

# Application of Image Processing Functions for Brain Tumor Enhancement in Intraoperative Ultrasound Image Data

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## Abstract

*Intraoperative ultrasound (iUS) imaging supports neurosurgeons significantly during brain tumor operations. At the beginning of the intervention the integration of the iUS image data within the navigation system guides the surgeon by optimally planning the position and size of the skull opening. After tumor resection, the visualization of the iUS image data enables to identify possible tumor residuals. However, the iUS image data can be complex to interpret. Existing segmentation and registration functions were assembled into pipeline to enhance brain tumor contours in the 3D iUS image data. A brain tumor model, semi-automatically segmented in the preoperative MR data of patients, is rigidly registered with the 3D iUS image using image gradient information. The contour of the registered tumor model is visualized on the monitor of the navigation system. The rigid registration step was offline evaluated on 15 patients who overcame a brain tumor operation. The registered tumor models were compared with manual segmentations of the brain tumor in the 3D iUS data. Averaged DSI values of 82.3% and 68.4% and averaged contour mean distances of 1.7 mm and 3.3 mm were obtained for brain metastases and glioblastomas respectively. Future works will include the improvement of the functions in the pipeline, the integration of the pipeline into a centralized assistance system including further functionalities and connected with the navigation system, and the evaluation of the system during brain tumor operations.*

## CCS Concepts

•Computing methodologies → 3D imaging; Image segmentation;

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## 1. Introduction

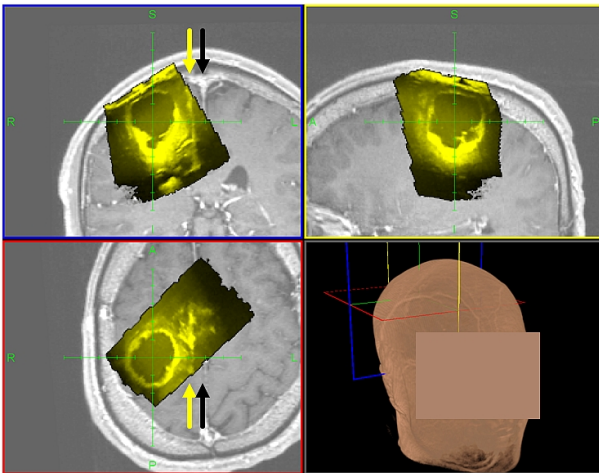
Microsurgical complete removal of brain tumor is an essential requirement for patients for long tumor free intervals with good quality of life. The goal of the surgical intervention is a radical resection as much as possible while preserving healthy brain parts. Magnetic resonance imaging (MRI) represents the standard method to plan the operation, preoperatively, and to estimate the operation outcome, postoperatively. Intraoperatively, computer assisted navigation systems perform the correspondence between the preoperative image data and the current position of surgical instruments. Navigation systems support neurosurgeons to achieve small and accurate skull openings, called craniotomies. However, they are less useful after dura opening when tissue deformation, loss of cerebrospinal fluid and tissue swelling occur. Therefore, intraoperative imaging is the most valuable method to compensate this limitation and provides an update representation of the brain status during the operation progress.

Intraoperative fluorescence is the standard method in the neurosurgery to visualize glial tumor tissue. This modality requires the

oral administration of a contrast agent, the 5-aminolevulinic acid, which accumulates in the glial tumor cells. It has fluorescence property which is revealed under light excitation using specific wave length. However, only tissue surface is visualized with this optical imaging method. Intraoperative ultrasound (iUS) imaging is a complementary method to visualize the tissue depth ([BCN16], [PSM\*16]). Two-dimensional B-mode ultrasound imaging is commonly used. However, its ability to distinguish between tumor borders, edema, surrounding tissue and tumor remnants is sometimes limited. Moreover, recent studies demonstrated the benefits of ultrasound contrast agents on the visualization of brain tumor tissue and margins ([ACM\*16], [HJW\*8], [PBF\*16], [PPM\*14]). The interpretation by surgeons of the iUS image data of the head during the operations is in general complex. The scanned brain region remains limited, the contrast in the images is low and the images can be impaired by artifacts.

Navigation systems which integrate an ultrasound device achieve the visualization of the iUS image data superimposed on the preoperative MR images as depicted in Figure 1 ([TML\*02], [URS\*06], [USB\*05]). The visual comparison of information

included in the iUS data with the preoperative MR images which offer better image contrast, a larger field of view, supports the interpretation. However, brain tissue deforms during the operation ([RHK\*98], [SBP\*16]). Similar brain structures are represented in different planes of the iUS and preoperative MR data. In Figure 1, the black and yellow arrows indicate the position of the falx which represents the brain centerline respectively in the preoperative MR and iUS data. The displacement which occurred already after the skull opening is clearly visible. Therefore, image registration algorithms were implemented with the goal to accurately overlap corresponding structures.



**Figure 1:** Visualization of a brain tumor revealed in 3D ultrasound data acquired during an operation with the navigation system SonoNavigator (Localite, Sankt Augustin, Germany). The arrows show the displacement of the brain centerline, which results from tissue deformation, already after the skull opening.

Many works for registering the iUS data with preoperative MR data have been already presented in the literature. Most of registration methods involve complex metrics calculated based on the image intensities ([CHM\*12], [FWM\*14], [JHR\*08]). Other approaches perform the registration based on extracted anatomical landmarks (for example the cerebral blood vessels in [RLU\*07] or the brain mid-line [CSF\*00]). Additional methods involve biomechanical deformation models ([FNM\*01]). These techniques use rigid and non-rigid transformations. The first set of methods can lack of robustness due to the different intensity representations of anatomical structures in the MR and iUS data ([AMC\*01]). The second set of methods requires the intraoperative segmentation of landmark structures in the iUS data. The last set of methods is complex and requires extensive computing time ([HBB\*05]). Moreover, the registration task becomes more complex at the end of the operation due to loss of anatomical landmarks (the tumor is being removed) and general decrease of image quality.

Therefore, the interpretation of the iUS image data could be supported by the extraction of target structures like brain tumor tissue, for visualization purposes. Manual delineation is the most robust method. It is however time consuming and cannot be performed

in the operating room by the medical staff because of sterility constraints and time limitations. On the other hand, automatic segmentation is complex in ultrasound image data because of the low signal to noise ratio and the unclear definition of object boundaries ([MD12], [PPD13]). Therefore, although the segmentation of brain tumors in MRI was extensively studied ([CDA16], [HDW\*17], [ICA\*16], [KZD\*15], [VRS\*16]), similar works on ultrasound image data are few. Active contour methods including snakes and level set techniques were evaluated to segment the full brain tumor on intraoperative 3D B-mode ultrasound images in [Nav05]. In [RLU\*07], the brain tumor extracted in the preoperative MR data was non-linearly registered on intraoperative B-mode US image. The transformation was estimated based on blood vessels surrounding the tumor and extracted in MR angiographic and Doppler US data. In [RPW15], a classification method using support vector machines was developed to extract brain tumor tissue. Time intensity curves extracted from the 2D+t perfusion iUS data acquired with contrast agent were modeled by functions whose parameters were the input of the algorithm. The authors of this paper presented an approach of automatic identification of tumor residuals in 3D iUS image data acquired at the end of brain tumor operation [ILA\*17]. It consisted in combining the relevant information included in different ultrasound imaging modalities. In B-mode images, anatomical structures like blood vessels, bone structures, possible tumor residuals, borders of the resection cavity but also artifacts are clearly depicted in high intensities. The use of an ultrasound contrast enables to reveal tumor residuals and vascular structures in contrast mode. Therefore, high intensity structures were automatically extracted in the iUS data using the Otsu multilevel thresholding method. The identification of suspicious brain tissue was performed by keeping the intersection of the segmented regions in both modalities. Indeed, structures that are enhanced in the contrast mode images and that are located in the neighborhood of the cavity border as depicted in the B-mode images have a high probability to be tumor residuals (Figure 3 c and d).

Goal of this project is to provide the neurosurgeon with tools to support the interpretation of the 3D iUS data during brain tumor operation. Visualization method to show the brain tumor contour, extracted in the iUS data, in the neuronavigation system [CLA\*12] and segmentation method for the identification of possible brain tumor residuals [ILA\*17] were already developed. In this paper, an approach to enhance the contours of entire brain tumor in the iUS data is presented and evaluated offline under laboratory conditions on B-mode and contrast mode data of patients. Future connection of this current work with the previous ones is shortly described in the discussion. This work was performed in close collaboration between the ICCAS institute of University of Leipzig and the neurosurgery department of the University Hospital of Leipzig, and with the support of the Engineering Division of the University of Guanajuato.

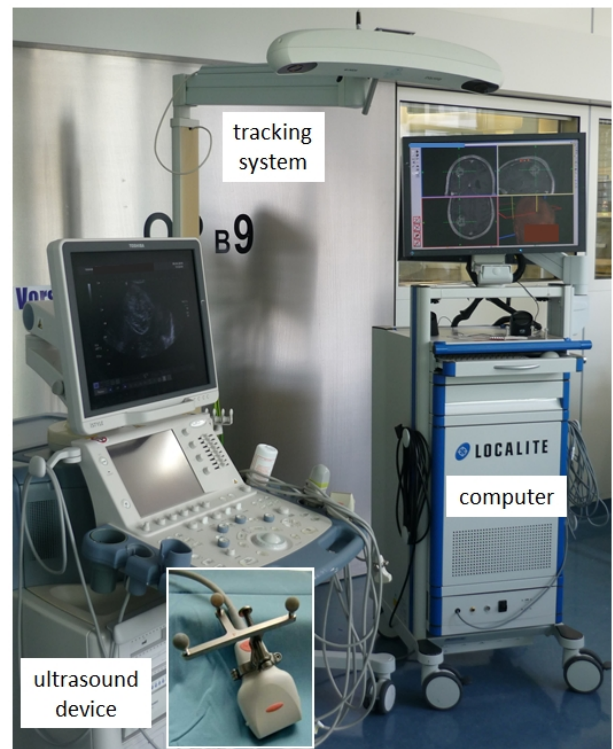
## 2. Material and Methods

### 2.1. Devices for the acquisition of the 3D iUS data sets of patients

Brain tumor operations performed in the neurosurgery department of the University Hospital of Leipzig are commonly supported using neuronavigation system and intraoperative ultrasound imaging. In the context of a clinical trial funded by the German Research Society (Deutsche Forschungsgemeinschaft) and accepted by the ethics commission of the University of Leipzig, a data base of 3D B-mode and contrast-enhanced iUS data including patients with different kinds of brain tumors were constituted. The commercial devices for the acquisition of the 3D iUS volumes consisted of a navigation system (SonoNavigator, Localite, Sankt Augustin, Germany) coupled with an ultrasound device (AplioXG, Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) (Figure 2). The acquisition of patient data was performed as described now. The surgeon scanned with the hand and through the skull opening the cerebral region of interest with the 2D ultrasound transducer whose free position was followed by the optical tracking module of the navigation system. A 3D dense ultrasound volume was then reconstructed from the 2D slices. The reconstruction algorithm makes use of intensity averaging and smoothing functions. The 3D iUS volumes are overlapped on the preoperative MR data on the monitor of the navigation system.

The image data were acquired at two time points of the operation: firstly at the beginning of the operation after craniotomy and when the dura matter enveloping brain tissue is still intact, secondly at the end of the operation when the tumor has been removed. Two iUS volumes were acquired at each time point: a 3D intraoperative B-mode (iBmode) volume and a 3D intraoperative contrast-enhanced ultrasound (iCEUS) volume. The 3D-iCEUS data were obtained by injecting 4.8 mL of an intravenous ultrasound contrast agent (SonoVue, Bracco s.p.a, Milan, Italy) at a rate of 3.0 mL/min using a syringe pump (ACIST VueJect, Bracco s.p.a, Milano, Italy) and the contrast harmonic imaging (CHI) modality.

In the original 2D ultrasound images, the pixel size is 0.422 mm x 0.422 mm, and the voxel size of the reconstructed 3D volumes is 1 x 1 x 1 mm<sup>3</sup>. Figure 3 shows an example of 2D iBmode and iCEUS images of one patient. At the beginning of the operation, the margins of the brain tumor are more clearly depicted in contrast enhanced mode (Figure 3b) than in B-mode (Figure 3a). After tumor resection, the borders of the resection cavity are sharp represented in B-mode but tumor residuals are visually hardly differentiable from blood layers (Figure 3c). On the other hand, vascular structures and possible tumor tissue are enhanced with the use of a contrast agent (Figure 3d). But the lack of representation of reference anatomical structures makes it difficult to understand the iCEUS images. The image datasets of patients with brain metastases and glioblastomas (Figure 3 a and b) were used to develop and test offline the image processing pipeline which is presented now.



**Figure 2:** The neuronavigation system includes a computer and an optical tracking system. It is connected to an ultrasound device. The US transducers are provided with markers which are tracked by the optical tracking system. Therefore, 3D ultrasound data are reconstructed from the acquired 2D US data.

### 2.2. Model-based enhancement of entire brain tumor contours in the 3D iUS image data

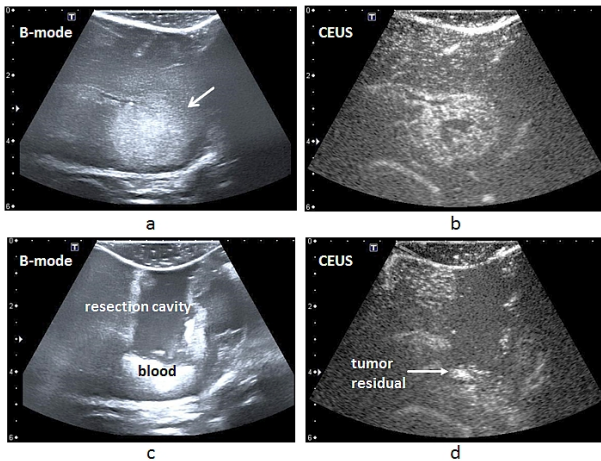
#### 2.2.1. Semi-automatic segmentation of the brain tumor in the preoperative MR data

A brain tumor model is obtained by semi-automatically segmenting the brain tumor in the preoperative MR data, available almost one day before the operation. A tool was implemented using the framework MeVisLab developed by Fraunhofer Institute for Medical Image Computing MEVIS (Figure 4). The user defines a region of interest which coarsely includes the target brain tumor in the MR data. High intensities corresponding to the active part of the tumor and at least located at the tumor boundary are extracted using the Otsu multilevel thresholding method. A 3D mesh surface is generated from the iso-contours of the binary segmented object. At this step, the user can interactively remove parts of the 3D model using 3D tools, which are considered as noise.

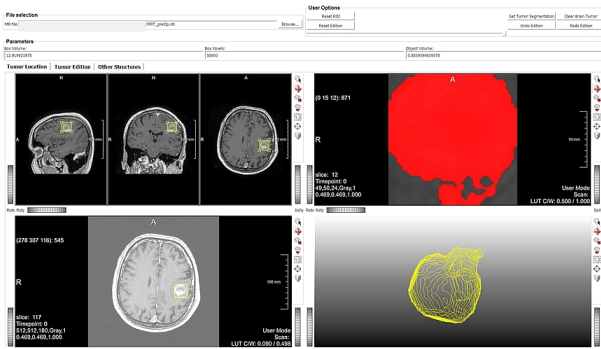
#### 2.2.2. Rigid registration of the 3D tumor model with the 3D iUS data

In Figure 6 the initial position of the 3D tumor model (in red), obtained for example using the tool described in the last section, is





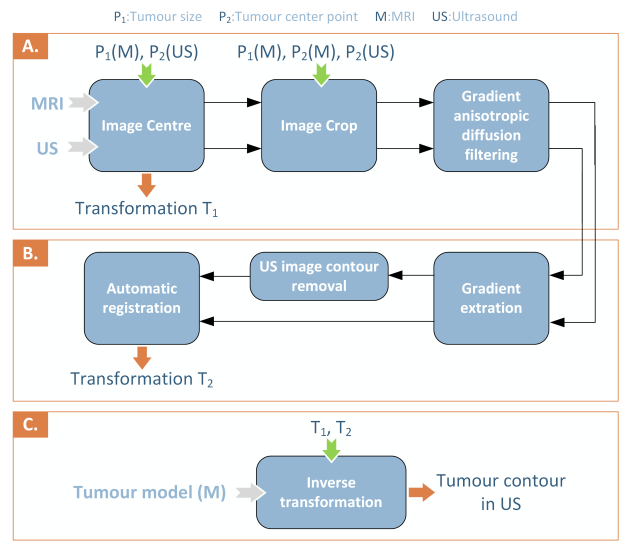
**Figure 3:** Intraoperative US data acquired at the beginning and at the end of a brain tumor operation. The brain tumor, here a glioblastoma, is depicted in B-mode (a) and contrast enhanced mode (b). The white arrow in (a) indicates blurred tumor margins. After tumor resection, the resection cavity and blood layers are well shown in B-mode (c), while possible tumor residuals are better revealed with the use of a contrast agent (d).



**Figure 4:** User interface for generation of a 3D patient specific brain tumor model developed with the MeVisLab framework. A Otsu multilevel thresholding algorithm extracts the high intensities corresponding to the brain tumor (upper right window) in a region of interest defined by the user in the preoperative MR data (upper left window). The generated 3D tumor model is displayed in the lower right window.

overlapped on the 3D iUS data, as it could be shown in the navigation system. The tumor model is clearly shifted relatively to the tumor in the 3D-iUS data because of brain tissue deformation. Therefore, it has to be registered with the tumor in the 3D-iUS data. The parameters of the transformations used in the rigid registration, here translations, are estimated based on object borders (Figure 5).

A) PREPROCESSING. The method uses three images as input: the preoperative MRI, the tumor model and the 3D-iUS (noted MRI, M and US in Figure 6). Additional input parameters are the tumor sizes  $P_1(M)$  of the bounding box including the tumor model



**Figure 5:** Pipeline of the model-based process for the extraction of brain tumors in 3D iUS data.

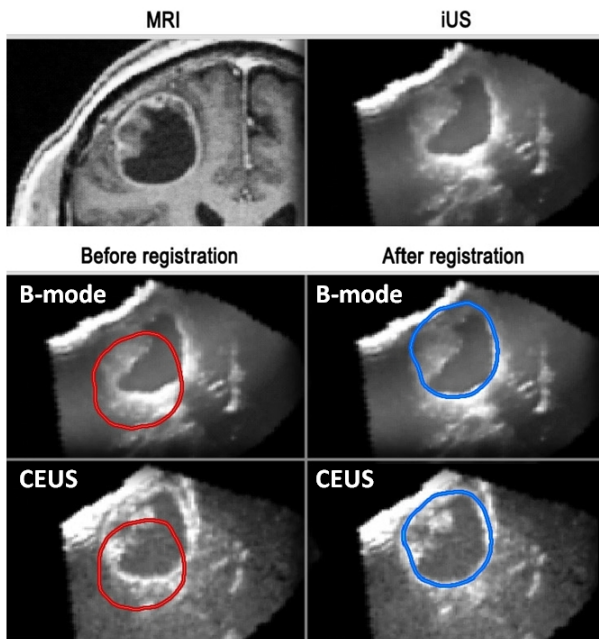
M in the x, y, z directions, center point  $P_2(M)$  in MRI, automatically computed from M, and the center point  $P_2(US)$  in 3D-iUS, manually given. MRI and US are firstly centered using the parameters  $P_2(M)$  and  $P_2(US)$ , providing the translation  $T_1$ . This fast step is realized in order to accelerate the registration in step B. Secondly, regions of interest including the tumor in MRI and US are extracted. The regions' centers are  $P_2(US)$ , their sizes are the sum of  $P_1(M)$  plus 15 voxels in the x, y, z directions. Thirdly, a gradient anisotropic diffusion filter is applied in order to reduce the noise in the image without losing the information of its edges.

B) RIGID REGISTRATION. Afterwards the gradient recursive Gaussian filter is applied to extract the gradient information in the images. The frame of the 3D-iUS image is however also detected as edges and has to be removed. The number of pixels to be removed (in general between three and five pixels) is depending on the image aspect. Then, an automatic rigid image registration algorithm using the translation transform, mean square metric and regular-step gradient descend optimizer aligns the US and MRI gradient images and returns the translation  $T_2$ .

C) TRANSFORMATION APPLICATION. Finally, M is aligned with US using the inverse transformation of  $T_1$  and  $T_2$ . The registered M represents the segmented tumor contour in US. The resulting contours are depicted in blue on the 3D iBmode and iCEUS data in Figure 6.

**2.2.3. Brain tumor margin enhancement**

The representation of the extracted tumor tissue is an important issue. The information has to be displayed in a suitable way to be able to optimally support the surgeon in the interpretation of the image data. The patient specific tumor model which has been registered with the brain tumor in the 3D iUS data is stored in a binary 3D image. The model contour is extracted, represented as a mesh and saved in VRML format. It is then imported from the navigation



**Figure 6:** Upper row: Slice of a preoperative MR image revealing a brain tumor and corresponding slice in the intraoperative B-mode image. Lower rows: Position of the patient specific tumor model before (red contours) and after (blue contours) rigid registration with the 3D intraoperative B-mode and contrast-enhanced ultrasound data.

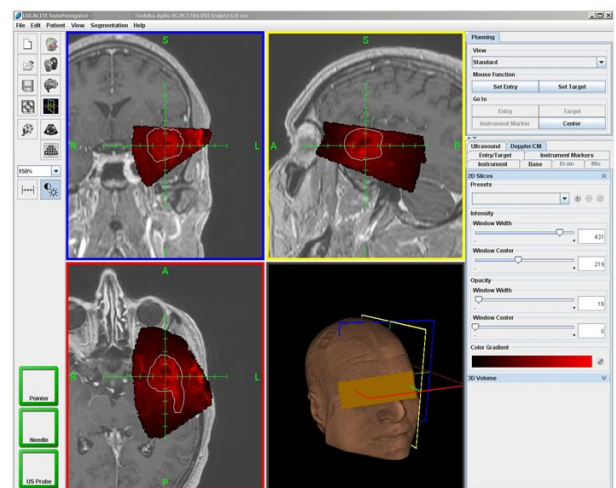
system. The boundary of the model is visualized overlaid to the 3D-iUS data (Figure 7) [CLA\*12]. Consequently, tumor margins are enhanced by the model. Grey intensities of the tumor are still visible to visually check the result of the segmentation algorithm.

### 2.3. Evaluation

Brain tumor contours extracted in the 3D iUS data by our approach were quantitatively compared with manual annotations considered as ground truth. A scientist segmented manually the brain tumors in the 3D intraoperative B-mode and contrast-enhanced mode data of patients using the ITK-SNAP free software. The results checked by two neurosurgeons who had long experience with acquisition and interpretation of intraoperative ultrasound images. Two comparison metrics were used: the Dice Similarity Index (DSI), given in percentage, and the mean contour distance (MCD), given in millimeter. The DSI provides global information about the overlapping rate of two objects. Its value is 1 if both objects have the same shapes and are exactly superimposed. Its value is 0 if the objects do not intersect. The MCD provides local information on the mean distance between the contours of the two objects in comparison. Moreover, the computing time of the algorithms was measured.

### 3. Results

The segmentation of the brain tumor model in the preoperative MR data is performed in a couple of minutes at the planning step of the



**Figure 7:** The preoperative MR image, the 3D intraoperative ultrasound data and the registered brain tumor model are represented on the monitor of the Localite SonoNavigator navigation system (this figure was published in [CLA\*12]).

operation. User interaction is still allowed at this step.

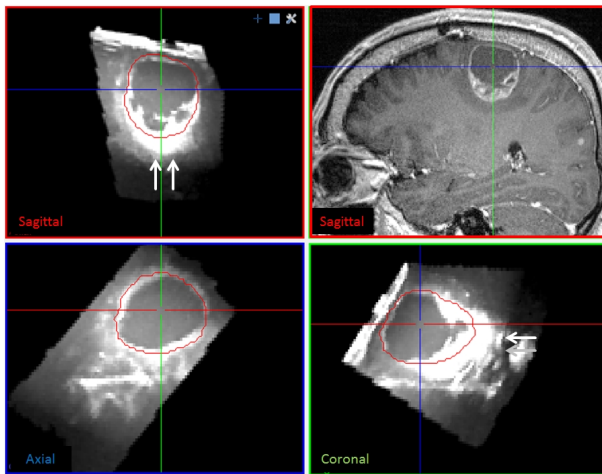
A preliminary evaluation of the rigid registration of the brain tumor model with the 3D iUS image data was performed on a sample of 3D iBmode and 3D iCEUS datasets of 11 patients with metastases and of four patients with glioblastomas. The quality of the image sample was evaluated as good to very good by a neurosurgeon. Figures 8 and 9 show the tumor contours obtained for one metastasis and one glioblastoma. In Figure 8, an image artifact at the tumor bottom is visible in hyperechogenic intensity in the sagittal and coronal views (double arrows). Part of metastasis boundary is therefore locally not distinguishable from neighboring brain tissue. Since the other borders are sharply represented, the tumor model was accurately registered and enabled to restore the information at positions where it lacks. In Figure 9, the tumor is visible but the boundary is smooth in the 3D-iUS. The algorithm could correctly identify the glioblastoma position. The model enabled proposing a position for the unclear boundary. The result is complex to evaluate visually but looks less accurate than for the metastasis. For example, the tumor contour seems having underestimated the tumor volume at the position indicated by the arrow.

The quantitative evaluation reported in Table 1 and Table 2 supports the visual observations. The Dice coefficient is larger than 70% for 28 out of 30 experiments, which indicates that the algorithm could correctly identify the tumor in the 3D-iUS data in B-mode and CEUS. A difference is moreover observable between metastases and glioblastomas. Metastases are encapsulated tumors whose boundary is well represented in ultrasound images. The mean Dice coefficient values obtained are therefore high ( $82.5 \pm 5.7\%$  and  $82.1 \pm 6.5\%$ ). On the other hand, glioblastomas are diffused tumors whose margins can look blurred in ultrasound images. The gradient images include less information and the performance of the algorithm is lower (mean Dice coefficients of  $74.6 \pm 2.4\%$  and  $62.1 \pm 29.7\%$ ). The larger mean values of the MCD for glioblastomas ( $1.9 \pm 0.4\%$  and  $4.6 \pm 3.7\%$ ) than for metastasis ( $1.6 \pm 0.7\%$

and  $1.7 \pm 0.7\%$ ) support these observations. The mean distance between the contours of the tumors manually annotated and provided by the algorithm is less than two millimeters for the metastases and up to nearly five millimeters for the glioblastomas in CEUS modality.

Moreover, although the performance of the algorithm is similar for the metastases in B-mode and CEUS mode concerning the Dice coefficients and the MCD, the results on the glioblastomas are heterogeneous. For patients 12 and 13, the segmentation method succeeded better on the 3D-iCEUS data. On the other hand, the DSI decreased and the MCD values increased for patients 14 and 15 with the use of contrast agent. Only part of the tumor was enhanced in patient 14. In patient 15, the brain tumor was located close to the falx (brain centerline which is enhanced by the contrast agent). This structure attracted the 3D tumor model more than the tumor boundary.

The rigid registration results were delivered in a couple of minutes in average. Computing time depends on the tumor size, on the metric and transformation function used in the registration approach.



**Figure 8:** Contour of a brain metastasis model obtained by semi-automatic segmentation in the preoperative MR data, and registered with the corresponding 3D intraoperative B-mode ultrasound data. The arrows show the presence of an image artifact which hides the position of the real tumor margin. The use of a patient specific brain tumor model allowed to reconstitute the correct information.

#### 4. Discussion

In this work, segmentation, registration and visualization functions were put together into pipeline to support the neurosurgeon in the interpretation of the 3D iUS image data during brain tumor operation. The limitations of the approach is discussed. Then, future works are presented.

##### 4.1. Limitation

The first limitation of the enhancement of the brain tumor contours is the semi-automatic segmentation of the tumor model in the

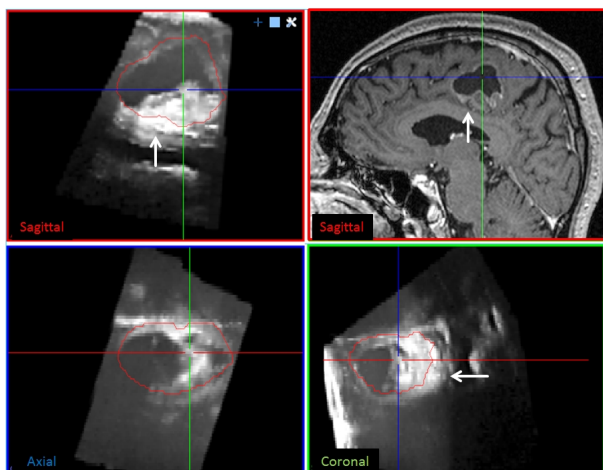
**Table 1:** Evaluation of the rigid registration functions on 3D-iBmode data of patients with metastasis and glioblastomas.

Patient	DSI (%)	MCD (mm)	Comp. time (s)
<b>Metastasis</b>			
1	88.6	0.8	132
2	74.2	2.7	127
3	75.9	2.0	148
4	84.2	1.0	185
5	81.3	1.7	124
6	85.3	1.3	253
7	88.9	0.9	344
8	81.3	2.7	626
9	85.3	1.6	363
10	74.1	1.9	97
11	88.9	1.1	158
<b>Mean values</b>	<b><math>82.5 \pm 5.7</math></b>	<b><math>1.6 \pm 0.7</math></b>	<b><math>232 \pm 158</math></b>
<b>Glioblastomas</b>			
12	74.5	2.3	191
13	76.0	1.4	337
14	76.6	2.1	188
15	71.2	1.9	267
<b>Mean values</b>	<b><math>74.6 \pm 2.4</math></b>	<b><math>1.9 \pm 0.4</math></b>	<b><math>246 \pm 71</math></b>

**Table 2:** Evaluation of the rigid registration functions on 3D-iCEUS data of patients with metastasis and glioblastomas.

Patient	DSI (%)	MCD (mm)	Comp. time (s)
<b>Metastasis</b>			
1	89.0	0.8	137
2	82.0	1.7	112
3	68.3	3.0	150
4	82.7	1.1	170
5	85.7	1.3	136
6	79.3	1.8	84
7	86.5	1.2	326
8	84.2	2.1	624
9	82.4	2.1	428
10	73.1	2.1	91
11	89.8	1.0	160
<b>Mean values</b>	<b><math>82.1 \pm 6.5</math></b>	<b><math>1.7 \pm 0.7</math></b>	<b><math>219 \pm 170</math></b>
<b>Glioblastomas</b>			
12	85.8	1.3	174
13	81.9	1.9	258
14	21.1	9.0	228
15	59.7	6.3	232
<b>Mean values</b>	<b><math>62.1 \pm 29.7</math></b>	<b><math>4.6 \pm 3.7</math></b>	<b><math>223 \pm 35</math></b>





**Figure 9:** Contour of a glioblastoma model obtained by semi-automatic segmentation in the preoperative MR data, and registered with the corresponding 3D intraoperative B-mode ultrasound data. In this case, the obtained contour seems to underestimate the brain tumor in the iUS data (arrows).

preoperative MR data. Since a translation was so far used in the rigid registration, the shape of the obtained tumor model has a direct impact on the final tumor contour in the iUS data. The boundaries of brain metastases and glioblastomas are in general clearly represented using MR imaging if the acquisition is not impaired by artifacts. However, it would be interesting to quantitatively estimate the impact of inter-individual segmentation. The second limitation is the quality of the iUS data. In the operating room, the presence of air between the ultrasound transducer and the brain surface induces image artifacts. Also, the acquisition of the iCEUS data has to be performed within a limited time window of few seconds, when the contrast agent optimally enhanced the examined structures. Finally, the 3D reconstruction algorithm smooths intensities of the original 2D image and reduces the sharpness of structure edges.

Also, the evaluation approach presents some limitations. Firstly, manual annotations is in general tedious and can therefore lack of accuracy. Moreover, it can be very complex to estimate the position of tumor margins with little contrast or if the information is hidden by image artifacts. On the other hand, there is so far no alternative evaluation approach. Intraoperative fluorescence is recognized as standard method for glial tumor operations. However only tissue surface is revealed and this modality can hardly be directly compared with ultrasound imaging. Secondly, the evaluation was performed on a limited number of patient data sets (15 patients). A further evaluation on a larger set of patient data and online tests during tumor removal operations have to be performed.

#### 4.2. Future works

Functions in the pipeline has to be improved before testing them in the operating room. In particular, robustness, computing time and

user interaction are features which have to fit constraints imposed by an intraoperative use.

**REGISTRATION IMPROVEMENT.** Improvement of the registration approach includes the test of additional transformation and metric functions. First experiments showed that 3D rigid transformation does not completely model the complex brain deformations. On the other hand, elastic transformations offer too many degrees of freedom in the deformation of the 3D tumor model. This leads to large overestimation of the brain tumor. The process is moreover hard to control.

**COMPUTING TIME.** Running time of the algorithms has to match requirements of the workflow in the operating room. Delivery of results under a couple of minutes is still acceptable in general. Choice of the metric, transform function and optimization algorithm used in the registration influences largely the running time of the algorithms.

**USER INTERACTION.** User interaction should be limited intraoperatively. The surgeon is sterile and is not allowed to interact with the system using traditional techniques, like the computer mouse. However, interaction could significantly improve the robustness of algorithms. For example in our approaches, the user provides interactively the coarse center point of the tumor in the 3D iUS data for the segmentation of brain tumor. Therefore, the development of optimal interaction methods compatible with an intraoperative use is necessary.

**PRESENTATION AND VISUALIZATION OF ADDITIONAL EXTRACTED STRUCTURES.** Visualization of extracted anatomical structures is a crucial issue for suitable interpretation of the image data by surgeons. The visualization of the tumor contour within the navigation system was presented. However, further developments are still needed. The extraction of additional brain structures (the skull), risk structures (ventricles, blood vessels), pathological tissue (tumor residuals) in the iUS data and the adequate visualization of such patient model in the navigation system should further support the neurosurgeon in the interpretation of the iUS data.

#### 5. Conclusion

The goal of this work is to provide neurosurgeons with tools to support the interpretation of iUS image data acquired during brain tumor operations. For that, a pipeline including existing segmentation, registration and visualization functions was developed to enhance brain tumor margins at the beginning of the operation. The offline evaluation showed promising results. Next steps are the improvement of the functions in the pipeline for an intraoperative use, the integration of the pipeline with further functionalities, the development of a direct connection with the navigation system, and the evaluation of the system during brain tumor operations.

#### Acknowledgments

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## References

- [ACM\*16] Arlt F, Chalopin C, MÃijns A, Meixensberger J, Lindner D. Intraoperative 3D contrast-enhanced ultrasound (CEUS): A prospective study of 50 patients with brain tumours. *Acta Neurochir* 2016; 158:685-694.
- [AMC\*01] Arbel T, Morandi X, Comeau RM, Collins DL. Automatic non-linear MRI-ultrasound registration for the correction of intra-operative brain deformations. In Niessen WJ and Viergever MA Eds, 4th International conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2001; 913-921.
- [BCN16] Bal J, Camp SJ, Nandi D. The use of ultrasound in intracranial tumor surgery. *Acta neurochir* 2016; 158(6):1179-1185.
- [CDA16] Cordier N, Delingette H, Ayache N. A patch-based approach for the segmentation of pathologies: Application to glioma labelling. *IEEE Transactions on Medical Imaging* 2016; 35(4):1066-1076.
- [CHM\*12] Coupe P, Hellier P, Morandi X, Barillot C. 3D rigid registration of intraoperative ultrasound and preoperative MR brain images based on hyperechogenic structures. *Int J Biomed Imag* 2012; 14 pages.
- [CLA\*12] Chalopin C, Lindenberg R, Arlt F, MÃijns A, Meixensberger J, Lindner D. Brain tumor enhancement revealed by 3D intraoperative ultrasound imaging in a navigation system. *Biomed Tech* 2012; 57(S1): 468-471.
- [CSF\*00] Comeau RM, Sadikot AF, Fenster A, Peters TM. Intraoperative ultrasound for guidance and tissue shift correction in image-guided neurosurgery. *Med Phys* 2000; 27(4):787-800.
- [FNM\*01] Ferrant M, Nabavi A, Macq B, Jolesz FA, Kikinis R, Warfield SK. Registration of 3D intraoperative MR images of the brain using a finite element biomechanical model. *IEEE trans med imaging* 2001;20:1384-1397.
- [FWM\*14] Fuerst B, Wein W, MÃijller M, Navab N. Automatic Ultrasound-MRI Registration for Neurosurgery using the 2D and 3D LC2 Metric. *Med Image Anal* 2014; 18(8):1312-9.
- [HDW\*17] Havaei M, Davy A, Warde-Farley D, Biard A, Courville A, Bengio Y, Pal C, Jodoin PM, Larochelle H. Brain tumor segmentation with deep neural networks. *Med Image Anal* 2017; 35: 18-31.
- [HBB\*05] Hawkes DJ, Baratt D, Blackall JM, et al. Tissue deformation and shape models in image-guided interventions: a discussion paper. *Med Image Anal* 2005; 9:163-175.
- [HJW\*08] He W, Jiang XQ, Wang S, Zhang MZ, Zhao JZ, Zhao Liu H, Ma J, Xiang DY, Wang LS. Intraoperative contrast-enhanced ultrasound for brain tumors. *Clin Imaging* 2000; 32:419-424.
- [ICA\*16] Ilunga-Mbuyamba E, Cruz-Duarte JM, Avina-Cervantes JG, Correa-Cely CR, Lindner D, Chalopin C. Active contours driven by cuckoo search strategy for brain tumour images segmentation. *Expert Systems with Applications* 2016; 56:59-68.
- [ILA\*17] Ilunga-Mbuyamba E, Lindner D, Avina-Cervantes JG, Arlt F, Rosto-Gonzales H, Cruz-Aceves I, Chalopin C. Fusion of intraoperative 3D B-mode and contrast enhanced ultrasound data for automatic identification of residual brain tumors. *Appl Sci* 2017; 7, 415, 17 pages.
- [JHR\*08] Ji S, Wu Z, Hartov A, Roberts DW, Paulsen KD. Mutual-information-based image to patient re-registration using intraoperative ultrasound in image-guided neurosurgery. *Med Phys* 2008; 35(10): 4612-4624.
- [KZD\*15] Kanas VG, Zacharaki EI, Davatzikos C, Sgarbas KN, Megalooikonomou V. A low cost approach for brain tumor segmentation based on intensity modeling and 3d random walker. *Biomedical Signal Processing and Control* 2015; 22:19-30.
- [MD12] Murali S, Dinesh MS. Classification of mass in breast ultrasound images using image processing techniques. *Int J of Computer Applications* 2012; 42(10): 29-36.
- [Nav05] Navestad GM. Segmentation of neuro tumours from MR and ultrasound data, Master Thesis, Norwegian University of Science and Technology (NTNU), 2005.
- [PBF\*16] Prada F, Bene MD, Fornaro R, Vetrano IG, Martegani A, Aiani L, Sconfienza LM, Mauri G, Solbiati L, Pollo B, et al. Identification of residual tumor with intraoperative contrast-enhanced ultrasound during glioblastoma resection. *Neurosurg Focus* 2016; 40, E7.
- [PPD13] Pradeep Kumar BP, Prathap C, Dharshith CN. An automatic approach for segmentation of ultrasound liver images. *Int J Emerging Technology and Advanced Engineering* 2013, 3(1): 337-340.
- [PPM\*14] Prada F, Perin A, Martegani A, Aiani L, Solbiati L, Lamperti M, Casali C, Legnani F, Mattei L, Saladino A, et al. Intraoperative contrast-enhanced ultrasound for brain tumor surgery. *Neurosurgery* 2014; 74:542-552.
- [PSM\*16] Prada F, Solbiati L, Martegani A, DiMeco F (eds) (2016) *Intraoperative ultrasound (IOUS) in neurosurgery. From standard B-mode to elastosonography*. Springer, Cham.
- [RHK\*98] Roberts DW, Hartov A, Kennedy FE, Miga MI, Paulsen KD. Intraoperative brain shift deformation: a quantitative analysis of cortical displacement in 28 cases. *Neurosurgery* 1998; 43(4): 749-758.
- [RLU\*07] Reinertsen I, Lindseth F, Unsgaard G, Collins DL. Clinical validation of vessel-based registration for correction of brain shift. *Medical Image Analysis* 2007; 11: 673-684
- [RPW15] Ritschel, K.; Pechlivanis, I.; Winter, S. Brain tumor classification on intraoperative contrast-enhanced ultrasound. *Int. J. Comput. Assist. Radiol. Surg.* 2015; 10:531-540.
- [SBP\*16] Sastry R, Bi WL, Pieper S, Frisken S, Kapur T, Wells W, Golby AJ (2016) *Applications of Ultrasound in the Resection of Brain Tumors*. *Journal of neuroimaging : official journal of the American Society of Neuroimaging*.



[TML\*02] Trantakis C, Meixensberger J, Lindner D, Strauss G, Grunst G, Schmidtgen A, Arnold S. Iterative neuronavigation using 3D ultrasound. A feasibility study. *Neurol Res* 2002; 24:666-670.

[URS\*06] Unsgaard G, Rygh OM, Selbekk T, MÅijller TB, Kolstad F, Lindseth F, Hernes TA. Intra-operative 3D ultrasound in neurosurgery. *Acta Neurochir* 2006; 148(3):235-253.

[USB\*05] Unsgaard G, Selbekk T, Brostrup Mueller T, Ommedal S, Torp SH, Myhr G, Bang J, Nagelhus Hernes TA. Ability of navigated 3D ultrasound to delineate gliomas and metastases comparison of image interpretations with histopathology. *Acta Neurochir* 2005; 147:1259-1269.

[VRS\*16] Vishnuvarthanan G, Rajasekaran MP, Subbaraj P, Vishnuvarthanan A. An unsupervised learning method with a clustering approach for tumor identification and tissue segmentation in magnetic resonance brain images. *Applied Soft Computing* 2016; 38: 190-212.