Improved validation platform for ultrasound-based monitoring of thermal ablation

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ABSTRACT

PURPOSE: Thermal ablation is a popular method in local cancer management; however it is extremely challenging to predict thermal changes in *vivo*. Ultrasound could be a convenient and inexpensive imaging modality for real-time monitoring of the ablation, but the required advanced image processing algorithms need extensive validation. Our goal is to design and develop a reliable test-bed for validation of these monitoring algorithms. METHOD: We previously developed a test-bed, consisting of ablated tissue sample and fiducial lines embedded in tissue-mimicking gel.[1] The gel block is imaged by ultrasound and sliced to acquire pathology images. Following fiducial localization in both image modalities, the pathology and US data were registered. Ground truth ablated region is retrieved from pathology images and compared to the result of the ultrasound-based processing in 3D space. We improved on this platform to resolve limitations that hindered its usage in a larger-scale validation study. A simulator for evaluating and optimizing different line fiducial structures was implemented, and a new fiducial line structure was proposed. RESULTS: The new proposed fiducial configuration outperforms the previous in terms of accuracy, fiducial visibility, and use of larger tissue samples. Simulation results show improvement in pose recovery accuracy using our proposed fiducial structure, reducing target registration error (TRE) by 34%. Inaccurate pixel spacing information and fiducial localization noise are the main sources of error in slice pose recovery. CONCLUSION: A new generation of test-bed was developed, with software that does not require lengthy manual data processing, and is easier to maintain and extend. Further experimental work is required to optimize phantom preparation and precise pixel spacing computation.

Keywords: ultrasound, pathology, tumor ablation, validation platform, registration, line fiducial pattern, pose recovery

1. PURPOSE

According to the U.S. National Cancer Institute, approximately 41 percent of Americans will be diagnosed with cancer during their lifetime and about 21 percent will die from cancer.[2] The annual cost of cancer treatment has increased from $41 billion in 1995 to $72 billion in 2004, and it continues to increase.[3] This trend has created a great economic burden. Therefore, further research is required to develop methods that enable physicians to treat cancer more effectively. Computer-assisted thermal ablation is considered to be the principal therapy for some focal malignancies. Advantages of ablative therapies compared with surgical resection include the reduction in morbidity and mortality, lower cost, suitability for real-time image guidance, and the ability to perform ablative procedures on outpatients. Such therapies use imaging techniques and computational methods to assist the surgeon in performing tasks where direct vision is impractical. The aim of computer-assisted thermal ablation therapy is to obliterate the entire tumor by heating it to a temperature between 60 ° and 100 °C in a minimally invasive fashion without damaging adjacent vital structures. Typically, ultrasound (US) is used to guide the placement of the needle-like ablator device to the correct location. However, standard US imaging protocols do not allow the physician to monitor the progress of ablation. Ablation efficacy is affected by temperature. It is crucial to monitor the ablation process as the 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 ablation monitoring, such as elastography[4] and backscattered energy predictors,[5] but they are all still in development phase. These methods are not used in clinical set up yet, mainly because

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of variations in blood flow, energy absorption rates between tissues as well as differences in radio frequency (RF) power delivery and its duration making it extremely challenging to predict thermal changes. For the development and optimization of these methods, it is essential to have a reliable and quantitative validation technique before beginning clinical trials on humans. There are some prototypes that try to solve this problem, however, they have several limitations. The goal of our work is to design and develop a test-bed for validation of various ultrasound-based ablation monitoring methods. We have focused on delivering a robust, practically usable system, by utilizing as much available established knowledge and method as possible.

Our research group previously developed a proof of concept test-bed (Pompeu-Robinson *et al.*[1]), which retrieves ground truth ablation information from pathology slices and provides quantitative comparison by registering the pathology images to ultrasound images. However, this system has the following limitations that make it impractical for use in a full-scale validation study.

- The sample tissue size is limited due to the presence of fiducial lines, which are used for the image registration.
- The process of segmenting fiducials and tissue contours is manual
- The registration algorithm works well only if all the fiducials are completely visible. Quite often not all fiducial lines are visible and thus those US slices must be removed from the validation data set.
- Requires lengthy manual post-processing for each acquired data set.
- The software, implemented in Matlab, is complex, comprising of monolithic architecture and couples user interface with data processing, all which making further extension or customization difficult and time-consuming.

2. METHODS

2.1 The first generation of ablation validation test-bed

The first version of the validation test-bed, developed by Pompeu-Robinson *et al.*,[1] consisted of a phantom box with integrated fiducial lines (Fig. 1(a)), and (chicken) tissue sample suspended in the medium using agar-based gel. The tissue was treated with an interstitial ultrasound ablator under RF ultrasound imaging with a linear probe. Thermocouples were inserted near the targeted tissue in order to measure the actual temperature and estimate thermal dose at a few points in the tissue. For pathology examination the gel block was sliced with a pathology trimming blade, and each slice was scanned using a high quality flatbed scanner (Fig. 1(c)). Details of the phantom preparation and the imaging protocol are described in Pompeu-Robinson's[1] paper. The zone of ablation was clearly visible in the pathology images as shown in Fig. 1(d) (this served as the ground truth), and it was also discerned with the given US-based ablation monitoring method that was being validated (elastography, RF time series analysis, etc.).

Pathology to ultrasound images were registered by determining position and orientation of each image slice from the positions of the fiducial line intersections with the slice plane. For this purpose, fiducial points in slice plane were registered with fiducial lines in phantom box using Susil *et al.*[6] registration method. The intersection points were marked manually on all images. Ablated tissue was manually contoured on all images and using the computed slice poses (position and orientation) the tissue surfaces were reconstructed in three-dimension.

2.2 Fiducial line configuration

Ideally, the fiducials must remain motionless both during construction and during slicing of the gel block. The lines must resist deformation while the hot gel is poured into the container box and they must also be sufficiently soft so that the blade can cut them without creating shear force in the gel block while maintaining good ultrasound visibility at the same time. The materials found to best meet these requirements are 0.3mm fishing line and wax-coated dental floss.

The fiducial configuration of the first generation system (three Z-shaped fiducial lines) limited the maximum tissue size and the diagonal fiducial lines of the two vertical Z-motifs were not visible in many ultrasound

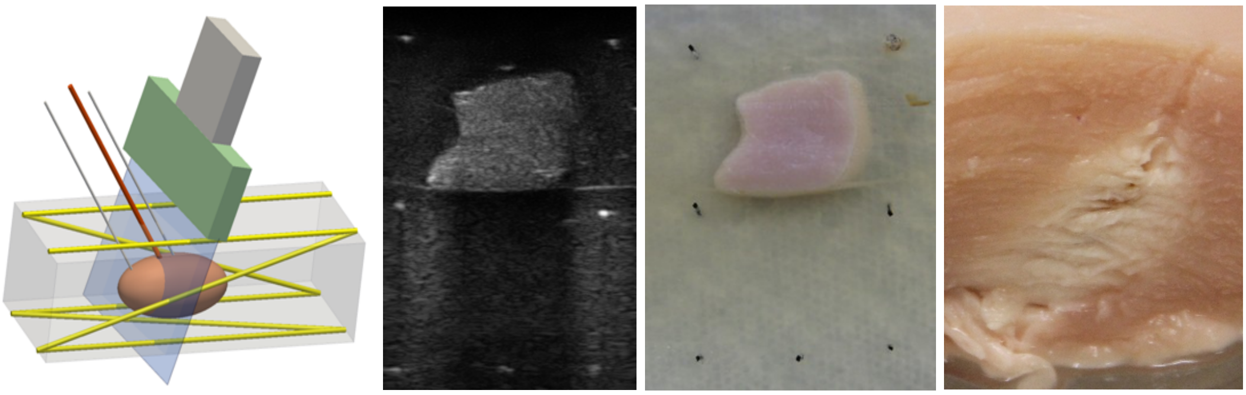

(a) (b) (c) (d)

Figure 1. (a) The first version of the validation test-bed experimental setup. (b) An ultrasound image slice with visible fiducial lines and sample tissue. Fishing line is used as fiducial lines. (c) A pathology image slice. (d) The ablated tissue zone is clearly visible in the pathology images.

images due to their angle with the US wave propagation direction. Therefore, several alternative fiducial line arrangements were evaluated, which do not have these problems, yet provide similar slice pose computation accuracy. The dimensions of the two vertical Z-motifs are of 137x40mm, while the horizontal one is of 137x30mm.

2.2.1 Slice pose recovery simulator

A slice pose recovery simulator was developed to evaluate several potential fiducial line configurations, without the need to actually build new phantoms and perform measurements. The simulator generates realistic sequence of slice poses, which mimics the motion of the freehand probe motion during US data acquisition. This is implemented by placing five control points equally spaced along a straight line segment, modifying their position with some random error, and interpolating it with a smooth Kochanek[7] interpolating spline. The simulator then computes the ground truth fiducial positions for each simulated slice pose. Fiducial detection error is introduced by randomly removing fiducials with a predefined probability. Positions of the detected fiducials are then computed from the slice pose and the fiducial line configuration. Fiducial localization error is simulated by adding a random value to the fiducial positions.

All the simulation parameters (variation in the slice position and orientation, fiducial detection probability, fiducial localization error, fiducial line configuration and number of slices) are estimated from measurements done on real image sequences, and specified in an xml file. The simulator computes the slice pose that can be recovered from the simulated fiducial locations, and determines a target reconstruction error (TRE) value. TRE is computed as the average difference between the ground truth and recovered position of the 3D position of ten typical target points. The target points are chosen to be in the center of the slice, at the perimeter of a 2cm diameter circle, which corresponds to a typical ablation region surface that has to be localized. Simulator results are discussed in section 3.2.

2.2.2 Evaluation of alternative fiducial configurations

Three alternative fiducial configurations were compared to the original fiducial structure (denoted by ZZZ). The ZZZ fiducial configuration consists of three connected Z-motifs, constructed by seven fiducial lines, as illustrated in Fig. 2(a).

To overcome the problems of limited tissue size and visibility in diagonal fiducial lines, the fiducial configuration can be changed by eliminating the slanted vertical fiducial lines. This new configuration is denoted by ZII (Fig. 2(b)). However, due to the symmetrical and parallel structure of the remaining five fiducial lines, the slice pose computation may lead to ambiguous results. Therefore line configuration was modified to make the top two fiducial lines slanted, instead of parallel (Fig. 2(d)). This way the total number of fiducial lines are kept unchanged, and all of them are about orthogonal to the ultrasound wave direction, thus they are well visible, and ambiguity is avoided. This configuration, with one V-shaped fiducial at the top and a Z-shaped fiducial at the bottom is denoted by ZV. In our design, the dimension of horizontal Z-motif and V-motif are of 137x30mm, while they are 40mm away from each other. The effect of fiducial configuration ambiguity is discussed in section 3.1.

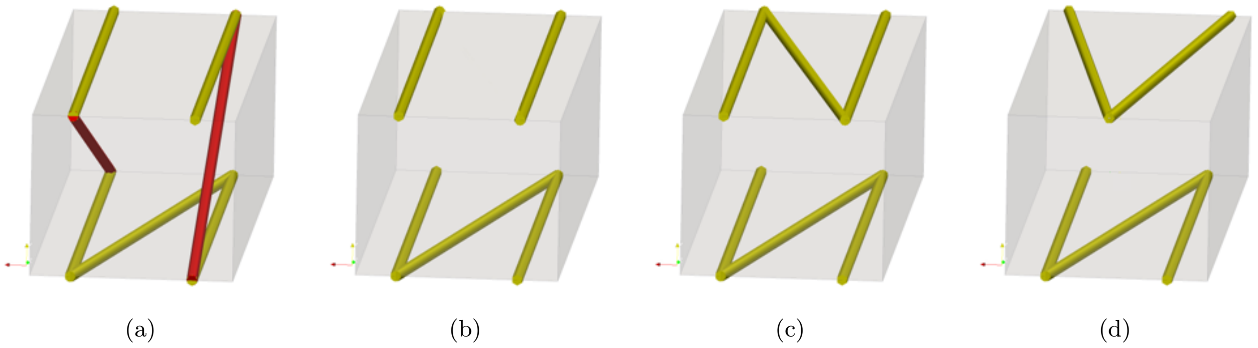

(a) (b) (c) (d)

Figure 2. (a) Current fiducial structure with seven fiducial lines in three connected Z-patterns (ZZZ). (b) The five horizontal line fiducial structure with a Z-shape at the bottom and a II-shape on the top (ZII). It is equivalent to the ZZZ configuration when the vertical diagonal fiducial lines are not visible in US images. (c) Chen's fiducial configuration with six fiducial lines in two horizontal Z-patterns (ZZ). (d) Our proposed asymmetric fiducial structure with five horizontal fiducial lines, a Z-shape at the bottom and a V-shape on the top (ZV).

Chen *et al.*[8] proposed a fiducial configuration with two parallel horizontal Z fiducials (one at the top and one at the bottom; denoted by ZZ), as shown in Fig. 2(c). This configuration increases the visibility of fiducial lines in ultrasound images. However, having one more fiducial line compared to ZV slightly increases the chance of deformation during pathology slicing, but expected to have smaller slice pose recovery error. Additionally, this configuration suffers from ambiguity and hence results are not reliable (Fig. 5(a)).

2.3 Slice position and orientation recovery

In order to accurately recover the pose of each slice it is of critical importance to achieve minimum fiducial localization error, and segment as many fiducial points as possible. There are four sources of fiducial localization error. These error sources and the corresponding techniques to mitigate them are well discussed in the literature.[1] The automatic segmentation method[9] used in our system has an average inaccuracy of 0.2mm standard deviation. Another source of pose recovery error is the pixel spacing information. Inaccurate spacing information causes ambiguity in slice pose recovery. This effect is discussed in section 3.1.

Popular fiducial line-based registration algorithms follow the method described by Brown.[10] We chose to integrate algorithm-4 (Minimization over position, orientation, and arc-lengths) developed by Lee *et al.*,[11] which is reported to be accurate, fast, robust to work with missing and inaccurately localized fiducials, and also usable for any arbitrary fiducial line configuration without algorithmic changes. This last property is particularly important for the slice pose recovery simulator, in order for testing various line configurations without software changes.

2.4 Software architecture and data flow

The proposed system was developed in C++ using open source software libraries and (ITK, VTK). The open source 3D slicer application was used for interactive data entry and visualization. New functions were implemented as ITK and VTK filters, which can be easily combined to create a complex data flow. The complete data flow is shown in Fig. 3, filters are represented by arrows. Standard file formats were used for storing all input, output, and intermediary data, which allowed easy import, export, and analysis in various software packages.

The software is capable of reading and manipulating B-mode and RF data files. The manual fiducial position detection in ultrasound images, which took most of the manual processing time in the first generation system, was replaced by an automatic algorithm, that requires no or minimal user interaction. This fiducial segmentation algorithm is presented in paper of Bartha *et al.*[9] Using the known geometry of fiducial structure, the position

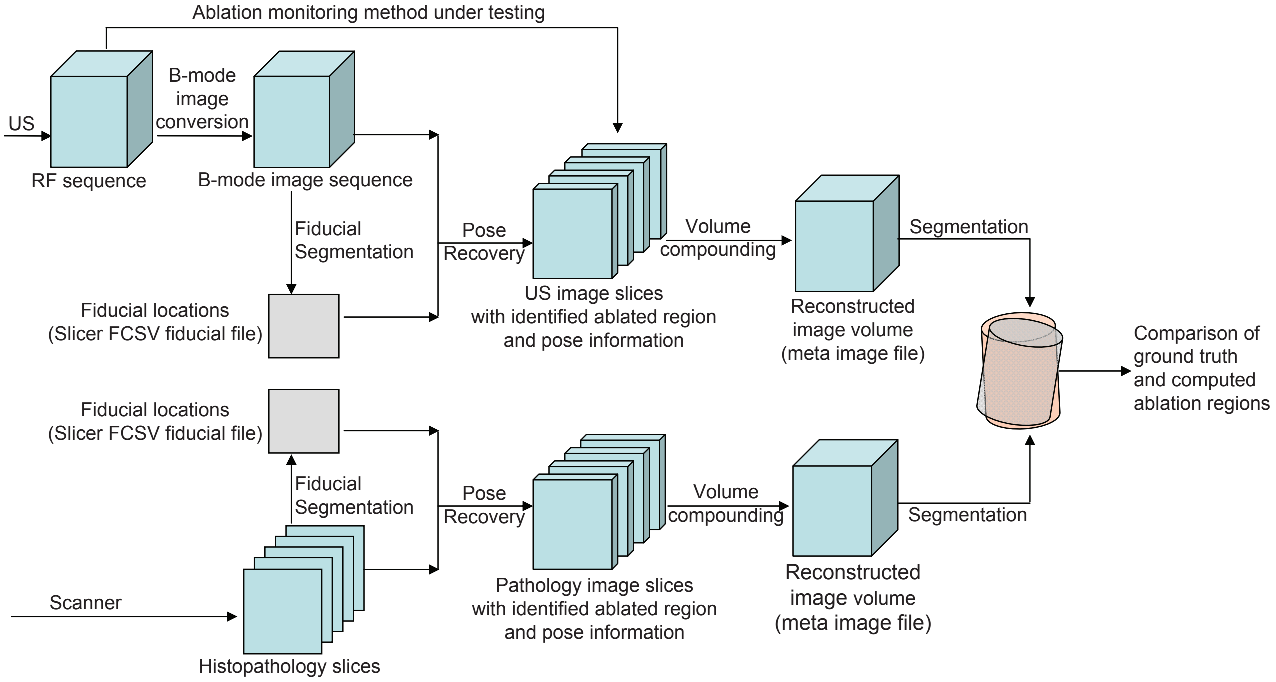
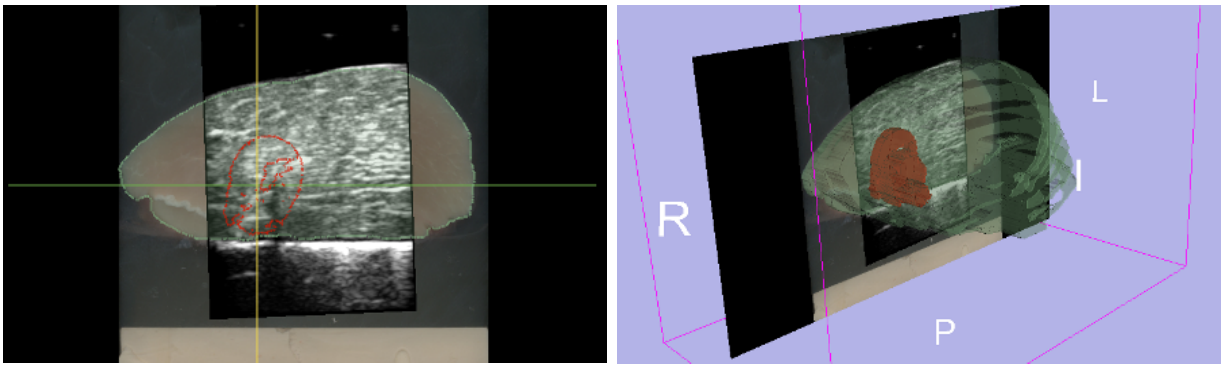


Figure 3. Data and control flow diagram.

and orientation of each image slice is computed for both pathology and ultrasound images, which provides the spatial registration. Using volume compounding technique a 3D volume of the ablated tissue region can be reconstructed for easier and more accurate segmentation, visualization and comparison (Fig. 4(b)).



(a) (b)

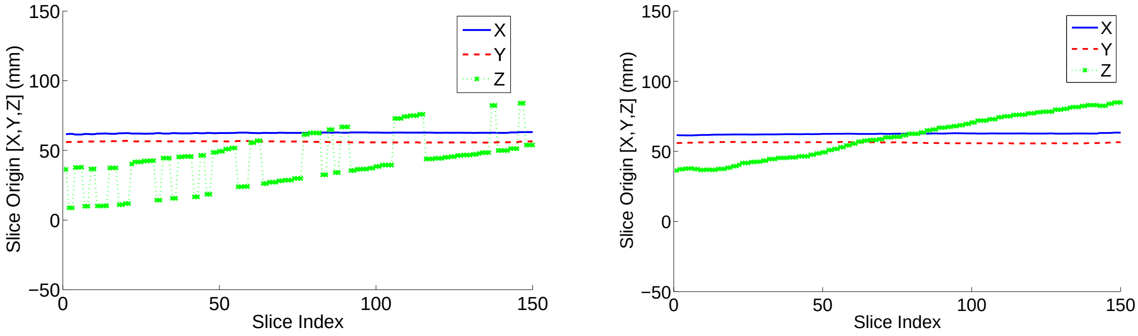
Figure 4. (a) Ablated zone in an ultrasound slice is shown in 3D Slicer. (b) Ablated region is reconstructed in 3D using volume compounding technique.

3. RESULTS

3.1 Phantom studies

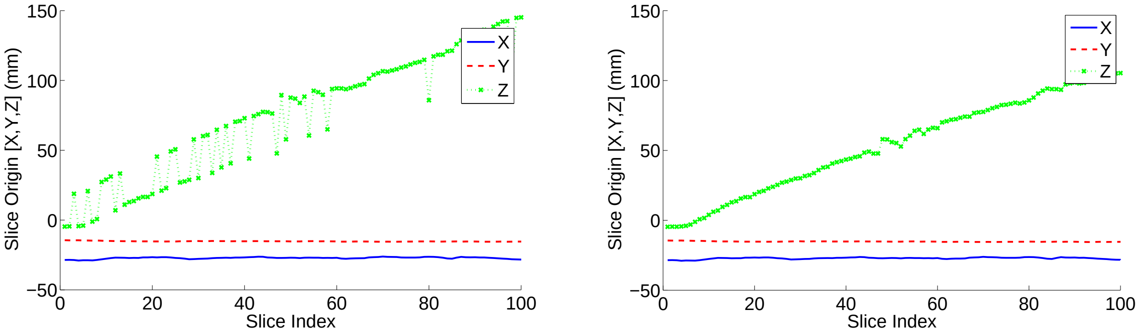
Our new system was evaluated on image sequences acquired from phantoms with ZZZ, ZZ, ZII and ZV fiducial configurations. At least five data sets were acquired with a linear probe (L14-5/38, Ultrasonix RP 3.1.9) for every fiducial configuration. Each data set has an average of hundred image frames. The ultrasound probe was moved in Z-direction along a straight line by hand. The recovered horizontal motion (orthogonal to the sweep direction) and vertical motion were found to be smooth. However, there are large (up to 30mm) spikes present in the sweep direction in phantoms with ZZZ, ZZ and ZII configuration (Fig. 5(a) and Fig. 6(a)). Further analysis showed that these large spikes were caused by ambiguity in the slice orientation computation. It was observed that missing fiducial points can result in an ambiguity in pose recovery. The ambiguity increases as the fiducial localization noise increases and if the pixel spacing information is not accurate. Therefore, it is not possible to register the fiducial points with the fiducial lines perfectly, and hence two similarly good poses may be recovered for each slice.

The ZZ configuration can be ambiguous since each slice at one end of the fiducial configuration can also be registered to the other end of fiducial configuration if flipped both horizontally and vertically or if rotated 180 degrees. ZII can be ambiguous since each slice at one end of the fiducial configuration can also be registered to the other end of fiducial configuration if flipped horizontally. The ZZZ configuration is identical to ZII when the vertical diagonal fiducial points are not visible (which is quite often). The recovered pose information from previous slices can be used for initialization of the registration method in order to converge faster to either of the two solutions faster, but it does not solve the ambiguity caused by incorrect pixel spacing or inaccurate fiducial segmentation. (Fig. 5(b) and Fig. 6(b)).



(a) (b)

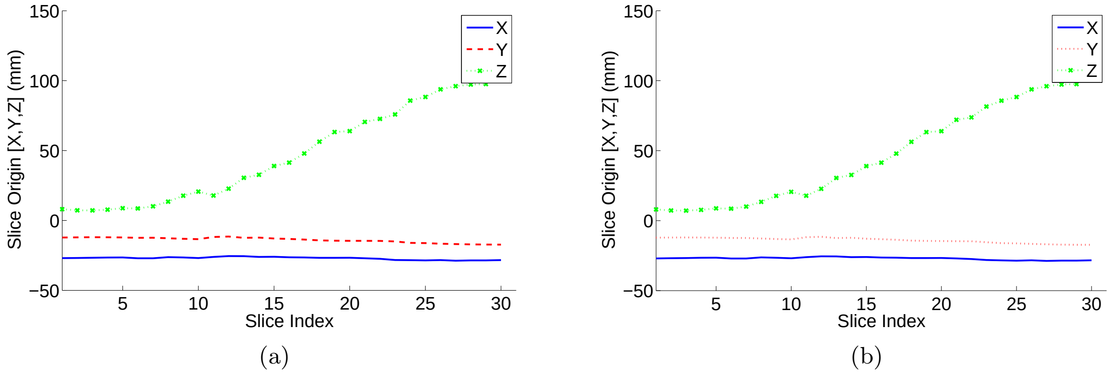
Figure 5. Variation of coordinates of the recovered translation vector on a real data set using ZZ fiducial configuration. The solid blue, dashed red and dotted green lines represent variation in X, Y and Z directions respectively. (a) Ambiguous results. (b) The recovered pose information from previous slices is used for initialization of the registration method. Hence the algorithm converges to the same pose for all the frames, which eliminates the ambiguity, however it does not improve the accuracy of the results.



(a) (b)

Figure 6. Variation of coordinates of the recovered translation vector on a real data set using ZZZ fiducial configuration when the two vertical fiducial points are not visible in US images (similar to ZII configuration). The solid blue, dashed red and dotted green lines represent variation in X, Y and Z directions respectively. (a) Ambiguous results. (b) The recovered pose information from previous slices is used for initialization of the registration method. Hence the algorithm converges to the same pose for all the frames, which eliminates the ambiguity, however it does not improve the accuracy of the results.

Our proposed asymmetric fiducial line configuration (ZV) provides a single pose for every slice(Fig. 7) and any horizontal or vertical flip of the image can be detected. Horizontal fiducial lines minimize the chance of missing fiducial lines. Moreover, fewer fiducial lines reduces fiducial localization error and the effect of deformation during slicing of the gel block, and also allows us to have a clear field of operation above the tissue sample.



(a)

(b)

Figure 7. Variation of coordinates of the recovered translation vector on a real data set using our proposed asymmetric fiducial structure (ZV). The solid blue, dashed red and dotted green lines represent variation in X, Y and Z directions respectively. (a) Recovered pose information from previous slices were not used for initialization of the registration method. (b) Recovered pose information from previous slices were used for initialization of the registration method. Same results are obtained in either case.

3.2 Simulator results

The accuracy of slice pose recovery by using the four different fiducial configurations was evaluated by computing the TRE on 150 simulated slices. The simulator made it possible to perform comparison on a large number of slices, in the exact same conditions (sweep path, fiducial localization error, etc.). Simulation results are as follows: TRE_{ZZZ}=1.75mm , TRE_{ZII}=5.62mm , TRE_{ZZ}=3.50mm and TRE_{ZV}=3.70mm. A normally distributed fiducial localization error with 1.0mm standard deviation was used for these TRE computations. See section 2.2.1 for details.

A comparison of different fiducial structures is shown in Table 1. The ZZZ configuration has the best accuracy, followed by ZZ, ZV and ZII. Tissue size is limited only in the ZZZ configuration. The vertical diagonal fiducial lines of the ZZZ configuration limit the size of sample tissue while they are not often visible in US images. Fiducial visibility is equally good for the ZII, ZV, and ZZ configurations, because they consist of only horizontal fiducial lines. Distortion during pathology slicing is smaller if there are less fiducials, in this sense the ZV and ZII configurations are better than the ZZ and ZZZ configurations. Access to the tissue is the best in case of ZV and ZII, as the tissue can be freely accessible for inserting the RF-ablator needle and thermocouples from the top and sides.

Table 1. A comparison of cons and pros of each fiducial structure.

	ZZZ	ZII	ZV	ZZ
Accuracy	++	− −	−	+
Tissue size	−	+	+	+
Fiducial visibility in US	−	+	+	+
Distortion during slicing	− −	+	+	−
Access to the tissue	−	+	+	−

Overall, while ZZZ configuration has the best accuracy (lowest TRE) in US image registration.The ZZ fiducial setup has a similar accuracy and does not suffer from tissue size and fiducial visibility problems. ZII and ZV configurations allow better access to the sample tissue and have less slicing distortion. Therefore, there is a compromise in the accuracy of US and pathology registration and also access to chicken tissue. According to our current results ZZ configuration seems to be the most suitable fiducial configuration for the US-based ablation monitoring test-bed. The ZV configuration may also be considered if access to the tissue is very important.

4. CONTRIBUTION

Our contribution is the implementation of a simulator for evaluating and optimizing different line fiducial structures, and proposing a new and improved fiducial configuration that is superior to the previously used in terms of accuracy, robustness of fiducial detection and use of larger tissue samples. We quantitatively analyzed and compared four different fiducial configurations using simulation results and phantom studies. Simulation results show a significant improvement in accuracy of pose recovery using our new proposed fiducial structure. With software reusability in mind an optimum fiducial line pose recovery method was implemented, and a new and accurate automatic fiducial segmentation algorithm was integrated in our new system. We also redesigned the software with a simple and extensible architecture which is based on open source tools, applications and standard data formats.

ACKNOWLEDGMENTS

The authors would like to thank Prof. Sangyoon Lee from Konkuk University in Korea for providing the Matlab implementation of fourth algorithm discussed in his paper.[11] We would also like to thank Dr. Ehsan Dehghan of Queen's University in Kingston for his insight and ideas. We also thank Alexandra M. Pompeu-Robinson and Jena Hall for their valuable contributions to the platform set up, and for the acquisition of the test image sequences. This work was funded by the Natural Sciences and Engineering Research Council of Canada under the Idea to Innovation program. Gabor Fichtinger was supported as Cancer Care Ontario Research Chair.

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