultrasound waves focused on the clot to cause vibration and eventually breakdown. The physician guides the application of the ultrasound waves using MR imagery.

Segmentation of the clot and lateral ventricles is a critical component in planning and assessment of MRgFUS. Existing manual segmentation (MS) lacks in accuracy, efficiency and consistency. Conventional manual segmentation may take over 2 hours per MRI, and takes approximately 120 hours per pig over the course of the entire MRgFUS workflow for the IVH clot. A semi-autonomous segmentation (SAS) workflow to resolve these issues is necessary.

There is a wealth of literature available for segmentation of brain ventricles and blood clots[9], but limited if any algorithms specifically designed for a porcine model. Pigs have an anatomically different ventricular system, with large anterior horns of the lateral ventricles in the comparatively large porcine olfactory bulbs. It is also essential that the SAS method is part of a free and open source platform, so it can be extended to meet the future goals of the MRgFUS clot ablation study. These goals include modifications for human trials, goals not relevant to segmentation, such as visualization of the ultrasound beam on the MR scan accompanied by the segmentation contours for planning of treatments and optimization of the location of the beam focal point, as well as other clinical goals that will extend to future surgical applications.

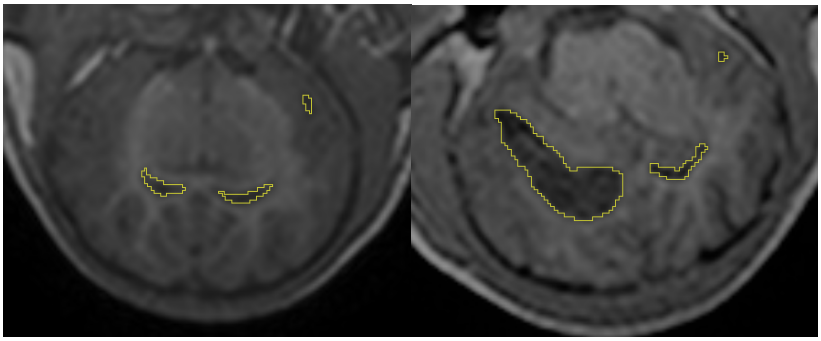
We propose a SAS workflow that is based on a cascade of filters and region growing algorithms applied to the MR image, in the free open-source image analysis and visualization software, 3D Slicer[10]. SAS reduces segmentation time by over 15 times, it improves consistency and it guarantees accuracy equivalent to manual segmentation by experts.

2. MATERIALS AND METHODS

2.1 MRgFUS porcine model

A previous established IVH porcine model for MRgFUS treatment was used[8]. In this model the pigs weighed between 3-3.5 kg, and thus had a relative brain size that emulated the brain of a preterm infant. A portion of the pig's skull is removed to create a window to the brain simulates the fontenelle, allowing acoustic coupling with the high intensity focused ultrasound. In this model, blood is infused into one of the porcine lateral ventricles through a catheter. The pigs are monitored for 21 days after they receive the clot. Experimental pigs are treated with MRgFUS on day 7 and control pigs remain untreated. The pigs receive MR scans on day 1 both pre-infusion and post-infusion, on day 7 pre-treatment, during treatment, post-treatment, or only once if control, and follow-up scans are taken on the 14th and 21st for both experimental and control pigs. Changes in clot and ventricle size are monitored through segmentation (Figure 1).

a) Day 1) Pre-clot T1-w Day 14) Untreated Post-clot T1-w



b) Day 7) Pre-treatment clot T2* Day 7) Post-treatment clot T2*

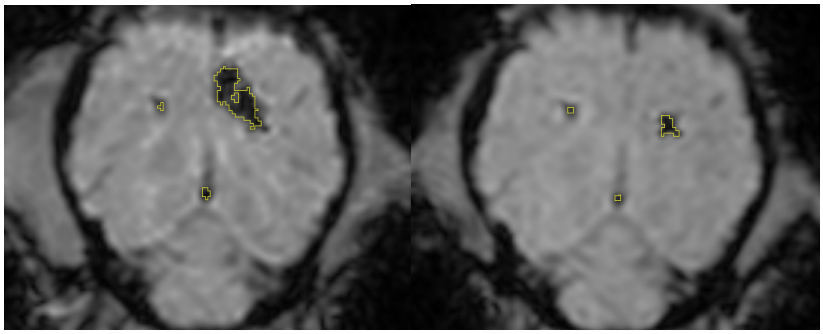


Figure 1. a) 14 days after clot infusion untreated porcine model ventricle size increased from 0.63cc to 1.37cc. **b)** After one day of treatment clot volume decreased from 0.63cc to 0.33cc. which is visible in the highly contrasted susceptibility weighted (T2*) MR scans.

2.2 Imaging protocol

The scans taken to monitor the pigs over the 21 days are T1-weighted (T1-w), T2-weighted (T2-w), and T2 susceptibility weighted (T2*) MR scans from the 3 Tesla Philips Achieva 3TX. T1-w scans with 0.5mm isotropic voxels are used to segment the lateral ventricles. T2* scans with 1mm isotropic voxels are used to segment the clot. T1-w scans are used to segment the ventricles because there is a greater contrast between the ventricular intensity and the bordering brain matter than in the T2-w scans. T2* scans are used to segment the blood clot because it exploits the difference between the susceptibility of different tissues, and produces an image in-which iron in blood hemoglobin is highly contrasted from other brain tissue, and thus the clot is more visible.

2.3 Semi-autonomous segmentation workflow

The workflow uses a combination of a competitive region growing and a threshold filtering algorithms (Figure 2). The threshold filtered normalized T1-w image provided the necessary seeds for growth. A reference set of MR scans from a pre-clot pig were selected. Based on the reference set a brain mask for clot segmentation and a ventricle mask for ventricle segmentation were created to restrict the thresholding to areas within the confines of the brain parenchyma and brain ventricles respectively. A margin was added to create a mask that would work not only on that selected pig but on all cases. Each step of the workflow is described in more depth below:

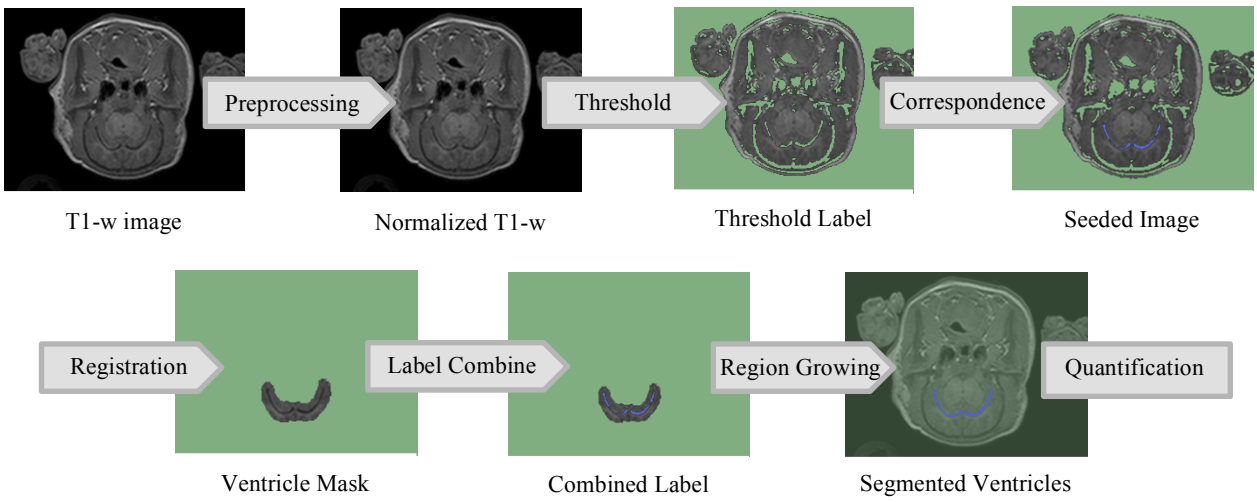
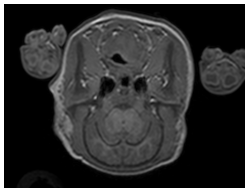
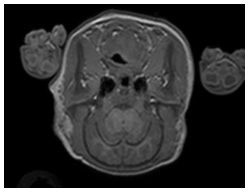


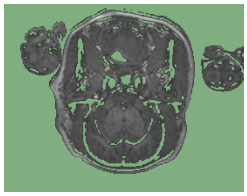
Figure 2. SAS workflow with corresponding ventricle segmentation screen captures.

1) 

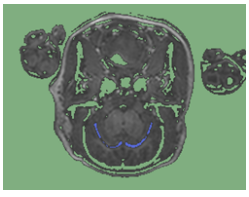
Input: T1-w, T2-w, and T2* MR scans. T1-w and T2* images are used for segmentation of the ventricle and clots respectively. T2-w images are used to register the reference image set to the input set of MR scans.

2) 

Preprocessing: the image is normalized to a reference image, so the image is between 0 to 255 gray levels. The image is threshold filtered to exclude voxels whose grayscale values are less than the mean, so air voxels are not taken into account in the match.

3) 

Threshold filtering: In order to create a label map that applies seeds in all the regions of interest in each slice, the intensities 0 - 58 and 0 - 40 were empirically determined to be the optimum values to threshold the ventricles and the blood clot respectively. The threshold filtering is not intended to segment the entire structure, but only to provide seeds for the region growing algorithm.

4) 

Creating correspondence: The user selects anywhere in the ventricle or clot and structure changes the label of all connected regions. This creates a correspondence between all connected areas in three dimensions, allowing quick seed creation. This also differentiates the seeds from the other areas of similar intensity that were labeled by the threshold filtering, as a new color label is assigned to the selected area.

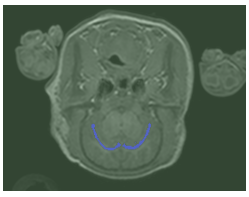
5) 

Registration and combination: A reference image is registered to the images to be segmented using mutual information rigid registration and an anisotropic scale. The scaling allows the mask to accommodate dilated ventricles. The transform created is applied to the brain mask and ventricle mask that corresponds with the reference image.

The mask labels have two values (0 or 1), and are multiplied the images to be segmented. The masks cover either the ventricular area or the brain parenchyma depending on whether it is a ventricle or clot mask respectively. Only the non-zero voxels in the input mask and the input image will remain non-zero in the output image because the multiplication is a binary AND operation. Thus remaining non-zero voxels in the output image will be the area surrounding the ventricles or the entire brain parenchyma. This image with only the regions of interest is thresholded to create a label that only includes the empty voxels (the area around the region of interest). Thus there is a new registered mask to focus the region growing algorithm on the structures of interest. The new ventricle mask excludes the CSF surrounding the ventricles and the new clot mask excludes the area around the brain parenchyma.

6) 

Region growth: The new mask labels and the threshold labels (from step 3) are combined. This places the seeds within the mask, preparing the image for the competitive region growing algorithm. The region growing algorithm is then applied to the combined label map. The algorithm iterates through all undefined label pixels and assigns a label based on weighted similarity metric of the current pixel in the preprocessed grayscale input image and all the pixels on that pixel's border. Computation ends when all the pixels are labeled.

7) 

Output: Ventricle and clot labels are separated from the background label (seen in green). The ventricle and clot labels are then combined, so they can be visualized together and in relation to each other, despite being derived from different MR scans.

8) **Quantification:** Volumetric data is obtained by multiplying the volume of each voxel by the number of colored voxels in the label map.

2.4 Implementation as a 3D Slicer application

Several algorithms from the image analysis and visualization software 3D Slicer[10] were used in the SAS workflow. The Histogram Matching module was used for normalization, ITK Binary Threshold Filter algorithm for thresholding, the Change Island Effect is used to create correspondence, the image is registered and scaled using the BrainsFit module[11], the labels are combined using the Image Label Combine module, the region growing algorithm implemented is GrowCut[12], Label Statistics module.

This workflow was implemented in Python programming language as a standalone application that is built on 3D Slicer. The application computes nearly all the steps of the workflow automatically, and requires minimal user interaction (loading data, selection of appropriate data, one button to initialize workflow, and selection of structures of interest to create correspondence). This application provides volumetric information and creates a 3D model. It includes a simple graphical user interface, which also allows for visualization of segmentation contours and creation of a 3D model (Figure 3).

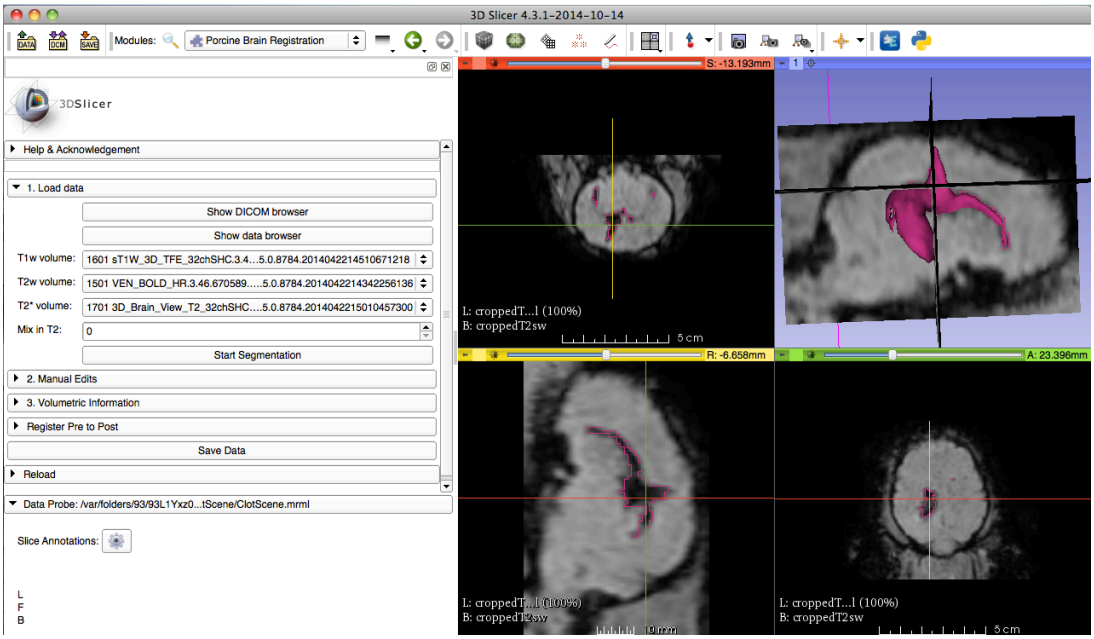


Figure 3. User interface in 3D Slicer showing a segmented blood clot and its 3D model.

3. RESULTS AND DISCUSSION

3.1 Testing of other algorithms

Within 3D Slicer several segmentation algorithms and methods of preprocessing were compared. Various region-growing algorithms were tested. Porcine lateral ventricles are much thinner than human ventricles. Thus the superior and inferior membranes of the ventricles frequently stick together and the ventricles appear discontinuous in MR images. Furthermore, the distribution of the blood within the ventricles may not be continuous, rather separated into multiple clots. Due to these disconnected structures the manual placement of seeds was not efficient because of the large number of seeds that would be required to create segmentations comparable to ground truth manual segmentations. Threshold filtering was also experimented with to create a label map of the ventricles and blood clot. The MR scans naturally include the skull, skin, and other anatomical features surrounding the brain. The intensities of many of these structures are similar to the intensities of the clot and the ventricles, so threshold filtering would segment these areas as well. Even when the threshold filter was fixed to only a specific region that contained the only structure of interest, the areas that bordered it were not sufficiently contrasted, and in order to threshold filter the entire structure the surrounding structures would also be partially segmented.

3. 2 Validation methods

Ground truth segmentation

To test the validity of SAS, ground truth manual segmentations were created. To ensure accuracy of ground truth manual segmentations three manually segmented MR images were randomly selected from the data set of over 20 manual segmentations and approved as accurate by a clinical expert.

Comparing similarity

Both volume and 95% Hausdorff distance (HD) were used to compare the SAS to the ground truth MS to ensure accurate evaluation of the segmentation The Hausdorff distance is the distance between the two closest points on two contours, and in this case the distance between the point on the MS contour and SAS contour. The result is a distribution of distances, and the 95th percentile of this distribution is used to compute segmentation error. This computation was done through the Contour Comparison module in 3D Slicer[13].

Statistics

Welch Two-Sample T-Test was used to calculate if consistency and efficiency of the SAS was significantly different and thus better than MS. MS is being used as the ground truth for the volume and contours of these anatomical features, so SAS segmentation must be equally as accurate. It would not be sufficient to determine that MS and SAS were not significantly different, because that does not indicate equivalence. The Two One-Sided Test was used to determine significant equivalence between SAS and MS for accuracy[14]. The equivalence margin (δ) is the maximum acceptable difference that would still allow the MS and SAS to be considered equivalent. δ was the MS standard deviation (described in 3.2). Significant equivalence is achieved when $(1–2\alpha) \times 100\%$ confidence interval for the difference in volume (SAS – MS) is contained within the interval $(-\delta, \delta)$. Version 3.1.1 of the statistics program R[15] was used to calculate the Welch Two Sample T-Tests and R's equivalence package[16] was used to calculate the Two One-Sided Test.

3.3 Consistency

The ventricles and the blood clot were segmented manually by the same expert and semi-autonomously five times on one MR image. Using the SAS method, standard deviations from the mean volume of the ventricle and clot volumes were both less than 0.001%. In the MS case, standard deviations of ventricle and clot volume were 14.73% and 5.18% from the mean volume respectively. The 95% HD was calculated from the two MS labels with the greatest difference in volumes. The distances were 1mm and 0.81mm for the clot and ventricle respectively. The 95% HD between two SAS labels was less than 0.001mm for the ventricles and clot. Based on a Welch Two Sample T-Test, SAS was significantly more consistent ($p < 0.05$) than MS.

3.4 Accuracy

Ten ventricles and clots from ten different MR images were segmented once semi-autonomously and manually. The accuracy of the SAS was determined by comparing the percent difference in volume between the SAS and the MS of each of the ten scans to the standard deviations of MS noted above. Two One-Sided Test was used to determine equivalence, with the equivalence margin being the MS standard deviation (14.73% and 5.18% of the volume for the ventricles and clot respectively). The SAS volume was significantly equivalent to the MS volume for both ventricles and clot ($p < 0.01$). The mean 95% HD between the MS and SAS labels was calculated to confirm that the SAS and MS occupied the same space. The mean 95% HD for the clot and ventricles were 0.66mm and 0.55mm respectively, which falls within the 95% HD between the manual segmentations compared for consistency above (1mm and 0.81mm for the clot and ventricle respectively). Thus SAS is as accurate as MS for position and volume.

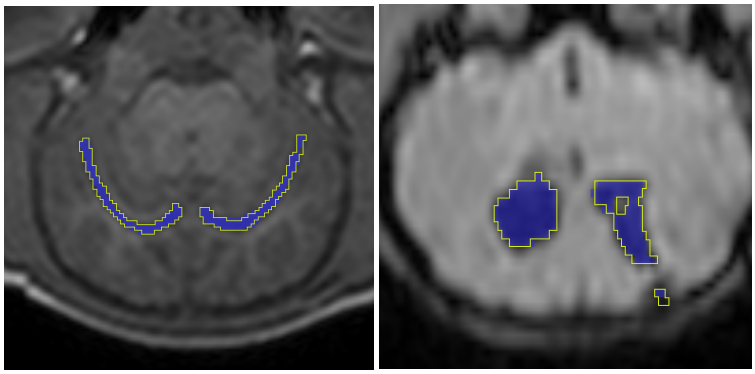


Figure 4. Examples of MS (yellow) and SAS (blue) in ventricles (left) and clot (right).

3.5 Time Efficiency

The two segmentation methods were compared in ten different MR images based on the average time required to perform ventricle and clot segmentation. The average time to manually segment and semi-autonomously segment the

ventricles and the clot was approximately 126 minutes and 8 minutes respectively. On average the SAS was significantly faster ($p < 0.01$), and increased speed by over 15 times. The average computation time of the SAS was 209 seconds, and the average time of manual involvement to select the ventricles and clot was 83 seconds, the remaining time was spent navigating 3D Slicer. This navigation time was eliminated by the creation of the 3D Slicer application that compiled the workflow.

4. CONCLUSION AND FUTURE WORK

A semi-autonomous segmentation of porcine lateral ventricles and IVH clots was significantly more consistent and time effective method than manual segmentation, while being as accurate as expert manual segmentation. The 3D Slicer application is currently being encoded into a so called Slicelet[17] module so it can be used outside of 3D Slicer. This will make it more user-friendly and ergonomically efficient for clinical experts that do not have experience with 3D Slicer.

Currently the application is very specifically targeted to porcine brain ventricles and clots. Efficiency will be increased with spline transformations, so segmentation can occur intraoperatively. Filtering parameters will be modified to work on human brain images, when experiments progress to human trials. To make this application more generalizable to other anatomical structures, a second 3D Slicer application will be created to prepare reference images, masks, and threshold ranges, which will then be imported into the current application, allowing segmentation of diverse anatomic features.

5. ACKNOWLEDGEMENTS

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