Validation platform for ultrasound-based monitoring of thermal ablation

Alexandra M. Pompeu-Robinson, James Gray, Joshua Marble, Hamed Peikari, Jena Hall, Paweena U-Thainual, Mohammad Aboofazeli, Andras Lasso, and Gabor Fichtinger

School of Computing, Queen's University at Kingston, Canada

ABSTRACT

PURPOSE: A ground-truth validation platform was developed to provide spatial correlation between ultrasound (US), temperature measurements and histopathology images to validate US based thermal ablation monitoring methods. METHOD: The test-bed apparatus consists of a container box with integrated fiducial lines. Tissue samples are suspended within the box using agar gel as the fixation medium. Following US imaging, the gel block is sliced and pathology images are acquired. Interactive software segments the fiducials as well as structures of interest in the pathology and US images. The software reconstructs the regions in 3D space and performs analysis and comparison of the features identified from both imaging modalities. RESULTS: The apparatus and software were constructed to meet technical requirements. Tissue samples were contoured, reconstructed and registered in the common coordinate system of fiducials. There was agreement between the sample shapes, but systematic shift of several millimeters was found between histopathology and US. This indicates that during pathology slicing shear forces tend to dislocate the fiducial lines. Softer fiducial lines and harder gel material can eliminate this problem. CONCLUSION: Viability of concept was presented. Despite our straightforward approach, further experimental work is required to optimize all materials and customize software.

Keywords: ultrasound, US, pathology, histopathology, validation platform, registration, thermal ablation

1. PURPOSE

Thermal ablation is a popular method in focal management of soft tissue cancer, such as metastatic liver and kidney cancer. Typically, ultrasound (US) is used to guide the placement of the slender needle-like ablator device, but US does not allow the physician to monitor the progress of ablation. Variations in blood flow and energy absorption rates between tissue make it extremely challenging to predict thermal changes. Insufficient ablation may lead to recurrence of the cancer while excessive ablation may cause serious side effects by damaging healthy tissues. A variety of methods have been proposed for US-based monitoring, such as elastography[1] and backscattered energy predictors.[2] In testing the applicability of US-based monitoring methods, the first step is ex-vivo validation based on spatial correlation between ultrasound, temperature measurements, histopathology images, and auxiliary imaging such as CT or MRI. In this paper, we present the proof of concept prototype of a validation platform that provides these functions.

2. METHODS

2.1 Layout and workflow

On the whole, the task is to compare representation of the ablated zone in pathology and US. The zone of ablation is well visible in the pathology images and it is also discerned by the US-based monitoring method (elastography, RF time series analysis, *etc.*) validated.

The ground-truth platform features a container box with integrated z-frame fiducial lines (Figure 1). The box contains an agar-based gel used to fixate the tissue sample, typically chicken breast or calf liver, as well as

Further author information: (Send correspondence to G. Fichtinger)
A.M.Pompeu-Robinson: E-mail: robinson@cs.queensu.ca
H. Peikari: E-mail:hamed.peikari@gmail.com
G. Fichtinger: E-mail: gabor@cs.queensu.ca, Telephone: 1 613 533 6050

Medical Imaging 2010: Visualization, Image-Guided Procedures, and Modeling, edited by Kenneth H. Wong, Michael I. Miga, Proc. of SPIE Vol. 7625, 76250T · © 2010 SPIE · CCC code: 1605-7422/10/$18 · doi: 10.1117/12.844053

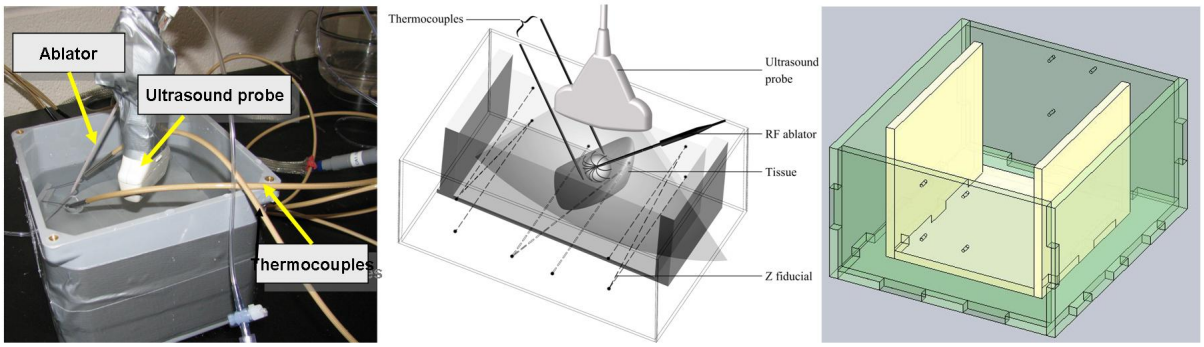

Figure 1. Experimental setup for US B-mode and RF data acquisition during ablation of a tissue sample. Actual picture of a preliminary experiment (left) and the schematic diagram of the apparatus (right).

the fiducials. Thermocouples are inserted near the targeted tissue to measure actual temperature and estimate thermal dose. In our experiments, the tissue was treated with an interstitial ultrasound ablator (Acoustic MedSystems, Champaign, IL, USA) under B-mode and RF ultrasound imaging with a linear probe (Ultrasonix RP, Vancouver, Canada). Acquisitions from the US-imaging contain both the tissue and fiducial lines for further analysis.

Following US-monitored ablation, the gel block is sliced with a pathology trimming blade (Fisher Scientific Co., Ottawa, Canada) for pathology examination. Slicing of the gel block is performed perpendicular to the straight fiducial lines in a parallel fashion. Each slice is photographed with a digital camera in an orthogonal view and with a metric ruler in the picture. The fiducials are made to be visible in both the US and pathology slices, thus allowing for spatial registration. Interactive software localizes fiducials and anatomical features in the pathology and US images. The cross sections of fiducial lines are segmented in both the B-mode US and the histopathology images. The zone of ablation is well visible in the pathology images and it is also discerned with the given US-based monitoring method (elastography, RF time series analysis, *etc.*). Using the known geometry of the Z-shape fiducial structure in both modalities, the contours are reconstructed in the fiducial coordinate system by using stereotactic reconstruction according to Brown *et al.*[3] The software then reconstructs the two regions in 3D space and performs an analysis and comparison between the two.

2.2 Stereotactic fiducials

The fiducials lines are attached through holes in the acrylic box, creating three Z-shape motifs, similarly to a Leksell Gamma Knife stereotactic head-frame (Elekta AB, Stockholm, Sweden, www.elekta.com). In our design, the dimensions of the two vertical Z-motifs are of 120x40mm, while the horizontal one is of 120x30mm. The horizontal lines are slanted at a 45-degree angle to maximize accuracy and sensitivity according to Susil *et al.*[4] In the embodiment shown in Figure 2, the Z-motifs are all separated, while the holes on the encasing in Figure 1, right, indicate a variant in which the Z-motifs share a straight line. The fiducial lines are made to be visible in B-mode US imaging (Figure 2, right) without creating shadows and artifacts. The cross sections of fiducial lines are also visible in the histopathology images (Figure 2, left). Ideally, the fiducials must remain motionless both during construction and during slicing of the gel block. The experiment has processed a variety of materials for this purpose. The material originally found to best meet these requirements is 25lb black ice-fishing line. The lines must be sufficiently soft so that the blade can cut them without creating shear force in the gel block and they must also resist deformation while the hot gel is poured into the container box.

2.3 Tissue stabilization medium

The tissue stabilization gel is made by combining 80 parts water, 2 parts agar and 4 parts gelatin in order to properly fixate the fiducials and tissue. The water is brought to 75°C, adding agar and then gelatin slowly to avoid bubble formation. Half of the gel is then cooled to 45°C and poured into the box to form a bottom layer to support the tissue. Once the gel has set enough to support some weight, an approximately $4cm^3$ section of tissue

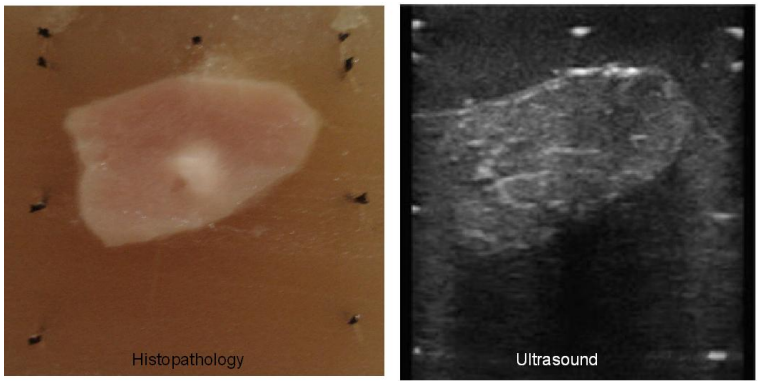

Figure 2. Histopathology image (left) and ultrasound image (right) of ablated tissue centered in the image and nine fiducial markers surrounding the image.

is placed on top. Finally, the second gel layer is added at 50°C to ensure minimal delineation between the two layers is visible in B-mode imaging. The entire apparatus is left to cool and harden overnight in a refrigerator.

2.4 Encasing

The gel, fiducials and tissue are housed in a 180x162x96mm container box. The latest prototype in Figure 1, right was machined from acrylic with water jet. The box consists of an outer, open-top box and a three-sided U-shape inner member, of 120x112x96mm. The outer box contains holes for the fiducial lines and contains the gel. The gel is poured into the box and let set gradually, typically for at least 24 hours. The U-shape inner member provides a "guide plane" for the slicing blade as the gel block housing the tissue is pushed from the distal end. With lay analogy, the process is similar to serving sliced ham from a tin can. The exact dimension of the box must be such that it conveniently holds the inner member inside which the fiducial lines are stretched. The dimensions of the inner member must be such that it encloses the tissue sample and US lines while fitting inside the field of view of the US image, which in turn depends on the probe and scanner used.

2.5 Software

The histopathology images are fed to a program, currently MATLAB with text file input. Work into porting the program into 3D Slicer has begun for better visualization possibilities. The fiducials and anatomical structures are segmented and transformed into fiducial coordinate space[3] , as shown in Figure 3, left. The fiducials are also segmented in the US images and the contours of the ablated region are imported from the ablation monitoring method tested. Surface reconstruction for the tissue samples are performed using Delaunay triangulation. The contour points serve as the cloud points from with a Crust algorithm then extracts the surface triangulation (Figure 3, center). The program visualizes the registered contours in 3D (Figure 3, right and center) and performs a comparison between the two 3D shapes (Figure 3, right).

3. RESULTS AND DISCUSSION

The critical element of this validation platform is to achieve minimum registration error between the ultrasound and pathology slices in the field of interest. This is called 'target registration error', based on the convention established by Fitzpatrick.[5] There are four sources of target registration error: (1) Dislocation of fiducial lines during pouring the gel, an effect which is mitigated by using tightly stretched lines and low-temperature pouring, performed in several steps and layers. (2) Dislocation of fiducial lines during slicing of the gel block, an effect which is mitigated by using soft fiducial lines, sharp blades, and a blade guide. (3) Fiducial segmentation in the US images, an effect well-studied in the literature.[6] (4) Fiducial segmentation error in the pathology images, a relatively straightforward task - although cross sections of slanted fiducial lines may sometimes appear to be "smudged" due to the dislocation during slicing (Figure 2, left).

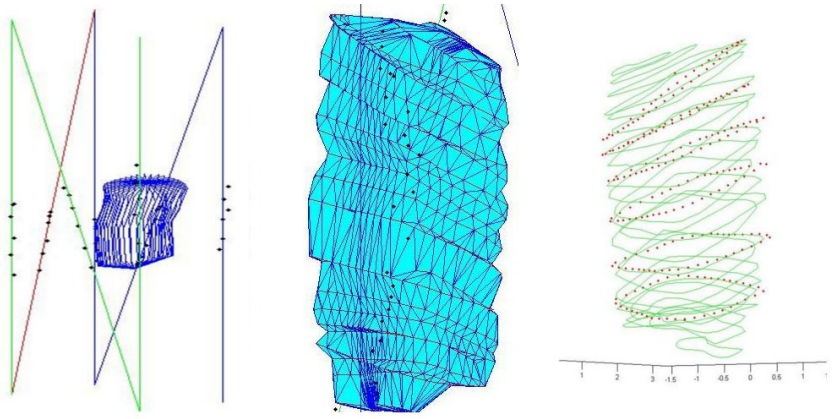

Figure 3. Reconstructed 3D wire mesh of a tissue sample from pathology with reconstructed fiducial points (left). Reconstructed 3D tissue surface using Delaunay triangulation of cloud points(center). Co-registered contours from US and pathology (right).

Table 1. Quantifying Correspondence of Pathology and Ultrasound Reconstructed Volumes

Percentage overlap between US and pathology	88.53
Dice Similarity Coefficient [0-1](cm)	.911605
Hausdorff distance(cm)	.189737

In the accuracy assessment test, a chicken breast was suspended in gel and contoured in both B-mode US and pathology. In the case of accurate system performance, the two reconstructed shapes must perfectly overlap. A systematic translation between the shapes was observed. Figure 3, left, suggests that the Z-motifs do not deform significantly during pathology slicing. Still, a systematic shift between the US and pathology shapes was observed, as seen in Figure 4, left. The voxel overlap, dice similarity coefficient(DSC), and Hausdorff distance (HD) metrics were employed to quantify correlation between the reconstructed pathology and US samples. The number of non-zero voxels for each volume was retrieved and then overlap was determined between pathology and US as seen in Table 1. Using voxel overlap provides a quick view of volumetric overlap between the different imaging modalities. Further quantification techniques were utilized to determine with greater certainty the amount of correspondence between pathology and US images. Hausdorff distance provides a measure of contour alignment between structures by providing the maximum distance between a set of points and the nearest point in another set. A low HD result corresponds to strong contour alignments. The DSC is a measure of volumetric overlap returning results within a range of zero to one, with one indicating perfect alignment.

The number of non-zero voxels served as one indicator of volume for each of the samples. The pathology volume registered a 85.93 percent overlapping voxel region. The lower percentage overlap can be caused by inherent issue with pathology volume acquisition techniques and/or shifted a pathology volume caused during the slicing step. Limitations of slice thickness when performing the histopathology on the sample translates into less overall volume data thus possibly reducing the final volume reconstruction. A systematic shift in the pathology sample could also create the low percentage overlap. The origin of both problematic areas stem from the currently employed slicing procedure. Improving pathology slicing and imaging methods will be discussed later in the paper. The low reported HD value denotes high contour alignment accuracy with less than a .2cm calculated distance. The high DSC value supports good volumetric correspondence between pathology and US. Reducing the Hausdorff distance as well as increasing DSC would require increased accuracy in the histopathology procedure.

Rigid Iterative Closest Point (ICP) registration[7] was performed on the shapes, in order to determine the extent and nature of mis-registration. ICP minimizes the difference between two point clouds through iterative transformation revisions, thus moving one cloud set to match the other with minimum error. Two different ICP registration methods were implemented. One ICP method considered scaling when performing the trans-

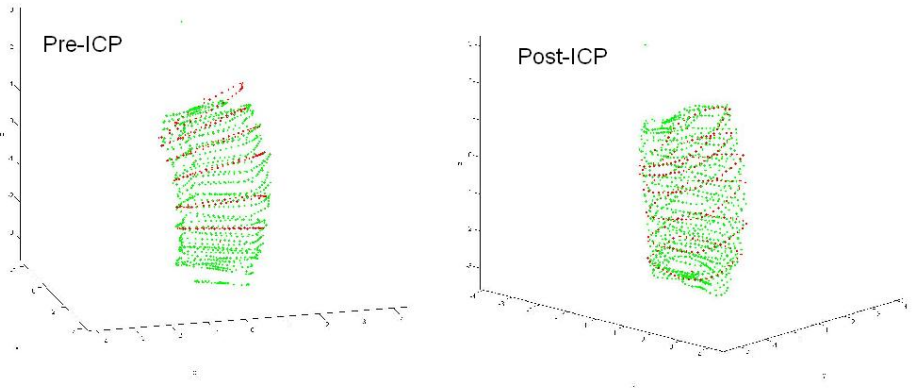

Figure 4. Superposition of the two contours in fiducial coordinate system before correction (left) and after ICP was used to remove rigid misregistration error (right).

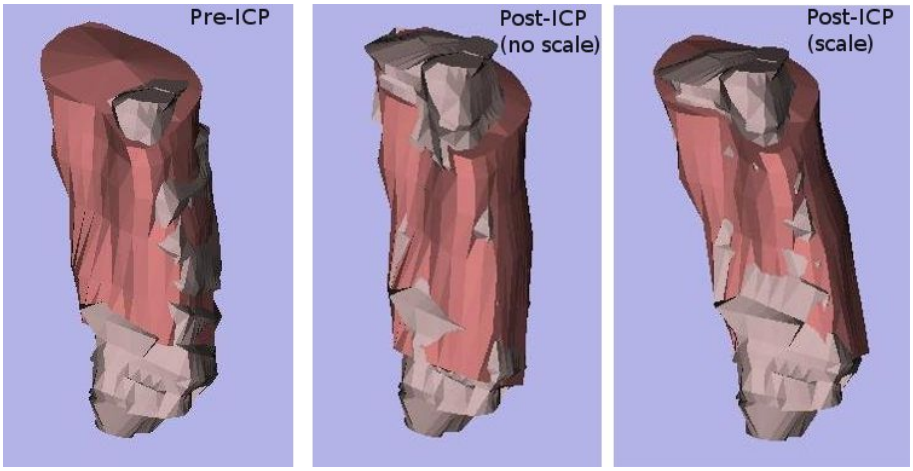

Figure 5. Superposition of the two surface rendering in fiducial coordinate system before correction (left) and after ICP was used to remove rigid mis-registration error (right).

formation, while the other ICP ignored scaling as a factor. Although the ICP-incorporated scale was visually more appealing, no significant improvement was recorded. Low residual error after ICP indicated an excellent agreement between the contours, demonstrated in Figure 4, right and Figure 5, right.

To counteract fiducial dislocation, softer fiducial material is required which can be cut without shear force and dislocation while maintaining good ultrasound visibility. In addition, the fixating agar gel should be hardened, while still maintaining acoustic visibility. Increasing image acquisition accuracy for pathology would also mitigate the possible dislocation error inherent in a camera/tripod set-up.

We contemplated dying the lines in order to enhance fiducial visibility in the pathology image. We foresee several possible solutions for dye placement: saturating the lines with dry dye, pulling the dye-saturated thread through the marker tracts post ultrasound imaging, or using plastic needles as ultrasound markers and then injecting dye into the needle tracts while slowly extracting the needles. Later still, a 3D Slicer and ITK based visualization and image processing software should replace the current MATLAB-based proof of concept software.

Preliminary studies into collecting better pathology images have shown promise. The basic set-up includes the use of a high quality scanner on which the gel is placed, thus removing possible non-planar image acquisitions with the camera. Issues with the scanner use include: poor contrast color due to excess light, slight glare due to

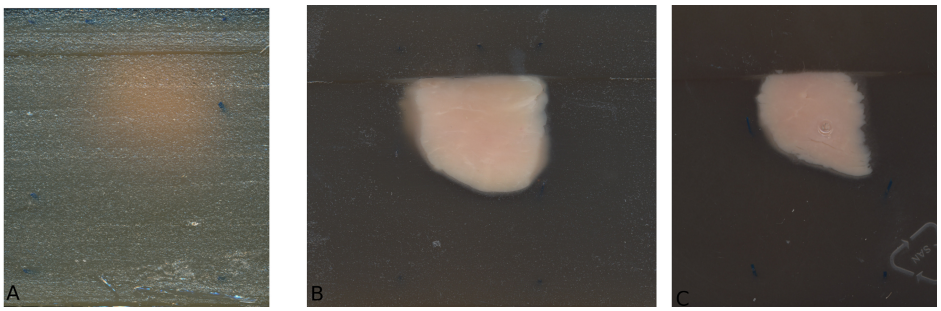

Figure 6. a.Gel block initial scan b.Gel block scan produced with block on top of cellophane c.Gel block scan produced when submerged in plastic container with 2-3mm of water.

the nature of a gel surface, and keeping the scanner bed clean between images (Figure 6a). The use of cellophane and transparency sheets have been contemplated to reduce clean up of the scanner bed, however, their use caused air bubble formation between mediums, which proved difficult to remove (Figure 6b). To remove excess light from entering the scanner bed, thinner slices were discussed, as well as covering the equipment with a box in order to remove interfering light. Submerging the gel block in a clear water-filled construct was also tested as a means of glare reduction and retaining a clean working surface. Scanned images returned from a plastic dish containing 2-3mm of water and the gel block were clear, free from air bubbles, and had reduced glare (Figure 6c). A large standard petri dish has been acquired and further testing with this methodology will proceed.

Implementing different fiducial materials was discussed to reduce "smugding" of fiducial lines during the slicing process. In determining a viable material, key components include maintainability of structural integrity during the gel pour step and ease of slicing during histopathology. Recently, the use of wax-coated dental floss has been executed, and preliminary results show it to be an effective fiducial. The use of Oral-B Indicator floss (blue wax coating) returned good quality images in ultrasound with strong contrast fiducials and negligible shadowing. During image acquisition, however, the floss color did not return a strong enough contrast to be easily discernible from the agar gel, as seen in Figure 6c. Research will continue on the use of wax-coated flosses due to early, strong results. Fiducial contrast can be increase in one of two ways: dying the agar gel during production or using a differently colored wax-coated dental floss.

In summary, we have constructed a proof of concept apparatus with preliminary registration and measurement software. A current outstanding issue is the residual mis-registration due to dislocation of the fiducial lines during pathology slicing, an issue which we plan to mitigate by softening the fiducial lines and hardening the gel. In all, we are approaching a practical solution for registration of US imaging and pathology sections in ex-vivo tissue experiments. While the primary context is thermal ablation, the platform can be more widely applicable, especially if combined with other imaging modalities (*e.g.,* CT and MRI)

4. CONTRIBUTION

The apparent straightforwardness of our approach must not belie the investment of effort needed to make a practical, accurate and robust experimental validation tool. Our contribution is the design and description of materials the prototype apparatus, which represents valuable know-how that one can acquire only through numerous cycles of trials and failures.

5. ACKNOWLEDGEMENTS

We thank Xiao Xiao Ma for the illustration in Figure 1.b, Victor Grzeda (Queen's University) and Everette C. Burdette, PhD (Acoustic MedSystems) for assistance with ultrasound ablation.

REFERENCES

[1] Rivaz, H., Fleming, I., Assumpcao, L., Fichtinger, G., Hamper, U., Choti, M., Hager, G., and Boctor, E., "Ablation monitoring with elastography: 2d in-vivo and 3d ex-vivo studies.," *Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv* **11**(Pt 2), 458–466 (2008).

[2] Arthur, R. M., Straube, W. L., Trobaugh, J. W., and Moros, E. G., "Non-invasive estimation of hyperthermia temperatures with ultrasound," *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group* **21**(6), 589–600 (2005).

[3] Brown, R. A., Roberts, T. S., and Osborn, A. G., "Stereotaxic frame and computer software for ct-directed neurosurgical localization.," *Invest Radiol* **15**(4), 308–312 (1980).

[4] Susil, R., Anderson, J., and Taylor, R., "A single image registration method for ct guided.," *Medical Image Computing and Computer-Assisted Intervention MICCAI99, Lecture Notes in Computer Science* **1679**(Pt 2), 798–808 (1999).

[5] Fitzpatrick, J. M., West, J. B., and Maurer, C. R., "Predicting error in rigid-body point-based registration.," *IEEE Trans Med Imaging* **17**, 694–702 (Oct 1998).

[6] Chen, T. K., Thurston, A. D., Ellis, R. E., and Abolmaesumi, P., "A real-time freehand ultrasound calibration system with automatic accuracy feedback and control.," *Ultrasound Med Biol* **35**, 79–93 (Jan 2009).

[7] Besl, P. J. and McKay, H. D., "A method for registration of 3-d shapes," *IEEE J PAMI* **14**, 239–256 (Feb. 1992).