Registration of In-vivo Prostate MRI and Pseudo Whole Mount Histology using Local Affine Transformation with Internal Structures (LATIS)

Chaitanya Kalavagunta[1], Xiangmin Zhou[1], Jonathan C Henriksen[2], Stephen Schmechel[2], and Gregory J Metzger[1]
[1]*Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, Minnesota, United States,* [2]*Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, United States*

INTRODUCTION: Prostate cancer (PCa) is the second leading cause of cancer deaths among men [1]. At present there is no single imaging modality uniquely capable of reliably differentiating normal from cancerous prostate tissue. Multi parametric maps of anatomic, vascular and metabolic data of PCa and benign tissue acquired using multiple imaging modalities can yield improved discrimination of the extent and aggressiveness of PCa. An important step in this direction is the registration of *in-vivo* MR images with histopathological sections from prostatectomy. This multi-modality registration would enable correlation with postoperative histopathological determination of extent and tumor grade, and molecular assessment of aggressiveness and thus validate the parametric maps.

Jo et al. have shown the registration of quarter mount histological sections (QMHS) with *in-vivo* MRI [2] using a non-rigid thin plate spline (TPS) registration method. Their method however, does not address the challenges of registering QMHS data to *in-vivo* MRI acquired with an endorectal coil (ERC). Our institution uses QMHS data because the resources to cut, stain, store and digitize whole mounts are not available. The first challenge of registering QMHS that are assembled into a pseudo whole mount (PWM) section are the discontinuities between the quarters which are difficult to handle with the previously described TPS method [2]. In addition, the TPS method requires the accurate definition of many smaller landmarks on both datasets to give accurate results.

In this work, we develop a novel technique using a Local Affine Transformation using large Internal Structures (LATIS) to perform registration. These larger structures are arguably easily identified both on pathology and MRI. In addition, this method can handle the discontinuities present in quarter sectioned pathology data mentioned earlier. Within the scope of this project, we validate this methodology on data acquired from men with diagnosed PCa that received prostatectomy.

METHODS: *In-Vivo MR Acquisition:* Eight patients with biopsy-proven prostate were imaged on a 3T Siemens scanner under an institutionally approved protocol. A surface array combined with an endorectal coil (ERC) was used for all imaging. The ERC was inflated with 60 ml of perfluorocarbon to reduce air induced susceptibility artifacts. T_2-weighted (T_2w) axial MR images were generated 2D Turbo Spin Echo acquisition, 4m42s scan duration, TR/TE 6860/107 ms; ETL 23, NEX 2, BW 190 Hz/Px, 3 mm slice thickness, 140° flip angle, 256^2 matrix, 19 slices 140×140 mm^2 FOV and R-L phase encoding direction.

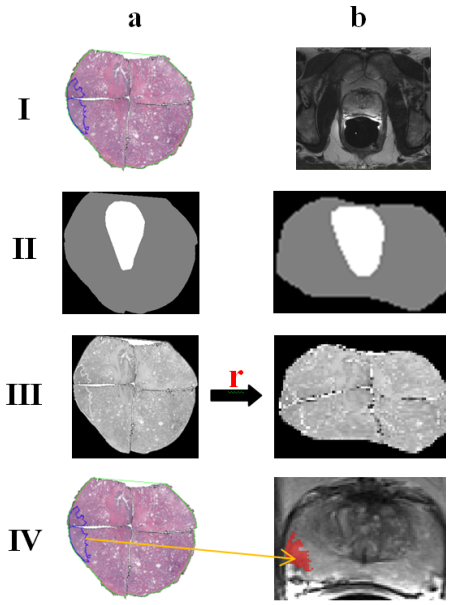

Fig1. Image registration flowchart

Pathology Processing: Excised prostates were formalin fixed, gross sectioned, paraffin embedded and cut at 3 µm. H&E stained slides were digitized using a whole slide scanner (ScanScope CS, Aperio, Vista, CA). Tumors regions within digital stained sections obtained at 20X magnification (resolution 0.58µm per pixel) were annotated by an experienced pathologist using a Wacom Cintiq 21UX pen tablet screen. Annotated quarter digital slides were then reassembled into a PWM using our in-house prostate stitching software and masks for annotated tumor regions were generated.

Image Registration: The image registration workflow for a sample case is shown in Fig 1. Steps Ia and Ib show the source (PWM: size 512×512) and target (T_2w: 256×256). The prostate region in the MR image was extracted using contours drawn in a semi-automated segmentation program (Segasist, Ontario, Canada) and translated to match the downscaled PWM. Large internal structure(s) visible on both the source and target were identified. Steps IIa and IIb show the source and target masks generated with the white region delineating the internal structure. Using the pre-defined controls (large internal structure and prostate boundary) found in the source and target, a local affine transformation guided by internal structures based non-rigid registration method was used to register these two images and a deformation matrix **r** was obtained. Steps IIIa and IIIb show the application of **r** to a grayscale PWM image and the resulting warped image. Step IVa shows the application of **r** to warp tumor region masks to obtain registered tumor regions overlaid on in-vivo MR in step IVb. All registration image processing was done in Matlab (MathWorks, MA, USA).

RESULTS: It has been shown by Fitzpatrick et al. [3] that visual inspection can detect 2 mm misregistrations of brain MRI images to brain CT images quite reliably. Similarly Wong et al. [4] have found that translations of 2mm along the x- and y- axes and 3mm along the z axis can be detected reliably [5]. Many studies have used expert delineated control points for validation of deformable image registration (DIR) [6, 7, 8, 9, 10].For each registered case, identical features (separate from the structure(s) chosen for registration) were identified by visual inspection manually on the PWM pathology and in-vivo MR image. Feature positions on the PWM image were masked using oval areas (area ~ 7 mm^2) to give a feature marked PWM image (fmPWM). An oval area of this magnitude was chosen to easily identify the feature in the registered source. The deformation matrix **r** obtained earlier for this case was applied to the fmPWM image. Transformed pixel positions were obtained from the registered fmPWM image. Target pixel positions were obtained from the in-vivo MR image. Target registration error (TRE) for registration of PWM pathology to in-vivo MR was calculated using the least square distance between the transformed and target pixel position. For the eight cases, a TRE of 1.92 ± 1.49 mm and 2.25 ± 0.92 mm was determined for positions near the boundary and positions away from the boundary, respectively. For all positions the combined TRE was 2.05 ± 1.27 mm.

DISCUSSION: The two main geometric issues in histopathology-MR image registration are the distortions in the prostate in-vivo MR resulting from the ERC and the longitudinal shrinking and radial expansion of excised prostates due to removal and fixation. These problems are addressed by identifying large internal structures along with the prostate boundary to guide registration within LATIS. While the method to assess the registration accuracy was subjective, it is an important first step in validation. Future studies will focus on providing a better metric for assessing registration accuracy. With the availability of improved validation, future studies will involve cascading LATIS with other deformable strategies to see if these methods can further improve local registration of features**.**

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