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3D surface-based registration of ultrasound and histology in prostate cancer imaging

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ABSTRACT

Several transrectal ultrasound (TRUS)-based techniques aiming at accurate localization of prostate cancer are emerging to improve diagnostics or to assist with focal therapy. However, precise validation prior to introduction into clinical practice is required. Histopathology after radical prostatectomy provides an excellent ground truth, but needs accurate registration with imaging. In this work, a 3D, surface-based, elastic registration method was developed to fuse TRUS images with histopathologic results. To maximize the applicability in clinical practice, no auxiliary sensors or dedicated hardware were used for the registration. The mean registration errors, measured *in vitro* and *in vivo*, were 1.5 ± 0.2 and 2.1 ± 0.5 mm, respectively.

1. Introduction

Prostate cancer (PCa) is the type of cancer with the highest incidence and second highest mortality among males in the United States [1]. Despite the statistics of this cancer type, the main diagnostic technique, systematic biopsy, has major drawbacks. Firstly, being invasive, it can cause infections and hematuria [2]. Secondly, tumors can be missed by the biopsy needle [3], resulting in poor sensitivity of this diagnostic tool. Thirdly, tumors can be undergraded when the more aggressive region of a tumor is missed [4], leading to undertreatment. Moreover, because of the lack of reliable localization methods, PCa is often overtreated out of precautionary considerations [5,6], increasing risk of urinary incontinence and impotence [5].

To overcome these limitations, several methods aiming at non-invasive PCa localization are currently under development. Determining the exact location of PCa would decrease the number of biopsies and the chance of missing cancerous tissue by use of targeted biopsies [7]. In addition, it can enable imaging-targeted focal therapy as a treatment option [7,8]. Currently, most studies involving PCa localization are based on magnetic resonance (MR) imaging [9–11]. However, studies using transrectal ultrasound (TRUS)-based methods – such as computer-assisted TRUS [12,13], (shear-wave) elastography [14–17], and dynamic contrast-enhanced ultrasound [18,19] – also show promising results. TRUS has the advantages over MR of being less expensive, widely used for targeting biopsies, and directly applicable by urologists.

Because of the lack of a medical imaging modality revealing the exact location of cancerous tissue in the prostate, histopathologic analysis after radical prostatectomy (RP, excision of the prostate) is frequently used as a gold standard for validation of new imaging techniques [9,20–24]. Usually, the excised prostate is sectioned into 3- to 4-mm-thick slices, after which the separate slices are compared with the images used for PCa localization [25]. However, due to the different orientation of the imaging planes and the histology slices, one image could span multiple histology planes. Deformation of the prostate caused by pressure from transrectal probe or due to surgery and preparation for histopathologic analysis can further complicate accurate validation. Moreover, the histology slice corresponding to the image has to be manually selected, endangering the objectivity of the validation. A 3-dimensional (3D) registration method could assist in making an objective and accurate comparison between the PCa imaging technique and the gold standard.

Extensive work has already been done on *in vivo* MR-pathology mapping of the prostate, which is a challenging task, because of the deformation due to surgery and to preparation of the tissue for

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histologic analysis. In some methods [26,27], the histology slices corresponding to the MR slices are manually selected after which 2D registration is applied. In another approach [28], the algorithm tries to find the corresponding slices automatically prior to their registration. However, in TRUS, the histology slices are typically not aligned with the imaging planes.

In other studies, fiducial markers [29,30], manually outlined natural landmarks [29], and a 3D-printed mold of the prostate [21,31,32] were used to assist with the registration. Some researchers [33,30] used *ex vivo* MR images to break down the registration in smaller steps. Although improving the registration accuracy, the extra steps could conflict with the clinical workflow in most hospitals.

In contrast to MR-histology registration, only few research groups have made attempts to register prostate ultrasound (US) imaging withhistology. Taylor et al. [34] implemented a semi-automatic 6-degrees-of-freedom (DOF) rigid body registration algorithm to match the surface of an excised prostate imaged by US with the surface of the same prostate after fixation for histology. The registration was used for validation of a cancer detection method using sonoelastography. However, the registration accuracy was estimated completely *ex vivo*. In [35], the authors described a method for elastic registration of a prostate recorded by *in vivo* TRUS imaging and histology. An ellipsoid fit and the position of the urethra were used to align the images by affine transformation, but no information on the registration error was given. Recently, a technique was proposed in [36] to jointly align histology slices to intra-operative 3D US by affine transformations using particle filtering. Again, except for the area overlap between the registered histology slices and the corresponding cross-sections in US, no information was provided on the accuracy of the method.

This paper describes a new method to elastically register TRUS and histology in 3D for validation or training of TRUS-based PCa imaging techniques. TRUS-histology registration is a challenging task for reasons concerning both TRUS and histology. The main challenges concerning TRUS are summarized below:

- the orientations of the TRUS imaging planes are unknown without use of additional sensors;
- usually, no reliable natural landmarks are visible in both TRUS imaging and histology to assist with the registration;
- introduction of the transrectal probe causes a local posterior deformation,

whereas these are the biggest obstacles concerning histology:

- for histological analysis, the prostate is cut into 3- to 4-mm-thick slices, providing poor resolution in that direction;
- after excision, the prostate is relieved from pressure caused by surrounding organs and tissue, resulting in a deformation;
- fixation of the prostate after RP causes a volume decrease [37].

To avoid the need of landmarks or a high level of detail, which are lacking in B-mode TRUS, the method presented here is surface-based, requiring prostate shape information only. Both the affine and local deformations of the prostate as a result of the probe pressure and deformation after excision are taken into account. Apart from acquiring the prostate shapes, no manual intervention is required during the registration process. Moreover, being independent of the underlying imaging modality, application of the method in validation of PCa imaging techniques using other modalities (*e.g.*, MR or CT) could be a feasible option.

In other work related to surface-based, elastic registration of prostates, Crouch et al. [38] estimated boundary displacements by minimizing deformation energy. After that, a uniform, nearly-incompressible material with linear elasticity was assumed to estimate internal deformation. Lee et al. [39] developed a technique for a joint estimation of elasticity and deformation of organs and tested it on ten prostates. Parameters describing the mechanical properties and forces acting on the boundary of the prostate were optimized through minimization of the distance between the prostate surfaces to register.

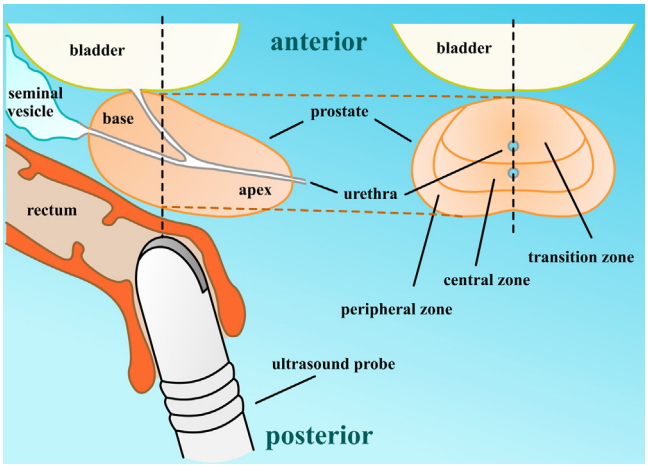

Fig. 1. Schematic illustration of the prostate with surrounding structures (left) and a transversal cut showing the zonal anatomy (right).

The method presented in this paper does not rely on the underlying patient-specific mechanical properties, which may be difficult to determine during an examination and may change during the fixation process as part of the preparation for histopathologic analysis. Moreover, values for Young's modulus of prostate tissue found in literature vary in order from 10 to 100 kPa [40–44]; additionally, varying values of stiffness among different prostate zones were reported [40]. For these reasons, internal deformation is estimated based on shape difference only. In this way, the method can be applied using data obtained during a routine prostate examination by TRUS imaging without the use of specialized equipment or training.

Because of the 2D nature of TRUS imaging as commonly used in clinical practice, an additional step consisted of the construction of a 3D surface model based on the prostate contours in multiple 2D TRUS images. The reconstruction of 3D surfaces from 2D images can be performed in various ways [45–48] and is not the focus of this paper. However, for completeness, the method we designed for our study is also described.

In an *in vitro* experiment, the registration algorithm's accuracy was assessed in 2 gelatin phantoms with fiducial markers. Additionally, in an *in vivo* experiment, we used the border between the peripheral and central zone (BPZ) to estimate the method's target registration error (TRE) in 7 patients. To the authors' knowledge, no quantitative *in vivo* validation has yet been reported for 3D registration between TRUS and histology.

2. Material and methods

2.1. Prostate anatomy

The prostate is part of the male reproductive system and is located between the bladder and the rectum. A schematic overview of the prostate anatomy is given in Fig. 1, in which the position of the TRUS imaging probe has also been drawn. This illustration indicates the locations of the base and apex, and posterior and anterior side, which are frequently mentioned throughout this paper. In addition, a schematic overview of the zonal anatomy is shown in a transversal plane.